Achtergrondstudie

Uitkomstenonderzoek dure geneesmiddelen. Pilot studies bortezomib en oxaliplatin: resultaten en methodologische aanbevelingen

Publicatiedatum 9 juli 2012

Uitgave College voor zorgverzekeringen
Postbus 320
1110 AH Diemen
Fax (020) 797 85 00
E-mail info@cvz.nl
Internet www.cvz.nl

Volgnummer 2012075715
Afdeling ZORG-ZA/ZORG-O&O
Begeleid door Dr. G.O. Delwel en Dr. ir. W.G. Goettsch
Doorkiesnummer Tel. (020) 797 80 57

1. Inleiding

Aanleiding

In het kader van de NZa beleidsregels 'Dure geneesmiddelen' en 'Weesgeneesmiddelen in academische ziekenhuizen' beoordeelt het CVZ sinds 1 januari 2006 of dure geneesmiddelen tijdelijk kunnen worden opgenomen in deze beleidsregels en daarmee aanspraak maken op additionele financiering. Deze aanspraak is gekoppeld aan het verzamelen van gegevens in de klinische praktijk, het uitkomstenonderzoek. Op basis van het uitkomstenonderzoek vindt na 4 jaar een herbeoordeling plaats, waarin naast de therapeutische waarde en het kostenbeslag ook de kosteneffectiviteit wordt beoordeeld. Tot 2012 adviseerde het CVZ de NZa en VWS op basis van deze herbeoordeling over continuering van additionele financiering middels de NZa beleidsregels.

NZa beleidsregels intramurale geneesmiddelen (2006-2011)

NZa beleidsregel Prestaties en tarieven medisch specialistische zorg (vanaf 2012)

Sinds 1 januari 2012 zijn voornoemde beleidsregels opgegaan in de NZa beleidsregel 'Prestaties en tarieven medisch specialistische zorg' . De zogenaamde t=0 en t=4 beoordelingen voor dure geneesmiddelen vinden nu plaats in het kader van deze beleidsregel, waarbij het CVZ een uitspraak doet over de toelating van dure geneesmiddelen tot het basispakket.

Uitkomsten-onderzoek

Het CVZ beoordeelt dure geneesmiddelen sinds 2006 op basis van uitkomstenonderzoek, i.e. het verzamelen van gegevens in de klinische praktijk op basis waarvan een uitspraak over de kosteneffectiviteit en doeltreffende toepassing van dure geneesmiddelen kan worden gedaan.

Pragmatisch

In 2006 heeft het CVZ een beoordelingsprocedure voor intramurale geneesmiddelen[1] en een beoordelingskader doelmatigheid[2] opgesteld. Daarnaast heeft het CVZ een werkgroep 'Beoordeling doelmatigheid intramurale geneesmiddelen' in het leven geroepen. Deze werkgroep heeft in de 'Leidraad voor uitkomstenonderzoek'[3] vastgelegd wat we verstaan onder uitkomstenonderzoek; welke gegevens we moeten verzamelen; welke bronnen hiervoor gebruikt kunnen worden; wie betrokken moeten zijn; wat de gewenste studieopzet is en wat de gewenste infrastructuur is. De aanbevelingen van de werkgroep zijn samengevat in een stroomschema waarin de pragmatische opzet van het uitkomstenonderzoek staat weergegeven alsmede het bijbehorende stappenplan.

---

[1] Procedure beoordeling intramurale geneesmiddelen (http://www.cvz.nl/binaries/content/documents/cvzinternet/nl/documenten/rapporten/2006/rpt0604+intramurale+geneesmiddelen.pdf)

[2] Beoordelingskader doelmatigheid intramurale geneesmiddelen (http://www.cvz.nl/binaries/content/documents/cvzinternet/nl/documenten/rubriek+zorgpakket/cfh/beoordeling+doelmatigheid+intramurale+geneesmiddelen.pdf)

[3] Leidraad voor uitkomstenonderzoek (http://www.cvz.nl/binaries/content/documents/cvzinternet/nl/documenten/rapporten/2008/rpt0812+leidraad+uitkomstenonderzoek.pdf)

De leidraad vormt een verbijzondering van de 'Richtlijnen voor farmaco-economisch onderzoek'[4] en bevat praktische informatie voor het verrichten van uitkomstenonderzoek.

Opdracht aan iMTA

Het CVZ heeft het iMTA opdracht gegeven om te onderzoeken hoe aan de beoordeling van de doelmatigheid van dure geneesmiddelen op basis van praktijkgegevens nader invulling kon worden gegeven. Specifiek werden de volgende vragen gesteld:

1) Een aantal methodologische vragen met betrekking tot uitkomstenonderzoek op basis van een internationale literatuurstudie te adresseren; het resultaat is meegenomen in de eerste bespreking van de Werkgroep 'Beoordeling doelmatigheid intramurale geneesmiddelen' in 2007.
2) Deze methodologische vragen, vanuit de concept-leidraad, te toetsen aan praktijkervaringen die gebaseerd zijn op een tweetal pilotstudies. Op basis van de resultaten van deze pilotstudies wordt de waarde van het uitkomstenonderzoek ingeschat en doet het iMTA een aantal methodologische aanbevelingen voor het doen van uitkomstenonderzoek.

In dit rapport worden de bortezomib en oxaliplatin pilot studies besproken alsmede de methodologische aanbevelingen die hieruit naar voren zijn gekomen. De volledige achtergrondstudies zijn opgenomen als bijlagen bij dit rapport.

Begeleidings commissie

De voortgang van de pilotstudies is regelmatig door de onderzoekers besproken met de begeleidingscommissie bestaande uit Prof. Dr. P.C. Huygens (VUMC), Prof. Dr. A. Steenhoek (ErasmusMc), Dr. G.O. Delwel (CVZ) en Dr. ir. W.G. Goettsch (CVZ).

2. Pilotstudies

Selectiecriteria voor de pilotstudies

Voor het uitvoeren van onderzoek in de praktijk moet onder andere rekening gehouden worden met de volgende factoren:

- De patiëntenpopulatie waarvoor het geneesmiddel is geregistreerd
- Het type geneesmiddel
- De grootte van de patiëntengroep
- De effectiviteitsparameters (levensduur; verbetering van ziektespecifieke klinische parameters)
- De behandeling van patiënten binnen of buiten studieverband
- De aanwezigheid van gegevens uit een gerandomiseerd

[4] Richtlijnen voor farmacoeconomisch onderzoek, geactualiseerde versie (http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rubriek+zorgpakket/cfh/richtlijnen+farmaco-economisch+onderzoek.pdf)

klinisch onderzoek of een patiëntenregister.

Bij de keuze van de pilotstudies is met deze factoren rekening gehouden, en wel zodanig dat de pilotstudies veel van elkaar verschilden op deze punten, om een zo breed mogelijk palet aan praktijkervaringen te toetsen. In overleg met het iMTA is gekozen voor de geneesmiddelen bortezomib voor de behandeling van recidiverend en refractair multipel myeloom en oxaliplatin voor de behandeling van stadium III en gemetastaseerd coloncarcinoom.

Bortezomib pilot

Kenmerken van de bortezomib pilot zijn:

- Indicatie: recidiverend en refractair multiple myeloom
- Kleinere patiënten aantallen
- Behandeling grotendeels in onderzoeksverband
- Veel dynamiek in klinisch handelen
- Registratie binnen HOVON studies
- Klinische fase III studies: APEX en HOVON

Oxaliplatin pilot

Kenmerken van de oxaliplatin pilot zijn:

- Indicatie: stadium III en gemetastaseerd coloncarcinoom
- Grote patiënten aantallen
- Behandeling niet in onderzoeksverband
- Weinig dynamiek in klinisch handelen
- Registratie in integrale kankerregistratie
- Klinische fase III studies: MOSAIC en CAIRO

Onderzoeksvragen

Het onderzoeksvoorstel van de bortezomib pilot richtte zich op de volgende vraag:

Bortezomib

Hoe wordt bortezomib in de praktijk gebruikt bij de tweede- en derdelijns behandeling van patiënten met een multipel myeloom, wat is het resultaat ervan en welke kosten brengt het gebruik van bortezomib met zich mee?

Studieopzet

Voor de bortezomib studie werden de patiënten gerekruteerd uit reeds afgesloten studies HOVON 24 en HOVON 50 en uit de registraties van integrale kankercentra. Voor deze studie worden verschillende vergelijkingsarmen worden geconstrueerd 1) de fase III klinische studie APEX; 2) de tweede- en/of derde lijnsbehandeling van de HOVON 24 patiënten; 3) de HOVON 50 studie.

Oxaliplatin

Het onderzoeksvoorstel van de oxaliplatin pilot richtte zich op de volgende vraag:

Studieopzet

Hoe wordt oxaliplatin in de Nederlandse praktijk gebruikt bij de behandeling van stadium III en IV colorectaal carcinoom en wat is het resultaat ervan. Welke kosten en baten brengt het gebruik van oxaliplatin met zich mee, vergeleken met de behandeling met 5-FU/LV?

Hiertoe werden twee afzonderlijke steekproeven verricht:

1. Een steekproef onder patiënten met een stadium III colorectaal carcinoom om de wijze van het gebruik van oxaliplatin en de uitkomsten in de praktijk te onderzoeken.
2. Een steekproef onder patiënten met een stadium IV

colorectaal carcinoom om de wijze van het gebruik van oxaliplatin en de uitkomsten in de praktijk te onderzoeken.

De steekproeven werden gebaseerd op de databases van een aantal Integrale Kanker Centra (IKC) en IKA. Daar er in de IKC databank slecht basale informatie beschikbaar is zullen vervolgens de statussen van deze patiënten worden onderzocht om alle detailinformatie te verzamelen.

Gegevens

In beide pilotstudies werden de volgende gegevens verzameld in een geplande studieduur van 2,5 jaar.

1) Patiënt en behandelkenmerken
2) Kostengegevens - alleen de directe medische kosten het is niet goed mogelijk is om retrospectief gegevens over indirecte kosten van de patiënten te verkrijgen van wie de effectdata wordt gebruikt.
3) Uitkomstmaten: respons percentage, tijd tot respons, tijd tot progressie, progressie vrije overleving, overleving, bijwerkingen, en eventueel kwaliteit van leven, de wijze van behandeling met bortezomib in de praktijk, de kwaliteit van de behandeling (gedefinieerd als voorschrijven volgens indicatie en/of specificatie gemaakte keuzen), levensjaren en progressie-vrije levensjaren.

De kosteneffectiviteitsanalyses werden uitgedrukt in kosten per gewonnen levensjaar, kosten per progressievrij levensjaar en (indien mogelijk) kosten per voor kwaliteit gecorrigeerd gewonnen levensjaar (QALY's). Daarnaast werden separate kosten- en effectiviteitsanalyses uitgevoerd.

Knelpunten

Bij het starten van het onderzoek werden de volgende knelpunten gedefinieerd:

- De kwaliteit van leven gegevens komen uit de literatuur en zijn gebaseerd op patiënten die behandeld zijn in studieverband.
- Het verschil tussen de patiëntengroepen in de vergelijkingsarmen. Het is waarschijnlijk dat het feit of patiënten wel of niet behandeld zijn met bortezomib of oxaliplatin niet berust op toeval maar afhangt van factoren zoals het ziekenhuis waar zij zijn behandeld, van de algemene toestand van de patiënt, eventuele co-morbiditeit en het inzicht van de behandelaar.

Praktische keuzen

Bij het opzetten van de pilotstudies zijn een aantal praktische keuzen gemaakt, ten dele ingegeven door de relatief korte onderzoeksperiode (2007–medio 2010, waarbij opgemerkt wordt dat het eerste jaar de logistieke aanlooptijd betrof, de gegevensverzameling liep vanaf 2008). Hierdoor zijn niet alle uitgangspunten zoals verwoord in de Leidraad getoetst in de praktijk. Zo hadden beide pilots een retrospectieve studieopzet i.t.t. de prospectieve opzet zoals aanbevolen in de Leidraad. De reden was dat gebruik werd gemaakt van de reeds beschikbare gegevens uit de HOVON trials en de

Geen prospectieve studieopzet

kankeregistratie, waarbij de gegevensverzameling vanuit deze retrospectieve databases overigens wel prospectief verliep. Voor beide pilots is geen t=0 doelmatigheidsindicatie beschikbaar, aangezien geen t=0 model aanwezig was.

Perspectief

Kwaliteit van leven

Uiteindelijk is een model ontwikkeld voor de oxaliplatin studie, op basis van dit model en de bevindingen uit de kankerregistratie is een uitspraak over de kosteneffectiviteit gedaan op t=n.
Het voorstel uitkomstenonderzoek is niet helemaal volgens het CVZ beoordelingskader opgezet, zo wordt geen maatschappelijk perspectief gehanteerd; en wordt de effectiviteitsmaat utiliteiten alleen in de oxaliplatin studie meegenomen. De 'T=4 beoordeling': doeltreffende toepassing en dynamiek klinisch handelen wordt in beide studies uitgevoerd, een uitspraak over de kosteneffectiviteit is uitsluitend in de oxaliplatin studie gedaan.

Resultaten

De resultaten vanuit de pilotstudies geven aan het mogelijk is op basis van uitkomstenonderzoek een uitspraak te doen over de doeltreffende toepassing en de kosteneffectiviteit van dure geneesmiddelen.

3. Methodologie

Methodologische aanbevelingen

De belangrijkste methodologische conclusies uit de twee pilotstudies zijn samengevat in de rapportage 'Methodologische vraagstukken'. In deze rapportage staan aanbevelingen voor het doen van uitkomstenonderzoek, daarnaast worden kritische succesfactoren en knelpunten benoemd.

Kritische succesfactoren

Volgens het iMTA waren de meest kritische succesfactoren voor het uitvoeren van goed uitkomstenonderzoek:

- beschikbaarheid van een goed onderzoeksdesign op t=0 (start van de voorwaardelijke financiering en het uitkomstenonderzoek);
- duidelijk uitgewerkte onderzoeksvraag;
- onderzoek moet gericht zijn op het reduceren van onzekerheid over de uitkomsten (effectiviteit en kosteneffectiviteit)
- samenwerking tussen partijen zoals de behandelaren, de regulatoire en vergoedings/ HTA organisaties;
- flexibiliteit en mogelijkheden om het uitkomstenonderzoek 'tailor-made' op te zetten.

Knelpunten/Risicofactoren

Het iMTA identificeerde ook een aantal knelpunten :

- Uitkomstenonderzoek kost veel tijd- en financiële investering;
- Observationele studies hebben veel last van 'bias' en 'confounding';
- Bestaande databronnen zijn vaak onvoldoende compleet voor uitkomstenonderzoek waardoor additionele dataverzameling noodzakelijk is. Zo

bevatten patiëntenstatussen vaak onvoldoende informatie over prognostische factoren en uitkomstmaten.
- Dynamiek in klinisch handelen kan de vergelijkbaarheid met klinische studies verstoren waardoor de schatting van een kosteneffectiviteitsratio moeilijk wordt.

Aanbevelingen

Het iMTA heeft ook een aantal aanbevelingen geformuleerd:
- Het onderzoeksdesign van het uitkomstenonderzoek moet altijd afhankelijk zijn van het type ziekte en geneesmiddel en de verwachte dynamiek in klinisch handelen;
- De duur van het uitkomstenonderzoek is ook afhankelijk van de te behandelen ziekte en het geneesmiddel;
- Ziektespecifieke patiëntenregistraties zijn van belang om voldoende vergelijkbaar behandelde patiënten te verzamelen en op een uniforme manier gegevens te kunnen verzamelen;
- Data uit de dagelijkse praktijk zijn essentieel om te achterhalen wie op welke manier deze geneesmiddelen ontvangen. Daarvoor moet een minimale dataset in de dagelijkse praktijk worden verzameld.
- Het is van belang dat het uitkomstenonderzoek zodanig is opgesteld dat veranderingen in klinisch handelen kunnen worden meegenomen;
- Indien nodig, dienen schattingen van de kosteneffectiviteit te worden bepaald op basis van een synthese van gegevens uit de dagelijkse praktijk en gegevens uit mogelijke andere relevante bronnen.

4. Vervolgstappen

Per 1-1-2012 pakketbeoordeling

Zoals hierboven vermeld zijn per 1 januari 2012 de Beleidsregels Dure en Weesgeneesmiddelen komen ter vervallen. Vanaf 1 januari 2012 beoordeelt het CVZ specialistische geneesmiddelen in het kader van het verzekerde basispakket en adviseert hierbij de minister van VWS en niet meer de NZa. Details van de procedure van deze beoordeling worden beschreven in de '*Procedure pakketbeheer specialistische geneesmiddelen'*. Dit betekent dat specialistische geneesmiddelen met een therapeutische (meer)waarde en die voldoen aan het kostencriterium (kostenbeslag meer dan €2,5 miljoen per jaar) op het moment van de zogenaamde t=0 beoordeling, in aanmerking kunnen komen voor voorwaardelijke financiering in het kader van de toelating tot het basispakket van deze dure specialistische geneesmiddelen. De voorwaarde voor deze financiering blijft analoog aan de addditionele bekostiging middels de opgeheven NZa Beleidsregels dure en weesgeneesmiddelen, dat additionele financiering ten behoeve van de toelating tot het basispakket gekoppeld is aan het verrichten van

uitkomstenonderzoek. Kortom: ook voor dure specialistische middelen moet (uitkomsten)onderzoek worden opgezet om gegevens over de kosteneffectiviteit in de dagelijkse praktijk te verzamelen.

Aanpassing Leidraad Uitkomsten en Farmaco-economische richtlijnen

Het CVZ is van oordeel dat de resultaten van het iMTA onderzoek kunnen worden gebruikt om de 'Leidraad voor Uitkomstenonderzoek' en de 'Farmaco-economische richtlijnen' aan te passen in het kader van de pakketbeoordelingen van deze dure specialistische geneesmiddelen. Daarbij stelt het CVZ voor om als onderdeel van een grondige herziening van deze richtlijnen ook de ervaringen met het uitkomstenonderzoek tussen 2006 en 2012 als onderdeel van de beoordelingen in het kader van de Beleidsregel Dure en weesgeneesmiddelen mee te nemen. Tenslotte zal het CVZ ook de resultaten van de verschillende onderzoeksprojecten die in het kader van het ZonMW programma HTA methodologie meenemen in deze herziening.

Pilot outcomes research:

Effects and costs of bortezomib in relapsed or refractory multiple myeloma

M.G. Franken[1]

J. Gaultney[1]

H.M. Blommestein[1]

S.S. Tan[1]

C.W.M. van Gils[1]

P.C. Huijgens[2]

P. Sonneveld[3]

W. Redekop[1]

C.A. Uyl- de Groot[1]

[1] Institute for Medical Technology Assessment, Erasmus University, Rotterdam

[2] Department of Haematology, VU University Medical Center, Amsterdam

[3] Department of Haematology, Erasmus University Medical Center, Rotterdam

July 2010

Acknowledgements:

The authors would like to thank all participating hospitals and all involved hospital data-managers and cancer registration (IK) staff and are grateful to Daniëlle Ammerlaan, Saskia de Groot, Aat van Klooster, Annemieke Leunis, Arewika Mamakanjan, Zjwan Rashaan, Anneke Spreij, Harm van Tinteren, Bruno Vieyra, and Anneloes van Walsem for their contribution to this study.

This study was supported by the Dutch Healthcare Insurance Board (CVZ).

Index

List of abbreviations

APEX trial	Assessment of Proteasome inhibition for Extending Remissions (clinical trial comparing bortezomib versus dexamethasone)
Bmib	Bortezomib
CAD	Cyclophosphamide Adriamycin Dexamethasone
Cox PH	Cox Proportional Hazard
CRF	Case Report Form
CVZ	Health Care Insurance Board *("College voor Zorgverzekeringen")*
DBC	Diagnosis Treatment Combination *("Diagnose Behandeling Combinatie")*
DIS	National DBC Information System
DOR	Duration Of Response
DS	Durie & Salmon (staging multiple myeloma disease)
FDA	United States Food and Drug Administration
GVS	Drug reimbursement system *("Geneesmiddelenvergoedingsysteem")*
HOVON	Dutch- Belgian Cooperative Trial Group for Haematology Oncology
HOVON50	Phase III clinical trial studying the treatment effect of thalidomide in newly diagnosed Durie & Salmon stage II and III multiple myeloma patients, aged 18–65 years
iMTA	Institute for Medical Technology Assessment
ISS	International Staging System (staging multiple myeloma disease)
MM	Multiple Myeloma
NICE	National Institute for Health and Clinical Excellence
NZa	Dutch Healthcare authority *("Nederlandse Zorg autoriteit")*
OR	Odds Ratio
OS	Overall Survival
PFS	Progression Free Survival
PS	Propensity Score
RCT	Randomised Clinical Trial
SFK	Foundation for Pharmaceutical Figures *("Stichting Farmaceutische Kengetallen")*
SUMMIT	Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy
TAD	Thalidomide Adriamycin Dexamethasone
TTNT	Time To Next Treatment
TTP	Time To Progression
VAD	Vincristine Adriamycin Dexamethasone

Summary

Introduction

Multiple myeloma is a progressive hematologic disease that remains incurable. In 2006, bortezomib (Velcade®), a novel first-in-class proteasome inhibitor, was admitted, based on APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial results, for treatment of relapsed or refractory multiple myeloma under the Dutch policy regulations for expensive pharmaceuticals. The APEX clinical trial compared bortezomib to dexamethasone and proved bortezomib to be more effective, i.e., increased overall survival, response rates and response duration. Hospitals receive additional funding for drugs enlisted on the expensive drug list. However, performing outcomes research (i.e. evidence development on appropriate drug use and real-world cost effectiveness) is required in order to continue financial compensation after three years. Outcomes research in this particular context is new in Dutch policy making and therefore experience in the application of outcomes research is lacking. This report investigates how bortezomib is used in daily practice and explores real-world treatment effects and costs in relapsed or refractory multiple myeloma in Dutch daily practice. This pilot outcomes research study was conducted as part of a comprehensive study of methodological issues related to outcomes research. The pilot study will contribute valuable information on these potential methodological issues. To our knowledge, this is the first study assessing both treatment effects and costs of bortezomib in relapsed multiple myeloma using patient level data from Dutch daily practice.

Method

The patient population was selected from patients who relapsed from treatment protocol of a clinical trial (HOVON50) for upfront therapy that was performed in daily practice. We retrospectively collected detailed case reports from hospital medical records available from the time of first relapsed or refractory disease until end of follow-up. We researched how bortezomib was used in daily clinical practice and investigated treatment regimes and dose modifications. To assess clinical effectiveness, the validity of outcome measures was explored and different adjustment methods, such as average covariate adjustment, regression adjustment by propensity scores and matched analysis, were compared. Treatment costs were computed from a hospital perspective and costs for individual patients were determined by applying unit costs to individual resource use.

Results

A total of 139 patients relapsing from HOVON50 protocol were included. The majority of multiple myeloma patients follow a relapsing disease course requiring subsequent treatment lines. All 139 patients were grouped according to the line in which bortezomib treatment was first administered, resulting in four groups: patients who never received bortezomib (n=67) and patients who received bortezomib for the first time in second (n=25), third (n=35) and fourth line or later (n=12).

Many patients were treated in more than one hospital, thereby requiring over 1700 hours for data collection in 42 different hospitals. The real-world data exposed large variation in treatment regimes. Compared to the APEX trial, daily practice patients received on average lower dosages and fewer treatment cycles. The availability of prognostic factors was limited since such information was often not reported in medical records and it was not clear whether physicians used universal response criteria.

The covariate and propensity score adjustment methods were deemed feasible. The confounder for assessing the effectiveness of bortezomib in relapsed disease was found to be thalidomide treatment of the HOVON50 protocol in the first treatment line. It was difficult to determine a valid outcome measure. After exploring the use of various outcomes, the use of overall survival (OS) from start of first relapse or refractory disease to initial treatment and time to next treatment line or time to progression were concluded to be inappropriate outcomes for demonstrating the effectiveness of bortezomib treatment compared to patients not receiving bortezomib. The former outcome was biased by the effect of previous thalidomide use, and the latter two outcomes revealed contradictory results. Due to the bias of previous treatment received in HOVON50, the preferred method is to report outcomes for each treatment group stratified by HOVON50 treatment arm (i.e., thalidomide versus vincristine). However, this was challenged by the small number of observations in each of the eight groups, and instead unadjusted and adjusted OS from diagnosis were estimated for all patient groups without stratification. Furthermore, when applying methods for adjustment of differences in baseline prognosis, the adjusted OS curves revealed minor differences compared to the unadjusted curves for all groups. Consequently, only the unadjusted estimates for each of the four treatment groups were retained for the final cost-effectiveness estimates.

The mean and median unadjusted OS from start of bortezomib treatment regardless of treatment line were 19.4 and 17.2 months, respectively. The mean unadjusted OS from diagnosis for patients treated in second line was 52.2 while the

median has not yet been reached. The mean and median unadjusted OS from diagnosis for patients treated in third line was 55.5 and 59.3 months compared to 50.1 and 48.5 months for patients treated in fourth line or later, respectively. Total mean costs from the start of first relapse or refractory disease to initial treatment for patients treated with bortezomib amounted to €81,626 but varied widely between patients (range €17,793 to €229,783), while active pharmaceutical treatment was responsible for 44% of the cost.

The mean and median unadjusted OS from diagnosis for patients never treated with bortezomib, which included both patients eligible and ineligible for bortezomib, was 45.9 and 56 months, respectively. Total mean costs from the start of first relapse or refractory disease to initial treatment for patients never treated with bortezomib were €52,760 (range €748 to €179,571), while active pharmaceutical treatment was responsible for 30% of the cost.

Discussion

Outcomes research provides valuable information on the utilisation of bortezomib in daily practice. In the last few years, there have been many advances in the treatment of multiple myeloma, reflected by the heterogeneity in our data. As a result, our retrospectively obtained real-world data challenged the assessment of the incremental cost-effectiveness of bortezomib treatment in the indication of relapsed disease in daily practice. The dynamics in daily practice, such as changes to the treatment guidelines and practice variation, incomparability of pilot patients, restrictive use of outcome measures and small patient numbers, severely limited the ability to compare patients treated and never treated with bortezomib. Consequently, it was impossible to estimate a valid and precise incremental estimate for the comparison between the two different patient groups. However, our real-world data provided valuable information on the appropriate use of bortezomib in daily practice. We revealed the diffusion of bortezomib, application of treatment regimes, dose modifications and treatment related toxicities. Furthermore, it was possible to estimate a cost-effectiveness measure (i.e. costs per month of survival) for bortezomib use in younger patients in daily practice for relapsed disease.

Both the bortezomib and oxaliplatin pilot study provide valuable information regarding methodological challenges of outcomes research as required by Dutch policy regulations for expensive hospital drugs. The pilot studies can be seen as empirical addendum to the Guidance for Outcomes Research (i.e. how to develop evidence on appropriate use and cost effectiveness in daily practice), more specific information on this

is provided in a separate report. The bortezomib pilot study underscores the need for refinement of practice and evidence-based professional guidelines for relapsed multiple myeloma. Furthermore, prospective observational data using a national and/or international registry could facilitate closer follow-up of patients, ensure uniform response criteria, enable the selection of comparable groups of similarly treated patients and thereby contribute to enhanced value of outcomes research.

Samenvatting

Introductie

Multipel myeloom is een hematologische ziekte die vooralsnog niet te genezen is. In 2006 werd de innovatieve proteasoomremmer bortezomib (Velcade®), op basis van de resultaten van de APEX studie (Assessment of Proteasome Inhibition for Extending Remissions), opgenomen op de beleidsregel dure geneesmiddelen voor de indicatie recidief of refractair multipel myeloom. De APEX studie heeft aangetoond dat een behandeling met bortezomib effectiever is dan een behandeling met dexamethasone. Bortezomib verlengt de algemene overleving, verbetert de respons en verlengt de respons tijd. Ziekenhuizen ontvangen additionele vergoeding wanneer zij een geneesmiddel gebruiken dat op de beleidsregel is opgenomen. Tevens verplicht opname op de beleidsregel tot het uitvoeren van uitkomstenonderzoek. Er is geen ervaring met uitkomstenonderzoek in deze context omdat dit nieuw is in het Nederlandse beleid. Dit rapport analyseert de effecten en kosten van een behandeling met bortezomib voor patiënten met een recidief of refractair multipel myeloom en beschrijft hoe bortezomib in Nederland wordt toegepast in de dagelijkse praktijk. Deze pilot studie werd uitgevoerd als onderdeel van het onderzoek naar de methodologische aspecten bij het uitvoeren van uitkomstenonderzoek.

Methode

De populatie bestond uit patiënten met een recidief of refractair multipel myeloom, gerekruteerd uit een voltooide klinische studie (HOVON50). Voor deze patiënten werden retrospectief gedetailleerde gegevens verzameld uit medische dossiers vanaf de eerste progressie van de ziekte. De dagelijkse praktijk werd in kaart gebracht en gegevens over behandelregimes, doseerschema's en redenen voor aanpassingen van doseringen werden geanalyseerd. Daarnaast werd de validiteit van diverse uitkomstmaten onderzocht en werden verschillende correctie methoden vergeleken, waaronder het corrigeren voor covariaten, 'propensity' score en 'matching' methode. De kosten van behandeling werden berekend vanuit het ziekenhuis perspectief. Zorggebruik werd gewaardeerd per individuele patiënt door middel van microcosting schattingen.

Resultaten

In totaal werden 139 patiënten geïncludeerd in de studie. De meeste multipel myeloom patiënten vertonen een terugkerend ziektebeloop waarvoor verschillende elkaar opeenvolgende behandelingen worden gegeven. Alle 139 patiënten werden ingedeeld in de behandellijn waarin zij bortezomib kregen. Dit resulteerde in vier patiënt groepen: patiënten die niet werden behandeld met bortezomib (n=67), patiënten die voor het eerst bortezomib kregen in de tweede behandellijn (n=25), derde behandellijn (n=35), en in de vierde of latere behandellijn (n=12).

Veel patiënten bezochten meerdere ziekenhuizen waardoor het noodzakelijk was om data te verzamelen in 42 verschillende ziekenhuizen. Dit vereiste meer dan 1700 uur data verzameling. De gegevens toonden aan dat er veel behandelvariatie is in de dagelijkse praktijk. Pilot patiënten ontvingen gemiddeld lagere doseringen bortezomib en minder behandelcycli vergeleken met patiënten uit de APEX studie. De beschikbaarheid van prognostische gegevens was beperkt en bovendien was het niet duidelijk of artsen in de dagelijkse praktijk universele uitkomstmaten gebruikten.

De co-variate en propensity score correctie methode werden uitvoerbaar bevonden. De grootste confounder was de inductiebehandeling in de HOVON50 studie, waardoor het kiezen van een valide uitkomstmaat werd bemoeilijkt. Nadat diverse uitkomstmaten werden onderzocht, werd geconcludeerd dat overleving vanaf start van behandeling, tijd tot volgende behandeling en tijd tot progressie geen geschikte uitkomstmaten waren. De eerste uitkomstmaat werd beïnvloed door thalidomide behandeling in de eerste lijn en beide andere uitkomstmaten gaven tegenstrijdige resultaten. Stratificeren naar HOVON50 behandeling (wel of geen thalidomide) zou de beste correctie methode zijn, dit werd echter bemoeilijkt door kleine patiënt aantallen per groep. Hierdoor werd het noodzakelijk om overleving vanaf diagnose als uitkomstmaat te gebruiken. Het corrigeren voor verschillen in baseline prognose had weinig invloed op de overlevingscurven. Voor het schatten van de kosteneffectiviteit werd gebruik gemaakt van de ongecorrigeerde overleving vanaf de eerste progressie/ recidief van de ziekte.

De gemiddelde en mediane ongecorrigeerde overlevingsduur vanaf de start van de bortezomib behandeling was 19,4 en 17,2 maanden. De gemiddelde ongecorrigeerde overlevingsduur vanaf diagnose was voor patiënten die in de tweede lijn werden behandeld 52,2 maanden, de mediaan is nog niet bereikt. Voor patiënten die in de derde lijn bortezomib kregen was de gemiddelde en mediane ongecorrigeerde overlevingsduur 55,5 en 59,3 maanden en voor patiënten die in de vierde lijn of later bortezomib kregen

50,1 en 48,5 maanden. Voor deze patiënten bedroegen de totale gemiddelde kosten vanaf de eerste progressie van de ziekte €81.626, met een grote variatie tussen patiënten (€17.793 tot €229.783), 44% van deze kosten zijn gerelateerd aan actieve behandeling.

Patiënten die niet met bortezomib werden behandeld, ongeacht de reden hiervoor, hadden achtereenvolgens een 45,9 en 56,0 maanden gemiddelde en mediane ongecorrigeerde overlevingsduur vanaf diagnose. Voor deze patiënten waren de gemiddelde kosten vanaf de eerste progressie van de ziekte €52.760 (€748 tot €179.571), 30% van deze kosten zijn gerelateerd aan actieve behandeling.

Discussie

Uitkomstenonderzoek levert waardevolle informatie op over het gebruik van bortezomib in de dagelijkse praktijk. In de afgelopen jaren zijn er veel veranderingen geweest in de behandeling van het multipel myeloom, wat zich uit in de heterogeniteit in onze gegevens. Er werd geconstateerd dat het retrospectief verzamelen van gegevens een uitdaging vormde voor het bepalen van een incrementele kosteneffectiviteitratio van een behandeling met bortezomib voor patiënten met een refractair of recidief multipel myeloom. De dynamiek van de dagelijkse praktijk, zoals veranderende professionele richtlijnen, behandelvariatie, onvergelijkbaarheid van pilot patiënten, beperkte keuze in geschikte uitkomstmaten en het kleine aantal geïncludeerde patiënten, beperkte de mogelijkheden om patiënten die met bortezomib werden behandeld te vergelijken met patiënten die niet met bortezomib werden behandeld. Hierdoor was het onmogelijk om een valide en nauwkeurige schatting te maken van verschillen tussen beide groepen. Desalniettemin bieden de pilot gegevens waardevolle informatie over de doeltreffende toepassing en het gebruik van bortezomib in de dagelijkse praktijk. Het was mogelijk de diffusie van bortezomib aan te tonen, behandel regimes te onderzoeken, dosis aanpassingen en behandelingsgerelateerde toxiciteit zichtbaar te maken. Tevens kon een schatting worden gemaakt van de kosteneffectiviteit van bortezomib in de dagelijkse praktijk (kosten per maand overleving) voor de behandeling van refractair of recidief multipel myeloom bij jongere patiënten.

Zowel de bortezomib als de oxaliplatin pilot studie bieden waardevolle informatie met betrekking tot methodologische aspecten bij het uitvoeren van uitkomstenonderzoek zoals vereist door de Beleidsregel dure geneesmiddelen. Beide studies zijn te zien als een empirische aanvulling op de Leidraad voor Uitkomstenonderzoek, dat wil zeggen hoe kunnen gegevens verzameld en gebruikt worden om de doeltreffende toepassing en de

kosteneffectiviteit in de dagelijkse praktijk te onderbouwen. Meer specifieke informatie wordt beschreven in het methodologie rapport.

De bortezomib studie toont het belang aan van professionele richtlijnen gebaseerd op zowel de dagelijkse praktijk als bewijs uit klinische trials. Bovendien zou prospectieve data verzameling in een (inter-)nationaal registratie systeem het volgen van patiënten, het gebruik van uniforme uitkomstmaten en de selectie van vergelijkbare groepen vereenvoudigen en zodoende een waardevolle bijdrage kunnen leveren aan uitkomstenonderzoek.

Background

The Dutch government introduced in 2002 policy regulations *("Beleidsregel dure geneesmiddelen")* to relieve the financial burden of hospitals for expensive inpatient drugs. These policy regulations were changed in 2006 at the request of the Minister of Healthcare, Welfare and Sports. Since 2006, drugs are temporarily admitted on the expensive drug or expensive orphan drug list of the Dutch Healthcare Insurance Board (NZa), and applicants are required to conduct outcomes research. Outcomes research refers to assessing appropriate use *("doeltreffende toepassing")* of a drug and establishing real-world cost-effectiveness *("doelmatigheid")* information by means of using data on the performance of a drug in daily clinical practice (Delwel 2008). In the reassessment phase, the decision whether or not to continue financial compensation for hospitals is based on outcomes research.

The institute for Medical Technology Assessment (iMTA) has investigated, by order of the Dutch Health Care Insurance Board (CVZ), methodological issues regarding outcomes research. Two pilot studies were at the core of this research. Results of the pilot studies contribute valuable information on potential methodological issues and provide empirical evidence as addendum to the Guidance for Outcomes Research (*"Leidraad voor Uitkomstenonderzoek"*). One of the pilot studies concerns the drug bortezomib (Velcade®). In 2006, this drug was added to the expensive drug list for the indication relapsed or refractory multiple myeloma. Bortezomib was assessed by the CVZ in 2005, 2007 and 2008. In 2006, this resulted in the admittance of bortezomib to the expensive drug list of the NZa for third line treatment of relapsed or refractory multiple myeloma disease and in 2007 bortezomib was enlisted under the outpatient drug reimbursement scheme (GVS) on Annex 1B and 2 for second line treatment. Finally, in 2008 bortezomib was admitted on the expensive drug list of the NZa for first line treatment of multiple myeloma patient ineligible for high dose chemotherapy in combination with stem cell transplantation.

This report describes the results of the pilot outcomes research of bortezomib. Information on methodological issues is provided in a separate report. The report focuses on the main research question for the bortezomib pilot study:
How is bortezomib used in daily clinical practice of relapsed or refractory multiple myeloma and what are the real-world effects and costs of bortezomib?

1. Introduction

Multiple Myeloma

Multiple myeloma (MM) is a progressive hematologic malignancy characterised by an excess amount of abnormal plasma cells producing high levels of monoclonal immunoglobulin (M-proteins) or Bence-Jones proteins (Multiple Myeloma Research Foundation 2009). Clinically, patients with multiple myeloma present with hypocalcaemia, anaemia, renal insufficiency, increased susceptibility to infection, diffuse osteoporosis and/ or lytic bone lesions. Worldwide, approximately 0.8% of all cancer diagnoses and 0.9% of all cancer deaths were attributable to multiple myeloma (Alexander et al. 2007). The disease occurs more frequently among males and incidence rates increase with age, particularly after the age 40.

In the Netherlands, incidence numbers are only available for all plasma cell malignancies, including multiple myeloma, plasma cell cytoma, plasma cell leukaemia and extracellular plasmacytomas. Therefore, the available incidence numbers overestimate the number of new multiple myeloma patients per year. The incidence from 1996 to 2006 was on average 862 new patients per year, fluctuating between the highest incidence of 949 in 2004 and the lowest incidence of 804 in 1999. These estimates result in, on average, 5.4 new patients per 100,000 persons per year (range 5.1 to 5.9)[1]. Dutch prevalence numbers were previously estimated to be around 2000 (Commissie Farmaceutische Hulp 2007b).

Multiple myeloma remains an incurable disease. Conventional treatments achieved a median survival duration of 3 to 4 years; the range, however, varies broadly from less than 6 months to more than 10 years (Greipp et al. 2005) . In the last few years, new generation therapies, such as thalidomide, bortezomib and lenalidomide, have entered the market. Incorporation of these novel agents with conventional treatment regimes offers promising opportunities in future treatment of multiple myeloma (Richardson et al. 2007a).

At diagnosis, the Durie & Salmon (DS) staging system predicts disease prognosis, based on level and type of monoclonal protein, haemoglobin, calcium and number of lytic bone lesions (Durie and Salmon 1975). In 2005, a new staging system, the International Staging System (ISS), was developed in order to simplify disease staging by only incorporating $ß_2$-microglobulin and serum albumin, while maintaining powerful prognostic reliability (Greipp et al. 2005). Both staging systems are further clarified in Annex I.

[1] Dutch incidence numbers available at: http://www.ikcnet.nl

The majority of patients follow a relapsing disease course, implying that different treatment regimes are administered after each instance of disease progression. The effectiveness of different treatments can be measured with uniform response criteria published by the International Myeloma Working Group (Morgan 2003). Annex II describes the interpretation of the different response criteria in more detail.

Bortezomib

Bortezomib is a novel, first-in-class proteasome inhibitor that was granted accelerated approval by the FDA (United States Food and Drug Administration) in 2003 for treatment of relapsed or refractory multiple myeloma patients who had received at least two prior therapies (Kane et al. 2006). European Market Authorisation by EMEA followed in 2004. In 2005, bortezomib shifted to an earlier regime and was approved by both the FDA and EMEA for patients progressing after at least one previous treatment regime. This approval was based on the phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial, where bortezomib was compared to dexamethasone treatment in patients with relapsed multiple myeloma who received one to three previous treatments (Richardson et al. 2005). The APEX trial showed that bortezomib increased overall survival (OR), response rates and response duration (Richardson et al. 2007b). Annex III provides a systematic literature review on the clinical effectiveness of bortezomib for multiple myeloma patients. Many articles published information on the effectiveness of bortezomib as mono-therapy or as combination therapy from phase I, II and III studies.

Pilot outcomes research of bortezomib

Economic evaluations alongside clinical trials are generally seen as the best scientific evidence of treatment costs and effects. However, the efficacy results in a clinical trial might not accurately present daily practice effectiveness results since trials are conducted under ideal circumstances and patients ineligible for trials receive the drug in daily practice. In 2006, bortezomib was assessed by the CVZ resulting in admittance to the list for expensive inpatient pharmaceuticals mainly based on the results of the APEX trial in which bortezomib proved to be superior compared to dexamethasone treatment. In accordance with this policy, outcomes research is required in order to determine the continuation of financial compensation for hospitals after three years. In outcomes research, data on the performance of a drug in daily practice is collected in order to assess appropriate use and evaluate real-world cost-effectiveness.

For both iMTA pilot studies, different existing patient data sources were used in order to compare the applicability of these sources for outcomes research. For the bortezomib pilot, we chose to select multiple myeloma patients previously enrolled in a clinical trial, whereas the oxaliplatin pilot study for colorectal cancer selected patients from the Dutch cancer registry.

This report describes the utilisation of bortezomib and the related treatment effects and costs in relapsed or refractory multiple myeloma in daily clinical practice within the Netherlands. The following research questions were investigated:

- What are the baseline patient and previous treatment-related characteristics of the pilot patients? (section 2.1 and 3.1)
- How is bortezomib used in daily clinical practice in the relapsed/refractory setting? (section 2.2 and 3.2)
- What are the real-world clinical effects for patients treated with bortezomib compared to those treated with other therapy? (section 2.3 and 3.3)
- What are the costs for treating patients in daily practice? (section 2.4 and 3.4)
- How do the pilot results compare to clinical trial results? (section 2.5 and 3.5)

2. Research method

2.1 Patient population

Patient selection

The patient population for the bortezomib pilot was selected from patients previously enrolled in the HOVON50 study population. According to the study coordinator, the HOVON50 population is a representative sample of Dutch multiple myeloma patients younger than 65 years. Generally, around 80% of younger multiple myeloma patients are enrolled in HOVON studies; this percentage is lower for the older population (Myeloomwerkgroep HOVON 2005).

The phase III HOVON50 trial enrolled 556 (543 Dutch) patients from November 2001 to June 2005. The HOVON50 study investigated the treatment effect of thalidomide in newly diagnosed DS stage II and III multiple myeloma patients aged 18 – 65 years (Lokhorst et al. 2008). The patients were randomly assigned to receive either VAD (vincristine, adriamycin and dexamethasone) or TAD (thalidomide, adriamycin and dexamethason), both in combination with stem cell mobilisation with CAD (cyclophosphamide, adriamycin and dexamethason), followed by high dose melphalan and stem cell reinfusion[2].

Patients progressing from the HOVON50 regime no longer receive protocol-based therapy. These patients were treated for relapsing disease by physicians in daily practice and were, thus, eligible for the pilot study concerning outcomes research of bortezomib in progressive, relapsed or refractory multiple myeloma. In order to ensure that the pilot patients were a representative sample of the HOVON50 population, (pre-HOVON) baseline characteristics were compared between the entire HOVON50 population and the selected pilot patients.

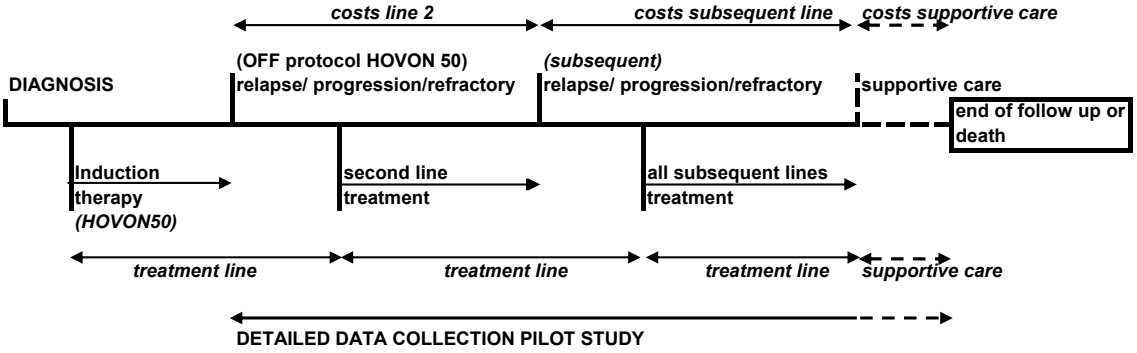
Data collection

Minimal case reports were obtained from the HOVON50 database for all 543 Dutch enrolled patients. This database contains information, among other things, about age, gender, date of diagnosis, baseline characteristics, HOVON50 treatment and response, progression from HOVON50 treatment, off-protocol treatment and survival status. Eligible

[2] HOVON50 protocol available at:
http://www.hovon.nl/studies/studies-per-ziektebeeld/mm.html?action=showstudie&studie_id=40&categorie_id=3

pilot patients were selected from the minimal case reports. As stated previously, the majority of multiple myeloma patients follow a relapsing disease course, receiving different treatment regimes consecutively. Figure 2.1 illustrates the relapsing disease course that patients experience from diagnosis until end of follow-up. It is important to note that patients receiving many treatments lines are not necessarily the most prognostically unfavourable patients. In fact, patients with a more favourable prognosis are more likely to survive long enough to receive more treatment lines compared to patients receiving fewer treatments. However, this is not always the case and it should be assumed that the association between the number of treatment lines received and prognosis is not clear.

Figure 2.1: Patients disease course from diagnosis until end of follow-up



All HOVON50 patients progressing to second line therapy were eligible for the pilot; only patients with a secondary malignancy and patients receiving bortezomib within an RCT setting were excluded. For all pilot patients we retrospectively completed detailed case reports using hospital medical records. From diagnosis until the end of follow-up, we collected data on treatments and their effects per treatment line. Data for resource use was collected in time periods from progression (relapse/refractory) to the next progression or end of follow-up. If patients only received supportive care after the last progression, data collection was limited to hospital admissions, outpatient visits and radiotherapy. Each treatment line can be seen as a treatment regime, starting with the first treatment therapy after diagnosis (HOVON50 induction regime) and successive lines beginning after either a progression or relapse of the disease or when the patient is refractory to the treatment. Detailed data on both costs and effects were collected starting from the time patients went off-protocol from the HOVON50 study. Minimal and maximum case report forms that were

used for data collection are enclosed in Annex IV and V. The aim was to include a minimum of 120 patients, with 60 patients receiving bortezomib and 60 patients never receiving bortezomib. The sample sizes were based on the differences in response percentages between the bortezomib and the high dexamethasone groups in the APEX trial (45% versus 26%). Assuming a similar difference in the pilot study, 96 patients in each group were assumed to be sufficient sample sizes for calculating two-sided tests with 95% confidence intervals. Anticipating that response might not be evaluated for approximately 20%, a minimum of 120 patients were required for inclusion in the pilot study.

Baseline characteristics

As the results of the HOVON50 trial show an advantage in terms of time-to-progression (TTP) for the thalidomide arm (Lokhorst et al. 2010), baseline characteristics include HOVON50 treatment-related characteristics in addition to patient characteristics. Baseline characteristics were stratified by patient groups defined by when the patient was first treated with bortezomib: second line, third line, fourth line or later and never. Statistically significant differences in means for continuous parameters were tested by the Kruskall-Wallis test for non-parametric comparisons among three or more groups. For categorical variables, differences were tested by the Pearson's chi square test. Fisher's exact test was used for categorical variables with counts less than five in any category.

Comparison of patient groups

The extent to which a valid incremental effectiveness estimate can be obtained for bortezomib based on the comparator patient group available from retrospective data collected in daily practice was taken into account. The validity of the incremental effectiveness estimate was suspected to be threatened by the possibility of bias due to non-random treatment exposure in observational studies, also called confounding by indication. Correction of this bias was explored as a result of the identified differences between the patient groups at baseline.

Confounding by indication can be corrected by a number of techniques. Commonly used techniques include adjustment of the treatment effect estimates by including the patient characteristics that were found to differ between the groups as covariates in a model or by creating comparable groups using propensity score methods. These methods require identification of prognostic factors that are predictive of receiving bortezomib at the moment of eligibility for treatment with the drug.

To identify predictive prognostic factors that can be used for adjustment of confounding by indication, all available baseline patient characteristics were first considered in a bivariate logistic regression, with the dependent outcome being receipt of bortezomib in second line and the independent variable the prognostic factor. A dummy variable was also included representing a '1' if the patient progressed to relapsed/refractory treatment after the year 2007, at which point the CVZ assessed the recommended use of bortezomib in second line and the HOVON guidelines were changed to reflect such recommendation (Lokhorst et al. 2008). Second line treatment with bortezomib was chosen as the dependent outcome as it represents the start of relapsed/refractory treatment, which is the first instance patients are eligible for bortezomib. If a prognostic factor was found to be bivariately associated with the dependent outcome of treatment with bortezomib in the second line at a significance level of $\alpha=0.05$, the parameter and all possible interactions were considered eligible for entrance into a multivariable model with the dependent outcome being receipt of bortezomib in second line.

To assess the validity of the parameters chosen as a result of the bivariate analysis, the selected parameters were compared to those identified by soliciting clinical opinion. Taking into account clinical opinion, the final set of selected parameters were entered in a multivariable logistic model and the final model was chosen by backwards selection.

The multivariable logistic model was used to calculate the conditional probability of receiving bortezomib in second line, given the set of identified pre-treatment characteristics. This conditional probability is also referred to as the 'propensity' to receive a particular treatment at a given time, with each patient referred to as having a 'propensity score' (PS) conditional on his or her values corresponding to the characteristics entered into the multivariate model (Rosenbaum and Rubin 1983). The multivariate logistic model is, in other words, a prediction model where the propensity is estimated from the identified pre-treatment characteristics with statistically significant predictive value of receiving bortezomib (D'Agostino 1998).

The distribution of the propensity to receive bortezomib in second line for patients in each treatment group was then compared. The feasibility of making valid comparisons between the patient groups was assessed by examining the extent of variation in PS to receive bortezomib in second line between the patient groups. Depending on the degree of

variation that was revealed, the need for adjustment methods was then explored during the effectiveness analysis.

2.2 Bortezomib usage in clinical practice

Clinical practice

There are several treatment options for multiple myeloma patients. Professional guidelines were examined in order to establish possible regimes. The treatments that pilot patients received in clinical practice were explored by treatment line and combinations of different treatments were investigated.

Bortezomib regimes, dose modifications and toxicities

Bortezomib treatment regimes from the APEX trial were described and compared to planned and actual regimes in daily practice. In addition, the proportion of the dose actually received by pilot patients was assessed. Dosages are expressed in units of mg per square meter of body surface area (mg/m^2). The reasons for dose modifications were summarised. Toxicities were only reported when resulting in a dose modification. Toxicities were distinguished as neurological, gastrointestinal, haematological and renal toxicities or any other circumstances related to patient condition. Finally, the proportion of the administered versus discarded dose of the total bortezomib dose available in the vial as packaged by the manufacturer was assessed.

Diffusion of bortezomib

The yearly diffusion of bortezomib was explored in the pilot study population. Furthermore, the diffusion of bortezomib for all Dutch multiple myeloma patients was researched by means of DBC (Diagnosis Treatment Combination) registration data obtained from the national DBC information system (DIS). The utilisation of bortezomib by different types of hospitals was examined in the years 2006, 2007 and 2008. In addition, SFK (Foundation for Pharmaceutical Figures) figures and sales data from the manufacturer (Janssen-Cilag) were analyzed in order to evaluate the annual diffusion of bortezomib in the Netherlands. To assess accessibility of bortezomib, regional prevalence numbers were estimated from available incidence and mortality numbers and compared with sales figures per region.

2.3 Clinical effectiveness

Clinical effectiveness outcomes

The possible choices of clinically valid effectiveness outcomes within multiple myeloma were explored, including OS from diagnosis, OS from start of relapsed/refractory treatment, time-to-progression (TTP) and time-to-next-treatment (TTNT) within each line of relapsed/refractory treatment, time to first response, time to best response, and duration of response (DOR). The pros and cons of using each of these effectiveness outcomes and the ability to validly compute each outcome given the restraints of the data was reviewed. Unadjusted estimates of the chosen outcome were calculated for each of the four patient groups.

We compared the baseline characteristics of all patient groups and determined whether certain prognostic factors were significantly different between the groups. For significantly different prognostic factors, we explored techniques to adjust for such differences between the patient groups in order to determine the best method to correct for these differences in baseline characteristics. We considered the following techniques that are commonly used to adjust crude survival estimates for confounding by indication:

- *Average covariate adjustment:* Survival analysis that included the mean of all covariates associated with the propensity (probability) of receiving bortezomib in second line (Nieto and Coresh 1996; Lee et al. 1992; Chang, Gelman, and Pagano 1982).
- *Regression adjustment by PS:* Survival analysis that includes the mean of the PS as a covariate (Rosenbaum and Rubin 1983).
- *Survival analysis matched on PS*: Survival analysis was conducted after matching all patients for the pre-treatment characteristics identified for inclusion in the multivariate logistic model (Rosenbaum and Rubin 1983; D'Agostino 1998). This method matches patients from each treatment group based on propensity score. The feasibility of matching techniques such as local optimal algorithms, as described by Gu and Rosenbaum (1993) and Smith and Todd (2005), was explored.

To assess the influence of the adjustment methods on the effectiveness estimates, unadjusted and adjusted effectiveness estimates were compared.

We reported the median estimates for reference by readers with a clinical background. For the economic evaluation of a particular health technology, the mean is preferred when looking at the potential effectiveness of any treatment for an entire group because it takes into account the shape of the survival curve, i.e., the proportion of short- and long-term survivors. With the median method, the shape of the survival curve is not taken into account when reporting the survival time at which 50% of the population has survived. Therefore, in economic evaluation studies, mean estimates of survival are preferred because of incorporation of the overall group distribution of survival.

Analytical technique

Unadjusted effectiveness estimates were calculated by the Kaplan-Meier estimator to estimate the survival function (Kaplan and Meier 1958). For adjusted effectiveness estimates, the use of a Cox proportional hazards (PH) model was assessed statistically (Cox 1972) for each covariate entered into the model. If found to uphold the PH assumption, Cox PH models were calculated firstly with adjustment for the variables included in the PS score and secondly for the PS. For both adjustment methods, the mean value for the total population was used for either the parameters included in the final model or for the PS of each patient group. Total follow-up was censored at the shortest follow-up observed in the entire group of patients (N=139).

Statistical analyses were conducted with the statistical software program SAS, version 9.1 (SAS Institute Inc., Cary, NC).

2.4 Costs in clinical practice

This section describes the methods of the cost analyses which were conducted from the hospital perspective. The following costs were calculated separately for patients ever and patients never receiving bortezomib:

- Total mean treatment costs
- Second line treatment costs
- Third line treatment costs
- Fourth+ line treatment costs

Total costs for individual patients were determined by the identification of resource use and unit costs of the following cost components: inpatient hospital days, intensive care

days, outpatient visits, consultations by telephone, day-care treatments, emergency room visits, radiotherapy, surgical procedures, laboratory services, medical imaging services, concomitant treatment, active treatment, donor leukocyte infusions and stem cell transplantations.

The cost analyses were based on the resource use of the full patient sample including patients still treated at the end of data collection. In order to determine whether the inclusion of these patients influenced our cost estimates, cost analyses were additionally conducted solely for patients whose resource use was collected until the end of treatment.

Unit costs

Table 2.1 presents the unit costs of inpatient hospital days, intensive care days, outpatient visits, consultations by telephone, day-care treatments and emergency room visits. The unit cost calculations were based on detailed micro costing studies reflecting full hospital costs, including overhead costs (Sonneveld et al. 2007; Tan et al. 2008; Tan et al. 2010). Some unit costs were weighted for their origin: 67% of the unit costs were based on data from the general hospitals and 33% on those from university hospitals. These shares reflect the distribution of patients among hospitals in Dutch daily practice. We conducted this micro costing study to compute haematological specific unit prices since they are known to be slightly higher compared to the average prices in the Dutch Costing Manual 2004.

Table 2.1 also presents the unit costs of radiotherapy, medical imaging services and laboratory services. The resource use of radiotherapy, surgical procedures and medical imaging services was valued using the fees as issued by the Dutch Healthcare Authority. Unit costs for laboratory services were based on a detailed inventory of the resource use of 12 patients (approximately 1,000 tests). Where necessary, all unit prices were inflated to 2009 euros.

Table 2.1: Unit costs (Euro 2009)

Resource Use	Unit Price
Haematological inpatient hospital day *	€ 516
Intensive care day	€ 2,080
Haematological outpatient visit *	€ 110
Haematological day-care treatment *	€ 167
Consultation by telephone	€ 13
Emergency room visit	€ 109
Radiotherapy standard	€ 1,656
Radiotherapy intensive	€ 7,971
Laboratory (per test)	€ 53
Cytology testing	€ 47
X-ray	€ 52
Skeletal scan	€ 177
CT scan	€ 208
MRI	€ 270
Radionucleide scan	€ 350
PET scan (total body)	€ 1,411
Echo (ultrasound)	€ 86
Bacterial culture	€ 14
Virale culture	€ 27

*weighting factor of 67:33 for general and university hospitals

Unit costs of concomitant treatment were acquired from the Pharmaceutical Advisory Committee *("Farmacotherapeutisch Kompas").* Table 2.2 presents the unit costs of concomitant treatment per day. Due to time and feasibility constraints, detailed daily concomitant treatment costs were only determined for 18 patients. These daily costs were considered representative for the remaining 121 patients. The average daily cost based on this sample of patients was applied to the remainder of the patient population if the patient had been administered concomitant medication for chronic and ongoing adverse events.

Per day unit costs were assumed to last either the entire total follow-up the patient spent in a particular line or for a proportion of the total follow-up in that line. Prophylactic antibacterials/antifungals/antivirals were assumed to be administered daily while acute administration was assumed to last for 10 days. Administration of bisphosphonates, analgesics and concomitant medication for gastrointestinal toxicity were assumed to last the entire follow-up time a patient spent in that line. Patients requiring erythropoietin for anaemia were assumed to have been administered a subcutaneous injection every three weeks for which a daily price was corrected for. Resource use was collected for the number of transfusion bags of red blood cells and platelets that were administered in a given treatment line and unit prices per bag were applied. A daily price for neurotoxicity

medication was applied after correction for the average time spent on medication for neurotoxicity based on the sample of 18 patients.

Table 2.2: Unit costs of concomitant treatment per day (Euro 2009)

Indication for use	**Unit price**
Antibacterial / antifungal / antiviral (prophylaxis)	€ 5.56
Antibacterial / antifungal / antiviral (acute infection)	€ 211.50
Biphosponates	€ 4.45
Anaemia (erythropoietin injection)	€ 3.21
Anaemia (red blood cells transfusion)*	€ 204.00
Thrombocytopenia (platelet transfusion)*	€ 492.80
Neurotoxicity	€ 9.57
Gastro-intestinal	€ 2.17
Analgesics	€ 1.70

* cost per bag

For active treatment, unit costs are shown in table 2.3. Unit prices for intravenously administered therapies were based on the cost of an entire vial. Unit costs of donor lymphocyte infusions, autologous and allogeneic stem cell transplantations were obtained from published micro costing studies and corrected for resource use which was retrospectively collected through the fully detailed case reports from hospital medical records to prevent double counting (Van Agthoven et al. 2001; Van Agthoven, Groot, and Uyl-de Groot 2001). Unit prices for thalidomide were taken from hospital pharmacies agreements with a health insurer. All other prices for active treatment were acquired from the Pharmaceutical Advisory Committee *("Farmacotherapeutisch Kompas")*.

Table 2.3: Unit costs of active treatment (Euro 2009)

Treatment	Unit	Price
Thalidomide (oral)	25/50/100 mg	€ 2.92
	150 mg	€ 4.37
	200 mg	€ 5.83
	300 mg	€ 8.75
	400 mg	€ 11.66
Bortezomib (iv)	3.5 mg vial	€ 954.52
Dexamethasone (oral)	1 mg	€ 0.06
Dexamethasone (iv)	5 mg	€ 2.66
	20 mg	€ 7.81
Doxorubicin (iv)	1 mg	€ 1.48
Vincristine (iv)	1 mg	€ 8.82
Melphalan (iv)	50 mg	€ 52.25
Melphalan (oral)	2 mg	€ 0.47
Prednison (iv)	25 mg	€ 2.42
Prednison (oral)	5 mg	€ 0.05
Cyclophosphamide (oral)	50 mg	€ 0.14
	100 mg	€ 0.27
Cyclophosphamide (iv)	200 mg	€ 11.21
	500 mg	€ 18.15
	1000 mg	€ 34.38
Interferon alpha (subcutaneous)	1.0 x 10^6 IE	€ 8.89
Fludarabine (iv)	50 mg	€ 266.94
Lomustine (oral)	40 mg capsule	€ 23.39
Lenalidomide (oral)	5 mg	€ 210.27
	10 mg	€ 222.26
	15 mg	€ 233.69
	25 mg	€ 256.66
Cytarabine (iv)	1600 mg	€ 72.31
Etoposide (iv)	200 mg	€ 40.25
Carboplatin (iv)	150 mg vial	€ 100.65
DLI	related	€ 2,342.03
	unrelated	€ 7,876.64
Auto SCT PBSCT*		€ 7,933.92
Allo SCT PBSCT*		€ 21,315.74
Allo SCT MUD*		€ 64,540.35

*excludes resource use collected from patient charts

Sensitivity analyses

To determine the uncertainty of the obtained cost estimates, one-way sensitivity analyses were carried out by varying the unit cost values of inpatient hospital day, outpatient visit and day-care treatment unit costs between 50% and 150%. Unit costs other than those of hospital days were considered to be fairly stable or of less influence and were therefore not subjected to sensitivity analyses.

Statistical analyses

Statistical analyses were conducted with the statistical software programmes SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). In addition to descriptive statistics, differences between treatment groups were assessed by means of the independent samples t-test for variables showing a normal distribution, the Mann-Whitney U test for variables not normally distributed and the Pearson Chi-square test for variable fractions. Whether a normal distribution could be assumed for each cost variable was assessed by means of the Kolmogorov-Smirnov test for normality. To adjust for multiple testing, one way analyses of variance with post hoc testing (type Bonferroni) were additionally performed. In all cases, $p = 0.05$ was taken as statistically significant. All costs were based on Euro 2009 cost data. Where necessary, costs were adjusted to 2009 using the general price index from the Dutch Central bureau of Statistics.

2.5 Clinical practice versus clinical trial

Comparison of pilot patients to APEX patients

To assess the extent to which a valid effectiveness measure could be obtained from the pilot patients, which were treated under uncontrolled conditions in daily practice, we first explored the extent to which the patients were representative of the cases included in the APEX trial that influenced the FDA approval in 2005 of bortezomib and subsequently in the Netherlands (Richardson et al. 2005). This was conducted by comparisons in terms of baseline characteristics, with baseline defined as the start of relapsed/refractory treatment with bortezomib conditional on having never received bortezomib in prior treatment lines. If demonstrated to be similar patient groups at baseline, the pilot patients treated with bortezomib were compared to the cases in the trial in terms of dosage schemes and effectiveness outcomes.

Effectiveness outcomes included 1-year survival and TTP. As many patients in daily practice proceed to subsequent treatment lines due to reasons other than progression and because the reason being progression was not always visible in the patient charts, TTP was calculated until either progression date if available or start of next treatment line. Consequently, the estimate for TTP calculated for the pilot patients can be interpreted as a combination of TTP and TTNT.

Comparison pilot cost analyses with published literature

The results of our cost analyses were compared with those obtained from published economic evaluations of bortezomib in the treatment of multiple myeloma. Published economic evaluations were retrieved from a systematic review as described in Annex VI.

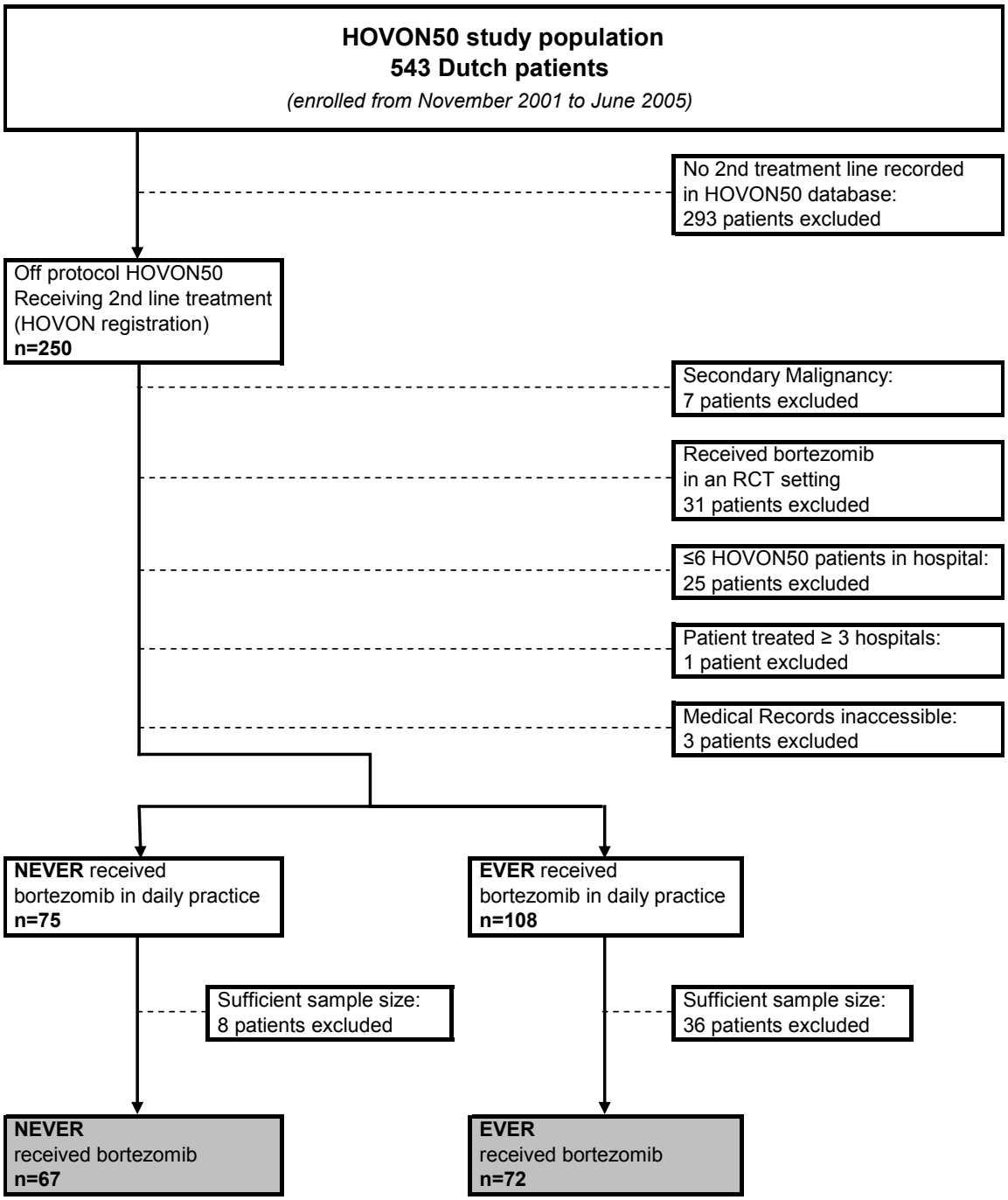
3. Results

3.1 Patient population

3.1.1 Patient selection and data collection

Figure 3.1 depicts the flowchart describing the selection process of pilot patients. All Dutch HOVON50 patients who progressed to second line therapy (n=250) were eligible for inclusion; patients with a secondary malignancy (n=7) and patients receiving bortezomib within an RCT (n=31) were excluded. For pragmatic reasons, we chose to exclude patients who were treated in a hospital that included six or less patients in the HOVON50 trial (n=25) and one patient who was both treated in more than three hospitals and was the only pilot patient in such hospitals. We started selecting patients in academic hospitals that included more than 20 patients in the HOVON50 trial and continued with other participating hospitals. Annex VII lists the participating hospitals. We discontinued including new patients once the desired study sample size was reached, thus further excluding 8 and 36 potential patients never and ever receiving bortezomib, respectively. Most patients were treated in more than one hospital, making the data collection challenging and time consuming. Consequently, over 1700 hours was needed for data collection in 42 different Dutch hospitals in order to collect data for a total of 139 patients. Despite this, it was difficult to find patients who never received bortezomib. The intended sample size (60 patients receiving bortezomib and 60 patients never receiving bortezomib) was increased because several patients initially included as ‘never receiving bortezomib’ based on the HOVON50 database actually received bortezomib in a later stage according to hospital medical records. In total, 139 patients were included in the pilot study: 67 patients never treated with bortezomib and 72 patients treated with bortezomib. All data were collected by the principal researcher and medical students under the guidance of this researcher between April 2008 and May 2009.

Figure 3.1: Flowchart of the selection process of pilot patients



3.1.2 Patient characteristics pilot versus HOVON50

Table 3.1 describes (pre-HOVON) baseline characteristics of the pilot patients and the HOVON50 population, as reported by Lokhorst et al. (2010). A comparison of the groups shows widespread similarities. Therefore, it is assumed that the selected pilot patients are a representative sample of the HOVON50 population. However, it should be noted that bias might have occurred during the selection process. For example, more pilot patients were assigned to the VAD treatment arm in the HOVON regime (65 versus 50%). This difference is larger for pilot patients never receiving bortezomib (73 versus 58%). Furthermore, only patients who progressed to second line therapy were selected because the objective of our research was to investigate the costs and effects of bortezomib for relapsed or refractory multiple myeloma. Consequently, we may have selected the worst off HOVON50 patients by excluding patients for whom the HOVON database did not yet report a second treatment line at time of data collection. This could potentially explain the discrepancy that more pilot patients were assigned to the HOVON50 VAD arm given that Lokhorst et al. (2010) reported that HOVON50 patients receiving thalidomide had a longer time to progression.

Table 3.1: Baseline characteristics HOVON50 and pilot patients

Characteristic	HOVON 50*** (N=536)	Pilot Total	EVER bortezomib (N=72)	NEVER bortezomib (N=67)	P-value (EVER vs NEVER)
Male Gender	63%	58%	56%	61%	0.6
Age at diagnosis [mean (range)]	56 (30-65)	55 (32-65)	55 (32-65)	56 (34-65)	0.2
HOVON 50 treatment arm					0.1
VAD	50%	65%	58%	73%	
TAD	50%	34%	40%	27%	
Myeloma Type					0.48
IgA	21%	22%	19%	24%	
IgG	60%	57%	63%	51%	
IgD	1%	2%	1%	3%	
IgM	0%				
Light Chain Disease	18%	16%	13%	19%	
Stage of disease					0.44
I A/B	**	2%	3%	1%	
IIA	20%	21%	19%	22%	
IIB	1%	1%	1%	0%	
IIIA	67%	66%	69%	63%	
IIIB	12%	9%	6%	13%	
WHO performance status					0.06*
Asymptomatic	NR	41%	50%	31%	
Symptomatic but ambulatory	NR	40%	35%	46%	
In bed < 50%	NR	12%	10%	13%	
In bed > 50%	NR	4%	1%	7%	
Bedridden	NR	0%	0%	0%	
Albumin (g/L) [mean (range)]	36 (4.2-59.1)	36 (16-82)	36 (16-82)	37 (25-55)	0.58
Serum B2 (mg/l) [mean (range)]	3.2 (.0-35.4)	4 (.6-16.5)	4 (1-16)	4.4 (.6-16.5)	0.21

NR=not recorded *p-value significant at an α=0.1 **12 patients (ineligible HOVON50) ***Source: Lokhorst et al. 2010

3.1.3 Baseline characteristics pilot patients

Baseline characteristics

Comparison of baseline characteristics of all patients, with baseline being start of relapsed/refractory treatment, reveals significant differences (Table 3.2). Differences were observed for the proportion of patients presenting with neurotoxicity, whether or not bortezomib was recommended for use as second line therapy in the year of progression, HOVON50 treatment-related characteristics and mean time until progression from initial treatment line.

Patients receiving bortezomib were more likely to present with neurotoxicity at baseline ($p = 0.03$). Those receiving bortezomib in second line were more likely to have progressed from initial therapy in the years when bortezomib was first recommended for use in treatment of initial progression (i.e., 2007 and 2008) ($p < 0.001$).

Treatment-related characteristics also differed among the groups, with patients treated with bortezomib in second line being more likely to have been randomised to the thalidomide arm of the HOVON50 trial ($p = 0.05$), to receive more cycles of (V)AD (AD if randomised to thalidomide and VAD if randomised to vincristine) ($p = 0.015$), HDM ($p = 0.005$), CAD ($p = 0.002$), and any maintenance therapy ($p = 0.02$), especially thalidomide maintenance. Due primarily to differences in treatment received during HOVON50, baseline comparison also demonstrated that time from diagnosis until first progression is significantly longer for patients treated with bortezomib in second and third line ($p < 0.001$). Differences in prognosis at diagnosis may also contribute to the differences in time from diagnosis until first progression. For instance, though not statistically significant, the baseline comparison also reveals that the patients treated with bortezomib in second line were on average younger, presented with a more prognostically favourable WHO performance status, lower levels of c-reactive protein, and better responses to initial therapy. However, comparisons of known prognostic factors did not reveal striking differences between the four groups.

Table 3.2: Baseline comparison of all pilot study patients stratified by bortezomib treatment status

Characteristic	Bortezomib Ever			Never (n=67)	P-value†
	2nd Line (n=25)	3rd Line (n=35)	4th Line+ (n=12)		
Patient-related characteristics					
Age	54 (42-65)	54 (32-64)	58 (45-65)	56 (34-65)	0.16
Female	40%	46%	50%	39%	0.84
Myeloma Type					
IgA	16%	23%	17%	24%	0.92
IgG	68%	57%	67%	51%	
IgD	0%	3%	0%	3%	
IgE	0%	0%	0%	0%	
Light Chain	8%	14%	17%	19%	
Unk	8%	3%	0%	3%	
WHO performance status					0.17
Asymptomatic	52%	57%	50%	33%	
Symptomatic but ambulatory	28%	37%	17%	39%	
In bed < 50%	12%	0%	8%	10%	
In bed > 50%	0%	0%	0%	6%	
Bedridden	4%	0%	0%	4%	
Not Reported	4%	6%	25%	7%	
Albumin (g/l) [mean (sd)]	39.8 (28-49.4)	40.7 (31-58.9)	38.3 (27-44)	38.4 (16.6-52)	0.92
Serum B2 (mg/l)	4 (1.5-16.7)	4.8 (1.3-13.3)	2.3 (2.1-2.83)	3 (1.1-5.7)	0.66
C-reactive protein (mg/l)	3 (1-5)	10 (1-42)	21.5 (1-67)	31.6 (1-171)	0.08
Creatinine clearance (mmol/l)	9.1 (1.9-16)	5.6 (3.3-8)	6.6 (5.2-8)	7.8 (2.3-16)	0.4
Haemoglobin (mmol/l)	7.5 (5-9.5)	7.7 (5.2-9.5)	7.1 (5.3-8.4)	7.1 (2.1-10)	0.3
Platelet count ($x10^9$/l)	182 (10-470)	218.5 (66-657)	264.6 (93-553)	227 (28-828)	0.2
Plasma cell infiltration > 50%	12%	11%	17%	10%	0.82
Present with neurotoxicity	48%	43%	42%	25%	0.03*
Bortezomib recommended for therapy of first progression at baseline (2007+)	56%	14%	0%	18%	<0.001*
Previous treatment-related characteristics					
Thalidomide arm	56%	29%	42%	27%	0.05*
Cycles (V)AD or AD	2.96 (2-3)	3 (3-3)	2.6 (1-3)	2.82 (1-3)	0.015*
Cyles HDM					
0	4%	9%	33%	31%	0.005*
1	96%	83%	67%	66%	
2	0%	9%	0%	3%	
CAD given	100%	97%	75%	78%	0.002*
Received SCT	24%	29%	25%	15%	0.33
Maintenance					0.02*
None	28%	51%	50%	63%	
IFNα	20%	20%	25%	24%	
Thalidomide	52%	29%	25%	13%	
Best response to HOVON50					0.15
Complete response	24%	9%	8%	10%	
Partial response	68%	77%	67%	60%	
Minor response	8%	0%	8%	10%	
No change	0%	6%	0%	4%	
Progressive disease	0%	0%	8%	9%	
Not Reported	0%	9%	8%	6%	
Reason for going off protocol					
Normal completion of HOVON protocol	24%	26%	25%	13%	0.34
Excessive Toxicity	32%	14%	17%	28%	0.3
Progression/Relapse	32%	31%	33%	28%	0.97
Mean time until first progression	35.9 (12.9-57.9)	25.6 (6.8-51.1)	16 (2-29.5)	22.4 (1.9-61.4)	<0.001*

†Continuous variables were compared by Kruskall-Wallis test, and either Pearson's chi-sqaure or Fisher's exact test was used to

Missing values were common for baseline parameters (Table 3.3). Meaningfully low numbers of available data occurred for prognostic factors at baseline, such as WHO performance status, albumin and serum β_2-microglobulin levels, c-reactive protein concentration, creatinine clearance, haemoglobin level, plasma infiltration, and assessment of neurotoxicity. Missing data may mask the differences between the four groups in terms of known prognostic factors, which contributes to the inability to reveal striking differences in baseline prognosis between the four groups.

Table 3.3: Frequency of available data for each baseline characteristic stratified by bortezomib treatment line

	Bortezomib Ever			
Baseline Prognostic Characteristic	**2nd Line (n=25)**	**3rd Line (n=35)**	**4th Line+ (n=12)**	**Never (n=67)**
Age	100.0%	100.0%	100.0%	100.0%
Gender	100.0%	100.0%	100.0%	100.0%
Type of Myeloma	92.0%	97.1%	100.0%	97.0%
WHO Performance status	96.0%	94.3%	75.0%	92.5%
Albumin	72.0%	68.6%	66.7%	62.7%
Serum β2-microglobulin	40.0%	34.3%	33.3%	20.9%
C-reactive protein	24.0%	25.7%	50.0%	62.7%
Creatinine clearance	24.0%	25.7%	16.7%	11.9%
Haemoglobin	64.0%	68.6%	83.3%	68.7%
Platelet count	100.0%	97.1%	100.0%	98.5%
Plasma infiltration	40.0%	42.9%	58.3%	53.7%
Neurotoxity assessment	80.0%	97.1%	91.7%	97.0%
Treatment arm HOVON 50	100.0%	100.0%	100.0%	100.0%
Cycles (V)AD or AD	100.0%	100.0%	100.0%	100.0%
HDM cycles	100.0%	100.0%	100.0%	97.0%
CAD given	100.0%	100.0%	100.0%	100.0%
Received SCT	100.0%	97.1%	100.0%	100.0%
Type of maintenance	100.0%	100.0%	100.0%	100.0%
Best response to previous regimen	100.0%	91.4%	100.0%	94.0%
Reason discontinuation previous regimen	100.0%	97.1%	100.0%	98.5%
Date of first progression	100.0%	100.0%	100.0%	98.5%

Comparison of patient groups

Table 3.4 reveals the results of the survey regarding clinical opinion concerning relevant prognostic factors that would be clinically significant for decision-making in the choice of bortezomib treatment at start of refractory treatment and their statistical significance in the bivariate logistic regression analysis. Comparison of the clinically significant prognostic factors to the statistically significant results of the bivariate analysis reveals many similarities, with time from diagnosis until first progression, presence of neurotoxicity, best response to initial therapy, HOVON50 treatment arm, and type of maintenance being significant in the bivariate analysis and stated to be clinically relevant by at least one of the two surveyed leaders in the field of haematology in the Netherlands. The dummy variable

for progression in 2007 or later was also significant in the bivariate analysis, indicating relevance of taking into account the diffusion of bortezomib in daily practice.

Results of the stepwise regression analysis after including all bivariately significant variables and their interaction variables revealed the following parameters to be predictive of bortezomib in second line in a multivariable model: whether or not patient presented with neurotoxicity, patient's best response to initial therapy, type of maintenance the patient received and whether the patient was eligible for treatment of progression/refractory disease in the years following recommendation for use of bortezomib in second line (Table 3.4). Interaction was also significant for the effect of neurotoxicity and best response to initial therapy.

Table 3.4: Clinically and statistically significant baseline prognostic factors predictive of second line bortezomib treatment

	Clinically significant		Statistically significant	
Independent predictors of exposure to bortezomin in 2nd treament regimen	**Clinical opinion #1**	**Clinical opinion #2**	**Bivariate Model**	**Multivariable Model**
Patient-related characteristics				
Age				
Gender				
Myeloma type	✓			
Time from start of previous treatment until start of next treatement	✓		✓	
Presence of neurotoxicity	✓	✓	✓	✓*
Albumin level				
Serum B2 level				
Haemoglobin level				
Platelet count	✓	✓		
C-reactive protein level				
Creatinine clearance	✓	✓		
Plasma cell infiltration				
WHO performance status	✓	✓		
Best response to initial treatment regimen	✓	✓	✓	✓*
Any reason for discontinuation previous regimen				
Reason for discontinuation previous regimen: Normal Discontinuation				
Reason for discontinuation previous regimen: Progression/Refractory/Relapse	✓			
Reason for discontinuation previous regimen: Toxicity	✓	✓		
HOVON 50 treatment-related characteristics				
Treatment arm (VAD vs TAD)	✓	✓	✓	
# of cycles (V)AD administered				
CAD given to the patient				
# of cycles HDM patient received				
Received allo-SCT (either in or out of HOVON protocol)	✓			
Type of maintenance		✓	✓	✓
Eligible for bortezomib in 2007+	Not asked	Not asked	✓	✓

*Interaction variable between neurotoxity and best response was found to be significant in the final multivariable model

The odds ratios (OR) for the parameters retained in the multivariable logistic regression model are shown in Table 3.5. The interpretation of the effects of the parameters on the odds of getting bortezomib in second line are as follows: patients presenting with neurotoxicity are less likely to receive bortezomib (OR = 0.97), patients treated with any maintenance are more likely to receive bortezomib compared to those receive no

maintenance (OR = 2.22), patients presenting with a less favourable response to initial therapy are less likely to receive bortezomib (OR = 0.57), patients progressing in the year 2007 or later are more likely to receive bortezomib (OR = 7.01), and, as suggested by the interaction between the main effect of presenting with neurotoxicity and best response to initial therapy, a patient who presents with a less favourable response to initial therapy is more likely to receive bortezomib if presenting with no signs of neurotoxicity compared to a patient who presents with signs of neurotoxicity with a similar response to initial therapy (OR = 1.03). Although the main effects of presenting with neurotoxicity and previous maintenance are not significant, they are retained in the model because their interaction is statistically significant.

Table 3.5: Logistic regression results when regressing independent predictors on the dependent outcome of receiving bortezomib in second line

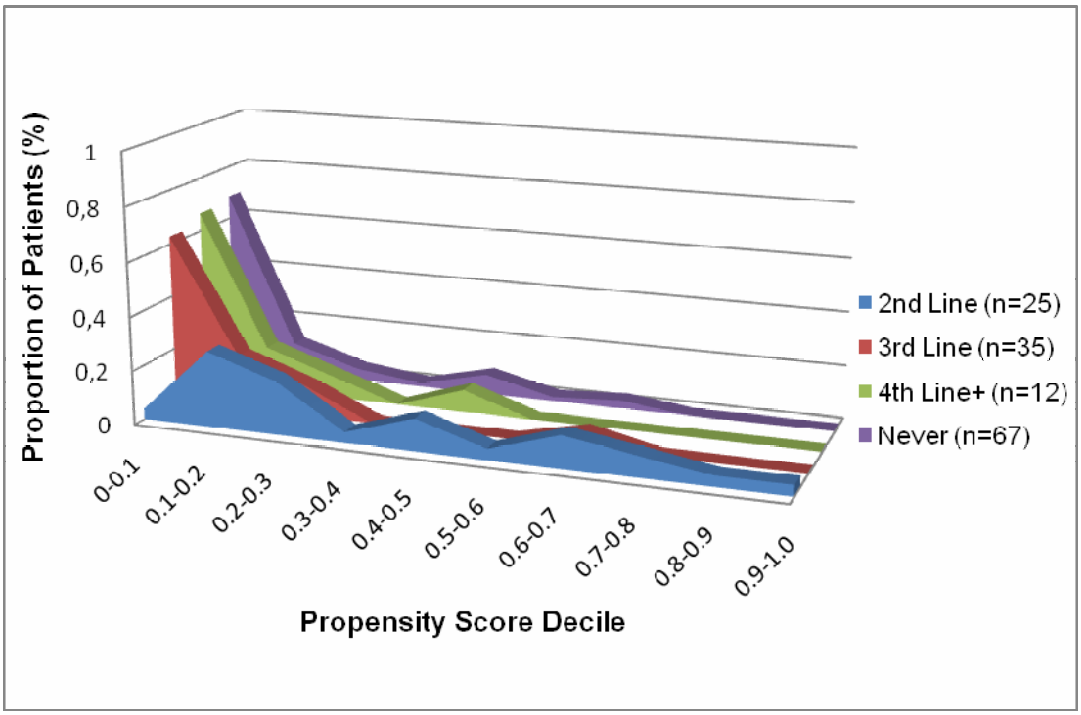
Independent predictors of treatment with bortezomib in 2nd line	OR (95% CI)	P-value
Presence of neurotoxicity (1=yes, 0=no)	0.97 (0.92-1.02)	0.2574
Type of maintenance (0=None, 1=IFNa, 2=Thal)	2.219 (1.15-4.28)	0.0173
Best response to previous treatment regimen (1=CR….5=PD)	0.57 (0.21-1.54)	0.2661
Progression to relapsed/refractory treatment in 2007 or later (1=yes, 0=no)	7.065 (2.45-20.4)	0.0003
Interaction: Best response to previous treatment * Presence of neurotoxicity	1.03 (1.01-1.06)	0.0536

Comparison of the distribution of propensity scores (probability) across all groups is shown in Figure 3.2. Because the propensity scores are essentially probabilities, the range of possible values is between 0 and 1. In the bar graph depicted in Figure 3.2, the propensity scores have been divided into 10 deciles along the horizontal axis while the proportion of patients include in each decile is shown on the vertical axis.

It is clear that the patients receiving bortezomib in second line differ from all other treatment groups, suggested by a more uniform distribution compared to that of all other groups. Though not identical, the left-skewed distributions of all non-second line treatment groups largely overlap. Based on the predictive value of the selected prognostic factors, patients treated in second line have a mean propensity to receive bortezomib equal to 0.40, while the mean for all patients not treated in second line was equal to 0.13, 0.124 and 0.134 for those treated with bortezomib instead in third line, fourth line or greater, or never, respectively. In other words, patients treated with bortezomib in second line, third line, fourth line or later or never had an average probability of treatment with bortezomib in second line equal to 40%, 13%, 12.4% and 13.4% based on their value for significant

baseline prognostic factors associated with treatment with bortezomib treatment at this time.

Figure 3.2: Comparison of the propensity score distribution by bortezomib treatment line



The results seen in Figure 3.2 are not surprising. Patients treated with bortezomib in second line are expected to have the highest probability of treatment with bortezomib in second line. What is surprising, however, is the similarity in probabilities for bortezomib treatment between patients treated in third line, fourth line or later and patients never treated with bortezomib. The results are likely to differ when performing a similar analysis on the propensity (probability) to get bortezomib in third line or fourth line or later, with patients receiving bortezomib in each respective line to be predicted a higher propensity compared to all other patient groups not treated in the respective line. Such analyses were not conducted but represent a possible extension to the analysis.

3.2 Bortezomib usage in clinical practice

3.2.1 Clinical practice

Professional guidelines

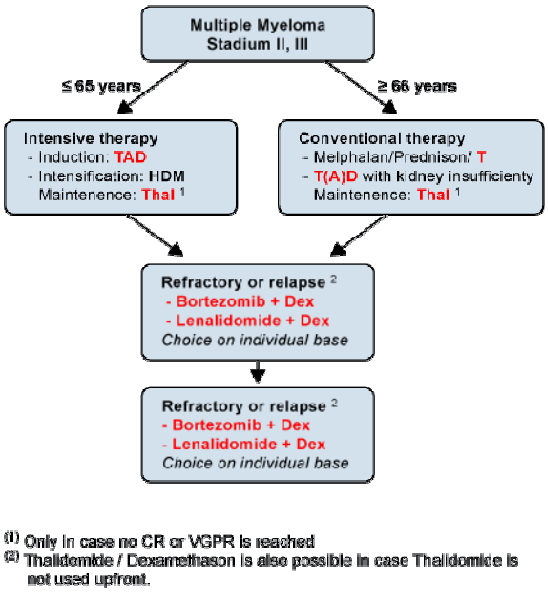
There are several treatment options for multiple myeloma patients. The Myeloma Working Party of HOVON has developed national guidelines based on both phase II and phase III studies and professional expertise (Multiple Myeloma Working Group 2009). It should be noted that HOVON has two responsibilities, namely conducting clinical trials and developing professional guidelines. The guidelines have been modified over the years as a consequence of chances in professional insights due to novel agents entering the market and evidence from ongoing trails in the field of haematology. The most important changes include recommendation of thalidomide as part of induction therapy and the shift of bortezomib and lenalidomide to earlier treatment regimes. This shift is also evident in CVZ's assessment reports of bortezomib regarding the NZa policy for expensive drugs[3]. Initially in October 2005, the CVZ advised that bortezomib was indicated as a third line therapy for multiple myeloma patients progressing (or refractory) on a treatment regime of thalidomide in combination with dexamethasone or cyclophosphamide, or for patients ineligible for this regime. Based on this advice, bortezomib was admitted on the expensive drug list from January 2006 onwards. In 2007, based on a GVS application, CVZ advised that bortezomib should be added on the outpatient drug reimbursement list (GVS Annex 1B and Annex 2) and could be administered after at least one multiple myeloma specific treatment. Finally, in November 2008 (application for the NZa expensive inpatient drug list), patients ineligible for high dose chemotherapy in combination with stem cell transplantation are entitled to receive bortezomib in combination with melphalan and prednisone as first line therapy. Therefore, bortezomib, alongside specific criteria, has shifted within only a few years from third to second to first line therapy in 2005, 2007 and 2008 respectively.

Current HOVON guidelines advise for DS stage I disease a 'wait-and-see' approach. Patients progressing to an advanced disease stage (DSII or DSIII) are pro-actively treated according to two different regimes based on the age of the patient (≤65 years, ≥66 years). Figure 3.3 depicts both treatment regimes. Bortezomib/ dexamethasone or lenalidomide/dexamethasone should be administered as second line therapy and is

[3] CVZ assessment reports available at: http://www.cvz.nl

recommended for subsequent relapses. The professional guideline states that choices between the treatment regimes have to be based on individual patient characteristics, according to previous treatments and a patient's side effect profile. Only younger patients are eligible for stem cell transplantation after induction therapy.

Figure 3.3: HOVON treatment protocol for multiple myeloma patients



(1) Only in case no CR or VGPR is reached
(2) Thalidomide / Dexamethason is also possible in case Thalidomide is not used upfront.

(Source: HOVON guidelines[4])

Besides professional guidelines for daily practice, multiple myeloma patients eligible and willing to participate in a clinical study are enrolled in ongoing trials. The Dutch HOVON trials are stratified based on age. Until recently (trial inclusion stopped in 2008), younger patients (≤65 years) received induction therapy in the HOVON65 trial (phase III study comparing bortezomib mono-therapy versus bortezomib combined with adriamycin and dexamethasone followed by high dose melphalan). The HOVON76 is a phase II study where younger patients receive lenalidomide as maintenance therapy after (tandem auto and allo) stem cell transplantation. Elderly patients, or younger patients ineligible for high dose chemotherapy and stem cell transplantation, are treated according the HOVON87 protocol (phase III trial for previously untreated patients comparing melphalan/ thalidomide with melphalan/ lenalidomide). Finally, within the HOVON86 protocol, which is a phase I/II

[4] HOVON guidelines available at: http://www.hovon.nl/working-groups/working-groups/myeloma.html

trial in elderly patients (60 – 80 years) at first relapse (or primary refractory), patients receive combination therapy of lenalidomide, bortezomib and dexamethasone.

Treatments received by pilot patients by line

Based on constant advances in treatment options, changing professional guidelines and the various ongoing clinical trials, it is expected that patients in daily clinical practice might receive several treatment regimes. Therefore, the treatments that pilot patients received were explored by treatment line. All 139 pilot patients had a second treatment line after the HOVON50 protocol, 65% received third line, 40% fourth line, 14% fifth line, 6% sixth line, 2% seventh line and 1% eighth line therapy. Table 3.6 describes the number of patients who received the available treatments by line. At least ten chemical agents were given as mono-therapy or in different combinations. Therefore, the sum of each line is higher compared to the number of patients treated. We could not identify a general treatment pattern because of a large degree of variation in regimes and drug usage often being administered in differing and/or reversed order. However, the percentage of patients treated with thalidomide decreased over the lines, whereas lenalidomide usage increased. Of all patients ever receiving bortezomib, with 79% previously treated with thalidomide. Bortezomib was given in all treatment lines, with the exception of line number eight. Six patients had bortezomib in more than one treatment line, four patients in two lines and two patients in three lines.

Table 3.6: Treatments received by pilot patients by line

	All pilot patients						
	Line 2	Line 3	Line 4	Line 5	Line 6	Line 7	Line 8
Treatment	**(N=139)**	**(n=90)**	**(n=55)**	**(n=20)**	**(n=8)**	**(n=3)**	**(n=2)**
bortezomib	25	35	12	6	1	1	0
lenalidomide	4	14	21	6	5	1	1
thalidomide	73	15	8	3	1	0	1
adriamycin	17	10	4	2	0	2	0
vincristine	11	6	4	2	0	0	0
melphalan	21	7	5	2	1	0	0
high dose melphalan (HDM)	9	4	1	0	0	0	0
dexamethasone	80	52	32	9	5	2	0
prednisone	28	12	13	10	4	2	1
cyclophosphamide	14	9	14	6	1	1	1
donor lymphocyte infusion (DLI)	19	11	4	2	1	0	0
stem cell transplantation (allo+auto)	19	7	2	1	0	0	0
interferon alpha	0	2	0	0	1	0	0
experimental	1	1	0	0	0	0	0
other	1	2	3	2	0	0	0

Treatment combinations

As expected from clinical guidelines and shown in Table 3.6, patients do not only receive mono-therapy but a combination of different therapies is common practice. The most frequent treatment combinations for all pilot patients from line two onwards are combinations of thalidomide/ dexamethasone (n=57), lenalidomide/ dexamethasone (n=38), melphalan/prednisone (n=32) and vincristine/ adriamycin/ dexamethasone (n=22). In addition, Table 3.7 describes the different treatments that were combined with bortezomib within one treatment line.

Table 3.7: Treatment combinations of bortezomib

bortezomib therapy	number of patients receiving treatment (combination)
bortezomib treatment (all lines)	80
bortezomib mono-therapy	23
bortezomib combination therapy	57
bortezomib combination therapy (1 other treatment)	46
dexamethasone	33
donor lymphocyte infusion	9
cyclophosphamide	1
thalidomide	1
prednisone	1
dendritic cells	1
bortezomib combination therapy (2 other treatments)	7
dexamethasone + thalidomide	1
dexamethasone + adriamycin	1
dexamethasone + cyclophosphamide	1
prednisone + ciclosporine	1
thalidomide + donor lymphocyte infusion	1
lenalidomide + donor lymphocyte infusion	1
allo stemcell transplantation + donor lymphocyte infusion	1
bortezomib combination therapy (3 or more other treatments)	4
dexamethasone + prednisone + cyclophosphamide	1
dexamethasone + high dose melphalan + allo stemcell transplantation	1
dexamethasone + adriamycin + lenalidomide + prednisone	1
dexamethasone + thalidomide + cyclophosphamide + prednisone	1

As previously mentioned, six patients received bortezomib in more than one treatment line. Therefore, a bortezomib regime was administered at 80 instances to 72 pilot patients: 29% as mono-therapy and 71% as combination therapy. As expected from professional guidelines, bortezomib was most often combined with dexamethasone (58%). However, we also found many other treatment combinations. Some combinations are attributable to hospital specific guidelines. For example, guidelines of one particular hospital advised administration of donor lymphocyte infusion after every second bortezomib cycle, while another hospital recommended the combination of bortezomib with cyclophosphamide maintenance therapy. Other combinations might be related to the fact that some physicians treat patients according to ongoing clinical trials, which demonstrates the transition from science to daily practice, such as bortezomib combined with dexamethasone and adriamycin (HOVON65) or combining bortezomib with lenalidomide (HOVON86).

3.2.2 Bortezomib regimes, dose modifications and toxicities

The previous section described the various treatments and treatment combinations pilot patients received. This section further explores the applied bortezomib regimes, dose modifications and toxicities. In the APEX trial, a bolus of bortezomib (1.3 mg per square meter of body surface area) was administered four times per cycle on days 1, 4, 8 and 11 for eight three-week cycles, followed by three five-week treatment cycles on days 1, 8, 15 and 22. The median length of bortezomib therapy was six cycles; 39% of patients received the planned eight cycles (Richardson et al. 2007b). Richardson et al. (2005) reported that 37% of the APEX patients had adverse events requiring discontinuation of bortezomib treatment but did not report dose modifications. In the CREST study, in which bortezomib was administered in two different dose regimes (1.0 mg and 1.3 mg/m^2), 11% of the patients receiving the lower doses required a dose modification compared to 35% in the higher dose group (Jagannath et al. 2008).

Table 3.8 reports the actual and planned bortezomib dose regimes of the pilot patients compared to the planned dose regimens of APEX trial by total cycle numbers received. The comparison reveals that 50% of the pilot patients received one to three treatment cycles, 29% received six or more cycles and only 17% received seven or more cycles. Bortezomib treatment for pilot patients was generally planned at lower dosages than those in the APEX trial. Most of the pilot patients were treated in comparable cycle regimes as the APEX trial. However, pilot patients received both fewer treatments per cycle as well as lower dosages per treatment. It should be noted that one patient did not receive a cycle based regime but received bortezomib twice per week for 16 weeks, which is illustrated by the maximum dosage of 42.2 mg/m^2 in the first cycle.

Table 3.8: Actual and planned bortezomib dose regimes stratified by total cycle numbers

	Patients treated with bortezomib (n=72)					
Total Cycles	**n (%) bortezomib administrations**	**Planned Dose* (mg/m^2)**	***APEX trial planned dose (mg/m^2)***	**Actual Dose* (mg/m^2)**	**Actual/ Planned***	***Actual/ APEX trial planned***
1	9 (11.2%)	9.8 (5.0-42.2)	*5.2*	9.5 (2.5-42.2)**	0.88 (0.50-1.0)	*1.83***
2	8 (10.0%)	10.2 (9.2-10.6)	*10.4*	9.4 (6.6-10.5)	0.92 (0.63-1.0)	*0.90*
3	23 (28.8%)	15.0 (13.4-16.0)	*15.6*	14.2 (10.8-16.0)	0.94 (0.69-1.0)	*0.91*
4	10 (12.5%)	18.9 (11.8-21.1)	*20.8*	17.5 (11.5-21.1)	0.93 (0.77-1.0)	*0.84*
5	7 (8.8%)	21.8 (16.1-26.2)	*26.0*	20.8 (16.1-26.0)	0.96 (0.85-1.0)	*0.80*
6	9 (11.2%)	28.5 (19.6-31.6)	*31.2*	27.4 (16.6-31.6)	0.96 (0.84-1.0)	*0.88*
7+	14 (17.5%)	38.7 (21.0-44.3)	*42.3*	37.9 (30.0-44.3)	0.98 (0.88-1.0)	*0.90*

** Estimates are presented as the mean (min-max)* *** One patient did not receive a cycle based regime*

On average, over all cycles, 94% of planned dosages were actually administered to pilot patients. It is important to realize that physicians often plan the dosage after a previous cycle. Thus, the 94% of the actual dose received must be interpreted carefully. Comparison of actual dosages in daily practice with planned APEX trial dosages per cycle shows that pilot patients received, on average, 87% of trial-planned bortezomib dosage over all cycles (excluding the first cycle because of one different regime). Interestingly, the CREST study also reported a median dose intensity of 86.9% for the patients receiving the 1.3 mg/m^2 dosage (Jagannath et al. 2008).

Based on the available data, it was not feasible to establish a pattern for dose modifications according to toxicities in different treatment lines. Therefore, we summarized the reasons for dose modifications and toxicities. Table 3.9 depicts the reasons for dose modifications. In total, 53% of all 80 bortezomib regimes for the 72 pilot patients required a dose modification, including any increase or decrease in dose as well as a delay in receipt of dosage or withholding a dosage within a cycle. The dose modification could occur in any cycle within the regime. Toxicities were only reported when they resulted in a dose modification. As expected, the most common reported toxicity was neurotoxicity. Often physicians only reported that the condition of the patient required a dose modification without describing the reason for poorer condition. It is remarkable that for one patient the physician lowered the dose due to good response on the previous bortezomib cycle.

Table 3.9: Reasons for dose modifications when administering bortezomib

Reason for Dose Modification		Frequency (n=80) (%)
Total bortezomib regimes (72 patients)		80
Total number of regimes requiring dose modification		42 (52.5%)
Toxicity/AE		33 (79%)
	Gastrointestinal	10
	Neurological	20
	Haematological	7
	Patient condition	11
	Renal	2
	Other*	6
Progressive disease		1
Treat and observe tolaration		1
Good response to previous regimen		1
Related to tox/AE from previous regime		3
Weight adjustment		1
Unknown		6

*1 had infection due to pneumonia, 1 became progressively deaf, 1 had herpes infection, 3 unknown

3.2.3 Proportion of bortezomib vial dose administered versus discarded

There is a debate in the Netherlands whether hospitals should receive additional funding per vial of the drug used as it is in the current situation or whether funding should be based on the actual milligram given to patients. The size of one bortezomib vial is 3.5 mg and costs €954.52, whereas the normal dosage is 1.3mg/ m^2, implying that the vial contains an excess of bortezomib for the fast majority of patients. In our pilot study, on average, 66% of the vial was used for the administration of bortezomib to patients and the remaining 34% was thus not used and might be called 'waste'. However, it is questionable to what extent this is actual 'waste' of the drug or 'waste' of money. It is important to realise that most hospitals and/or hospital pharmacies have protocols stating that for safety reasons vials are not supposed to be pooled among patients. Furthermore, after preparation, bortezomib is only stable for a short period of time. The relatively low prevalence of multiple myeloma and thus the small amount of patients eligible for bortezomib treatment means that it would be difficult to pool patients by sharing vials and thus administer bortezomib at the same day in the same hospital to two, three or more patients.

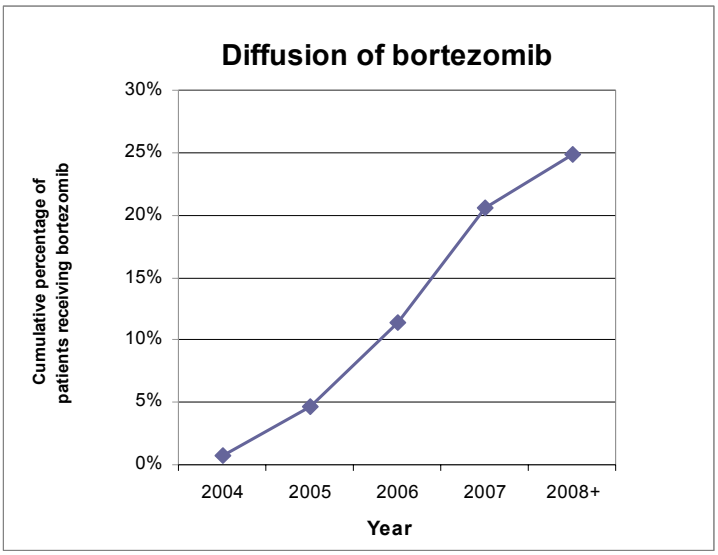
It should be realised that decreasing the amount of mg of bortezomib in a vial will not be related to a similar proportional decrease of the price of one vial. However, we

assume that there might be possibilities to improve efficiency, for example by stimulating the manufacturer to supply bortezomib in smaller vial sizes with varying dosages. Nevertheless, it is important to realise that this might provoke an incentive to give a (slightly) lower dose (per m^2) to patients in order to save money at the cost of potentially lower effectiveness of the drug.

3.2.4 Diffusion of bortezomib

In 2006, the Dutch policy regulations for expensive inpatient drugs were revised after signals of 'postal code' prescribing of trastuzumab. Therefore, we examined national and regional diffusion of bortezomib to investigate whether or not accessibility issues exist. The yearly diffusion of bortezomib within the HOVON50 population is illustrated in Figure 3.4. This figure shows the cumulative percentage of all Dutch HOVON50 patients who received bortezomib in daily practice (n=108) or within an RCT setting (n=31) from 2004 onwards. The sharpest increase was seen in 2006 and 2007, possibly related to the fact that in 2006 bortezomib was admitted to the list for expensive pharmaceuticals. In total, 25% of all Dutch patients included in the HOVON50 study were treated with bortezomib. The diffusion pattern could be due to the time period of our data collection and pilot patient population. It is expected that the proportion of HOVON50 patients eventually treated with bortezomib will increase as more patients relapse from treatment protocol.

Figure 3.4: Diffusion of bortezomib



Subsequently, we investigated the diffusion of bortezomib within the entire population of Dutch multiple myeloma patients. The independent national DBC (Diagnosis Treatment Combination) registration information system (DIS) records DBC data of Dutch hospitals. Table 3.10 shows DIS data on national bortezomib utilisation for 2006, 2007 and 2008. Per hospital type, the number of bortezomib care track registrations, performance registrations, average bortezomib administrations per patient, and hospitals registering bortezomib are described. A bortezomib care track registration indicates the number of patients receiving bortezomib, whereas the bortezomib performance registration indicates how often these patients received bortezomib. The table shows that the number of patients treated with bortezomib and the average number of administrations per patient increased over the years for most hospital types. In addition, each of the different types of hospitals registered bortezomib treatment. However, the table also indicates that the DBC data is incomplete. For example, according to the DBC data, only two academic hospitals used bortezomib. We collected data from patients receiving bortezomib in six different academic hospitals, thus revealing that not all (academic) hospitals register bortezomib utilisation. Additionally, dividing performance registrations by the care track registrations indicates the average number of bortezomib administrations per patient. According to the DIS data, patients receive on average 6 to 13 prescriptions, while pilot patients received on average 17.26 bortezomib administrations. Therefore, the results must be interpreted cautiously and the DIS data can only be used to indicate an increased usage over the years and to show that all types of hospitals administer bortezomib.

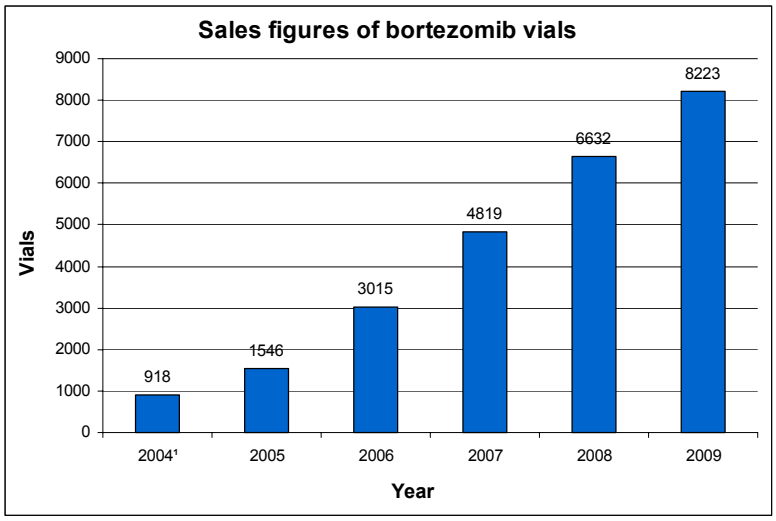
Table 3.10: DIS registration of hospitals using bortezomib

Type of hospital	Year	2006	2007	2008	Total
General hospital small (n=37)					
	bortezomib care track registrations	10	25	33	68
	bortezomib performance registrations	77	288	435	800
	average number of administrations per patient	7.7	11.5	13.2	11.8
	number of hospitals registering bortezomib	7	12	13	
General hospital medium (n=28)					
	bortezomib care track registrations	15	27	45	87
	bortezomib performance registrations	90	273	452	815
	average number of administrations per patient	6.0	10.1	10.0	9.4
	number of hospitals registering bortezomib	7	11	12	
General hospital large (n=10)					
	bortezomib care track registrations	8	7	17	32
	bortezomib performance registrations	85	82	155	322
	average number of administrations per patient	10.6	11.7	9.1	10.1
	number of hospitals registering bortezomib	2	3	4	
General hospital topclinical (n=20)					
	bortezomib care track registrations	27	48	74	149
	bortezomib performance registrations	241	608	757	1606
	average number of administrations per patient	8.9	12.7	10.2	10.8
	number of hospitals registering bortezomib	5	11	14	
Academic hospital (n=8)					
	bortezomib care track registrations	6	6	8	20
	bortezomib performance registrations	43	78	62	183
	average number of administrations per patient	7.1	13.0	7.75	9.15
	number of hospitals registering bortezomib	1	1	2	
Unknown					
	bortezomib care track registrations			8	8
	bortezomib performance registrations			51	51
	average number of administrations per patient			6.4	6.4
	number of hospitals registering bortezomib			2	
Total					
	bortezomib care track registrations	66	113	185	364
	bortezomib performance registrations	536	1329	1912	3777
	average number of administrations per patient	8.1	11.8	10.3	10.4
	number of hospitals registering bortezomib	22	38	47	

The Dutch Foundation for Pharmaceutical Figures (SFK) monitors expenditure for expensive inpatients pharmaceuticals. Their report shows a similar trend in the diffusion of bortezomib according to the DBC data. In 2006, national bortezomib expenditure was €3.3 million, and this increased to €5.7 million in 2007 (Stichting Farmaceutische Kengetallen 2009).

Finally, sales data provided by the manufacturer (Janssen-Cilag) shows a similar diffusion pattern over the years. Figure 3.5 depicts the number of packages delivered to Dutch hospitals from 2004 to 2009, excluding bortezomib used in clinical trials.

Figure 3.5: Bortezomib sales figures



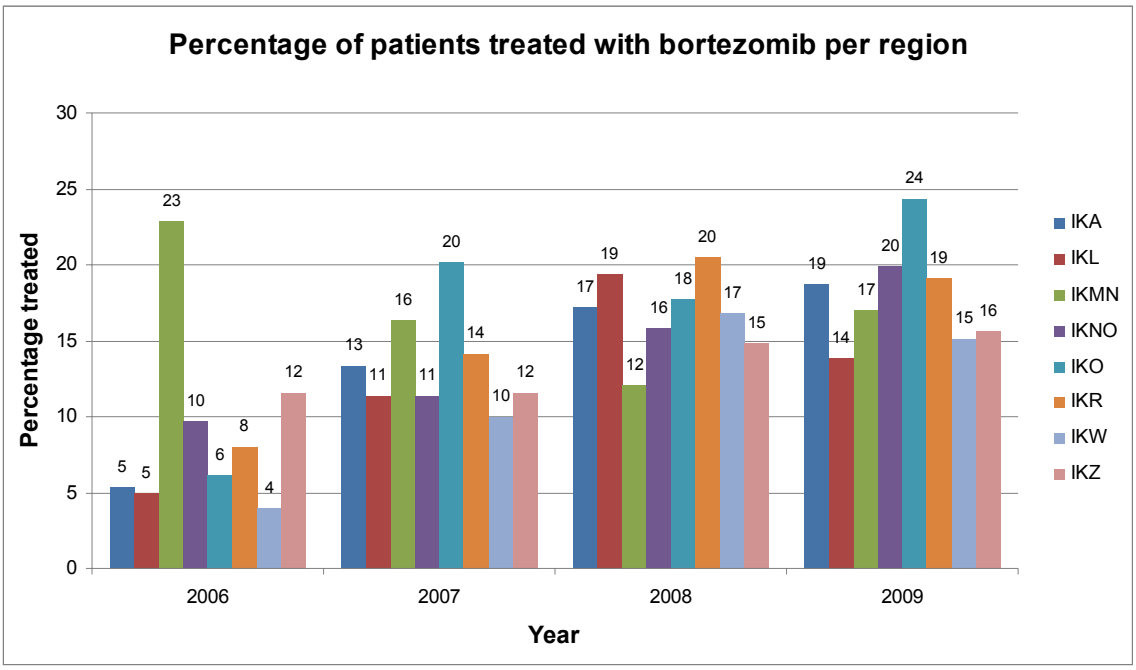
¹ Estimated annual figures based on available figures (November/December 2004)

Source: Janssen-Cilag

Furthermore, we compared the estimated prevalence of multiple myeloma with sales data from the manufacturer. Figure 3.6 presents the percentage of multiple myeloma patients treated in daily practice with bortezomib per cancer registration region from 2006 to 2009. The figure shows a similar increasing trend of bortezomib utilisation over the years and indicates a long adjustment period. Although several assumptions were made to calculate the prevalence, there appears to be a residual regional difference in 2009. These results indicate that while the policy for expensive pharmaceuticals might have had a positive effect on bortezomib utilisation over the years, residual regional variation may exist which might point towards residual accessibility issues despite the revision of the policy regulations. It should be noted that the estimations are based on sales data and must be carefully interpreted since bortezomib usage in clinical trials is not included. For example, our data revealed that 31 of the 543 HOVON50 patients received bortezomib in a clinical trial (see Figure 3.1). Further investigation is required to reveal if these differences are caused by regional variation in trial participation or related to accessibility issues or due to

assumptions made for calculations, such as incidence fluctuations over time, regional variation in patient characteristics, or due to chance.

Figure 3.6: Percentage of patients treated with bortezomib per cancer registration region



3.3 Clinical effectiveness

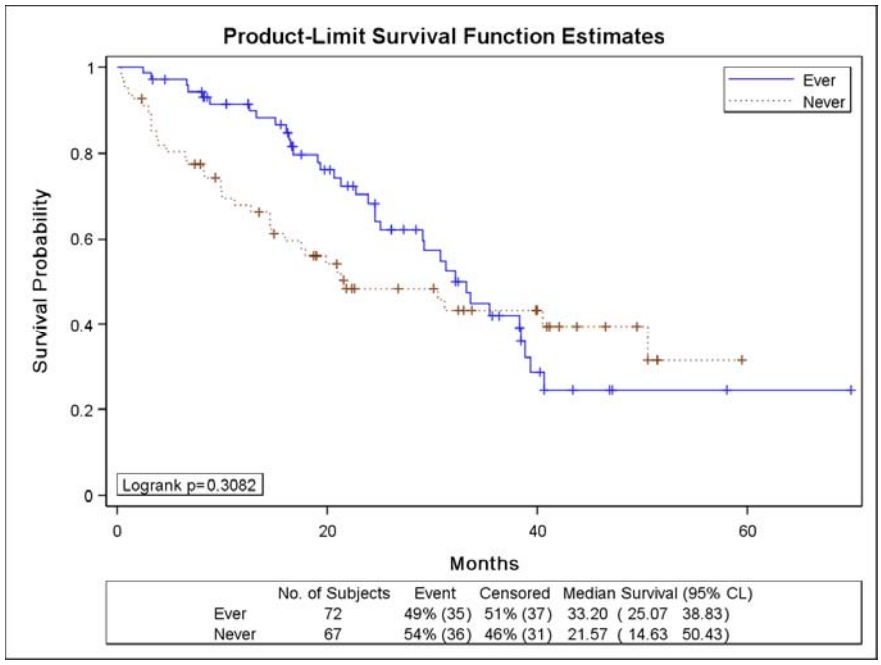
We explored the feasibility and validity of the possible outcomes available to demonstrate effectiveness of bortezomib in daily clinical practice.

Overall survival (OS)

OS can be measured in this patient population either from diagnosis or start of treatment for relapsed/refractory disease. We first considered the outcome OS from start of relapsed/refractory treatment, as this is the relevant survival measure reported in the literature when assessing effectiveness of relapsed/refractory treatment for multiple myeloma. Figure 3.7 reveals bortezomib to have no statistically significant advantage in OS from start of relapsed/refractory (mean: 29.5; median: 33.2) compared to those who never received bortezomib (mean: 28; median: 21.6), despite a longer mean and median survival (logrank p = 0.308). However, the Wilcoxan statistic, which is a non-parametric test statistic that is more sensitive to the differences in survival at early points in time, was

significant (p = 0.01). Therefore, the survival curves for both groups are significantly different when considering the ratio of hazards at the early points in times rather than equally throughout time. This is not a surprising result as we see that the curves are far apart at early points in time and eventually cross around 40 months of survival (Figure 3.7). The crossing of the curves is likely due to the low number of patients still in follow-up after approximately 36 months. That is, 14 patients remain after 36 months in each group, accounting for 19% and 21% of the patient population in the group of patients ever versus never receiving bortezomib, respectively.

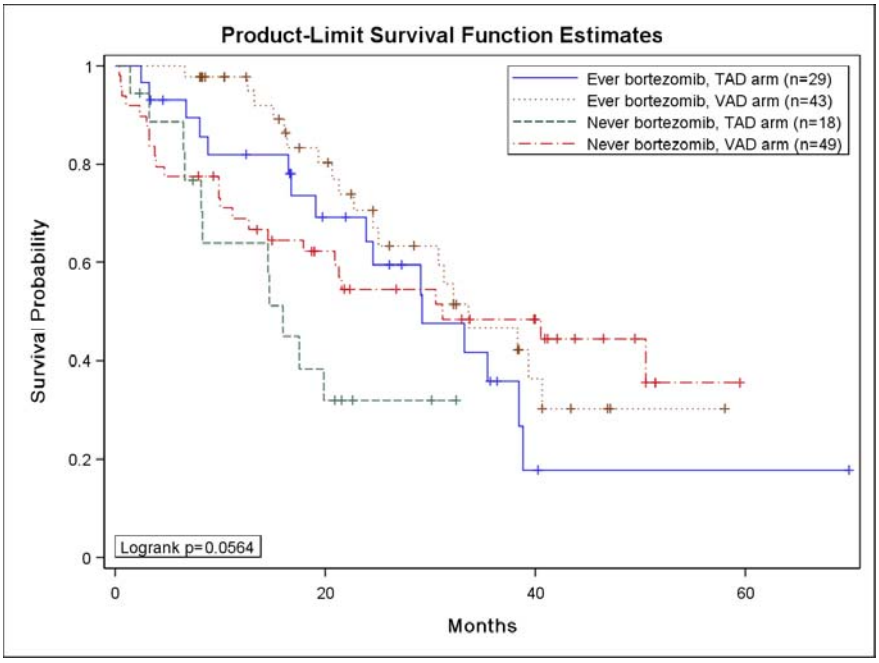
Figure 3.7: Kaplan-Meier curves of overall survival from start of relapsed/refractory treatment stratified by receipt of bortezomib



Due to the relevance of previous treatment to the effectiveness of subsequent treatment, we further stratified the outcome based on HOVON50 treatment arm and found a marginally insignificant logrank statistic (p = 0.056) but a significant Wilcoxan statistic (p = 0.015) (Figure 3.8). It is reasonable to conclude that the patient groups when defined by never versus ever receiving bortezomib have statistically significant differences in OS in the early months following relapsed/refractory treatment but that the difference is not carried over throughout the remaining survival due to low number of observations. It is also reasonable to conclude that HOVON50 treatment has a further effect on survival in addition to that of receipt of bortezomib, with patients receiving no thalidomide prior to

bortezomib treatment doing better in terms of OS from start of relapsed/refractory treatment compared to those receiving thalidomide.

Figure 3.8: Kaplan-Meier curves of overall survival from start of relapsed/refractory treatment stratified by receipt of bortezomib and HOVON50 treatment randomization



To assess whether patients who received bortezomib at the earliest moment of eligibility, i.e., second line, OS from start of relapsed/refractory treatment was compared between patients receiving bortezomib in second line to those not receiving it in second line. A statistically significant advantage for bortezomib treatment was absent when comparing patients who received bortezomib in second line compared those who either never received bortezomib or received it in third line or later (logrank p = 0.791; Wilcoxan p: 0.83) and when further stratifying by HOVON50 treatment arm (logrank p = 0.328; Wilcoxan: 0.58) (Figures 3.9 and 3.10). These results suggest no advantage in OS from start of relapsed/refractory treatment for patients receiving bortezomib in second line compared to those either never receiving it or receiving it at a later point in relapsed/refractory treatment.

Figure 3.9: Kaplan-Meier curves of overall survival from start of relapsed/refractory treatment stratified by receipt of bortezomib in 2nd line

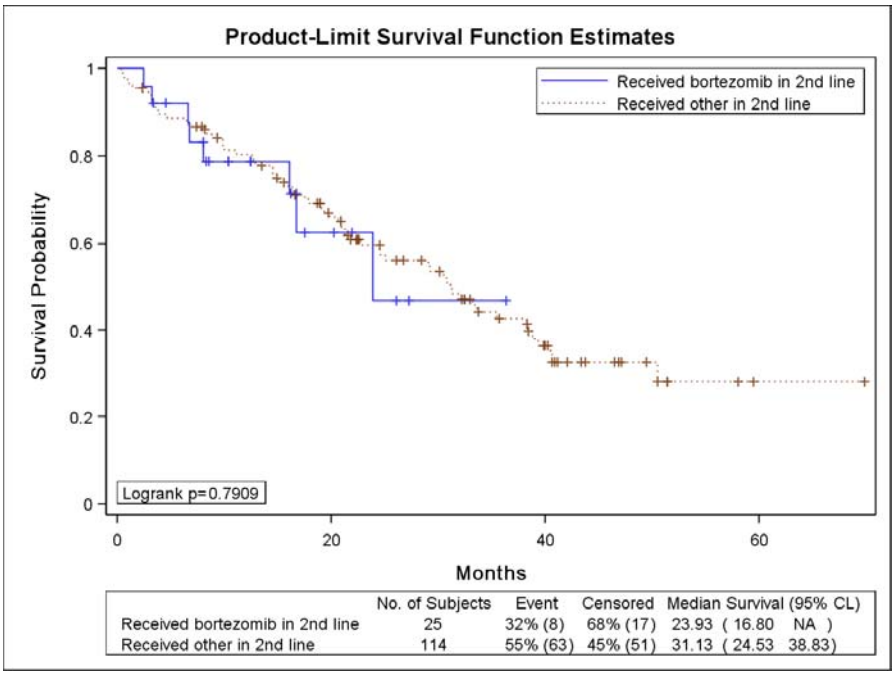
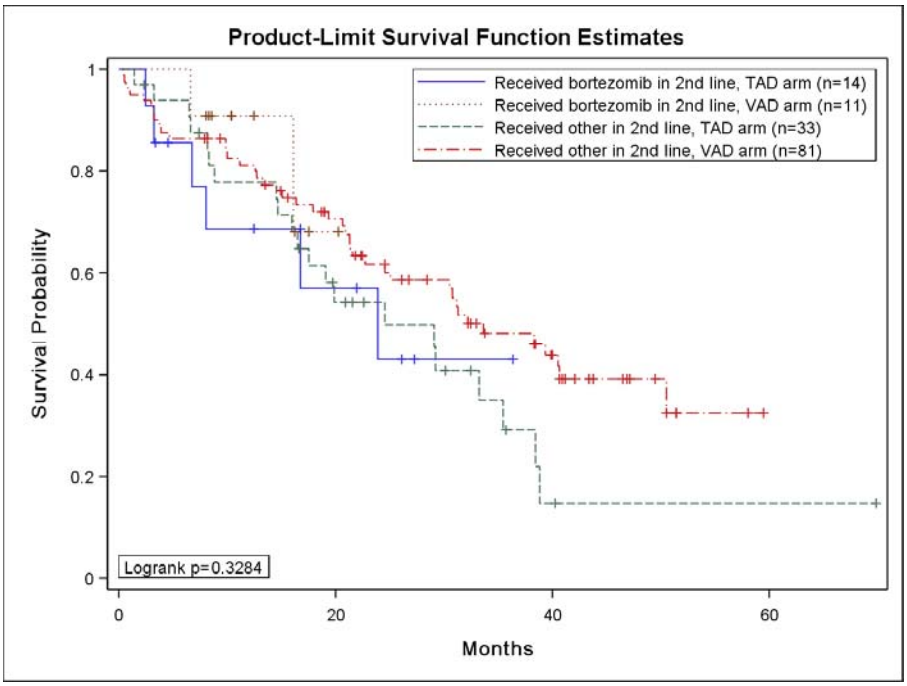
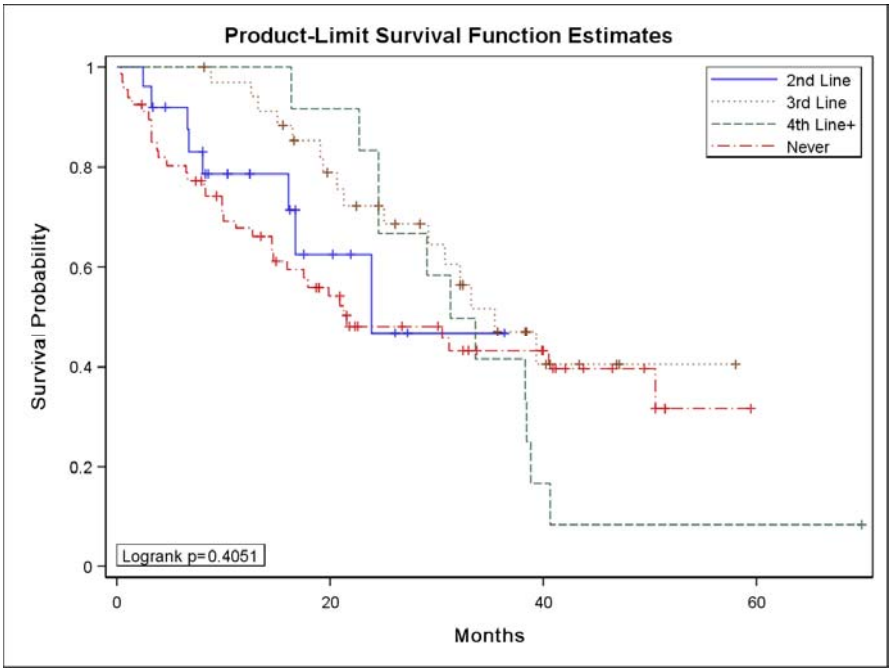


Figure 3.10: Kaplan-Meier curves of overall survival from start of relapsed/refractory treatment stratified by receipt of bortezomib in 2nd line and HOVON50 treatment arm



We explored the difference in survival between all four groups defined by treatment line of bortezomib from start of relapsed/refractory treatment (Figure 3.11). When examining OS from start of relapsed/refractory treatment for the four patient groups, again the difference in survival was significant only when weighted by the proportion of events occurring at early points in time (logrank p = 0.41; Wilcoxan p = 0.04). Mean and median OS favoured receipt of bortezomib in third line (mean: 31; median: 35.4) followed by receipt in fourth line or later (mean: 31.6; median: 32.5). Patients receiving bortezomib in second line were the worse off when comparing mean estimates (mean: 18.8; median: 24); and patients never receiving bortezomib were worse off when comparing medians (mean: 28; median: 21.6). Considering the significant results of the Wilcoxan test, it is reasonable to conclude that the four patient groups are distinct and should be assessed individually.

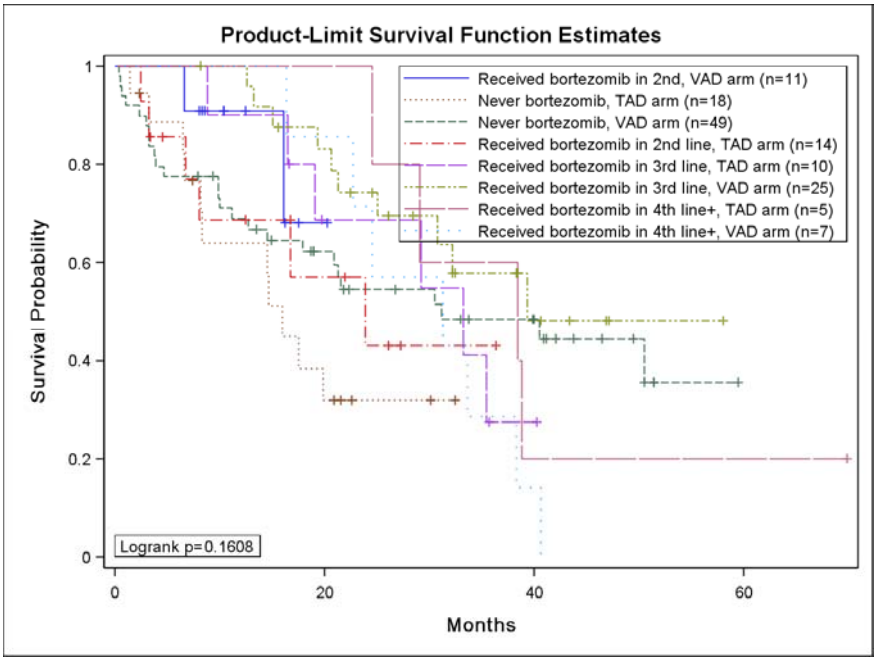
Figure 3.11: Kaplan-Meier curves of overall survival from start of relapsed/refractory treatment stratified by line of bortezomib treatment



Further stratification by HOVON50 treatment resulted in a statistically insignificant effect on OS from start of relapsed/refractory treatment between the four groups (logrank p = 0.16; Wilcoxan: p = 0.08) (Figure 3.12). However, a pattern favouring an advantage for bortezomib patients receiving no thalidomide in HOVON50 as demonstrated previously was difficult to discern due to the small number of observations in each of the 8 groups.

Therefore, the effect of HOVON50 treatment was no longer considered when comparing the 4 patient groups.

Figure 3.12: Kaplan-Meier curves of overall survival from start of relapsed/refractory treatment stratified by line of bortezomib treatment and HOVON50 treatment arm



As many studies report the OS from start of treatment with the baseline being start of bortezomib treatment, regardless of the treatment line it is received in, the mean and median OS from start of bortezomib treatment for all bortezomib patients was also calculated to facilitate comparisons to previous studies. The mean and median OS estimates from the start of bortezomib treatment were 19.4 and 17.2 months, respectively.

It is also relevant to report the OS from start of bortezomib treatment for the respective line when bortezomib was administered. This outcome would be useful in assessing how the cost-effectiveness of bortezomib changes when administered farther along in relapsed/refractory treatment. Mean and median OS estimates from start of respective line when bortezomib was administered in second line are discussed above (mean: 18.8; median: 24). Mean and median OS estimates from start of third line for patients treated with bortezomib in third line was 21.5 and 24.2 months, respectively (curves not shown). For patients receiving bortezomib in fourth line or later, mean and median OS estimates from fourth line was 10.4 and 11.6 months, respectively (curves not shown).

Time-to-next-treatment (TTNT) and time-to-progression (TTP)

Time-to-event curves when examining the outcomes TTNT and TTP within each line stratified on receipt of bortezomib versus any other treatment revealed counterintuitive results which also suggested no advantage to bortezomib treatment (data not shown). Patients treated with bortezomib either progressed or started subsequent treatment lines sooner compared to patients who received other treatment during each line conditional on no history of receiving bortezomib in previous lines. For example, in second line, median TTNT for bortezomib patients was 11.7 months compared to 13.9 for patients not treated with bortezomib in second line. Similarly, in third line, median TTNT for bortezomib patients was 10.8 months compared to 11.4 for patients not treated with bortezomib in third line conditional on never having received bortezomib previously. Consequently, TTP and TTNT were decided to be inappropriate for outcomes for demonstrating the incremental effectiveness of bortezomib in daily practice. As progression-free survival (PFS) is correlated with both TTP and TTNT, its use as an outcome was assumed to be inappropriate as well and, consequently, was not assessed.

The primary outcome measures of time to first response, time to best response, and DOR are not possible with the pilot data because detailed follow-up regarding response to treatment was not collected, as it was not available in patient charts; only best response was recorded by treatment line.

Selected effectiveness outcome

After an exploration of the possible outcomes available to demonstrate the effectiveness of bortezomib in daily clinical practice, it was decided that clinical effectiveness would be calculated in terms of overall survival (OS), with baseline being diagnosis. This decision was based on the inconclusive results obtained when examining the outcome of OS from start of relapsed/refractory treatment and the counterintuitive results obtained when examining either TTP or TTNT within each line.

As mentioned previously, the validity of an incremental effectiveness estimate depends on the extent to which confounding by indication is present. To explore the extent to which we could correct confounding by indication, adjustment of survival curves was attempted by the following methods: average covariate adjustment, PS adjustment and matched survival analysis. The methods of average covariate and PS adjustment were feasible. The method of matched survival analysis was deemed uninformative after exploration of the feasibility of creating matched groups. The limitation to conducting the

matched method was primarily due to low numbers of eligible matches. A total of 4 matches were found to be possible, with 1 patient from each of the 4 groups being matched to one another on the basis of PS. A total population of 16 was deemed insufficient to gather informative results. Therefore, only the results of the covariate and PS adjusted survival analysis are presented.

Clinical effectiveness is shown separately for patients treated with bortezomib from those never treated with bortezomib. The rationale for presenting the patients treated with bortezomib from those not treated with bortezomib is to discourage comparison of the groups and instead to first objectively examine the OS for both groups without forcing comparison of groups for which may be inappropriate.

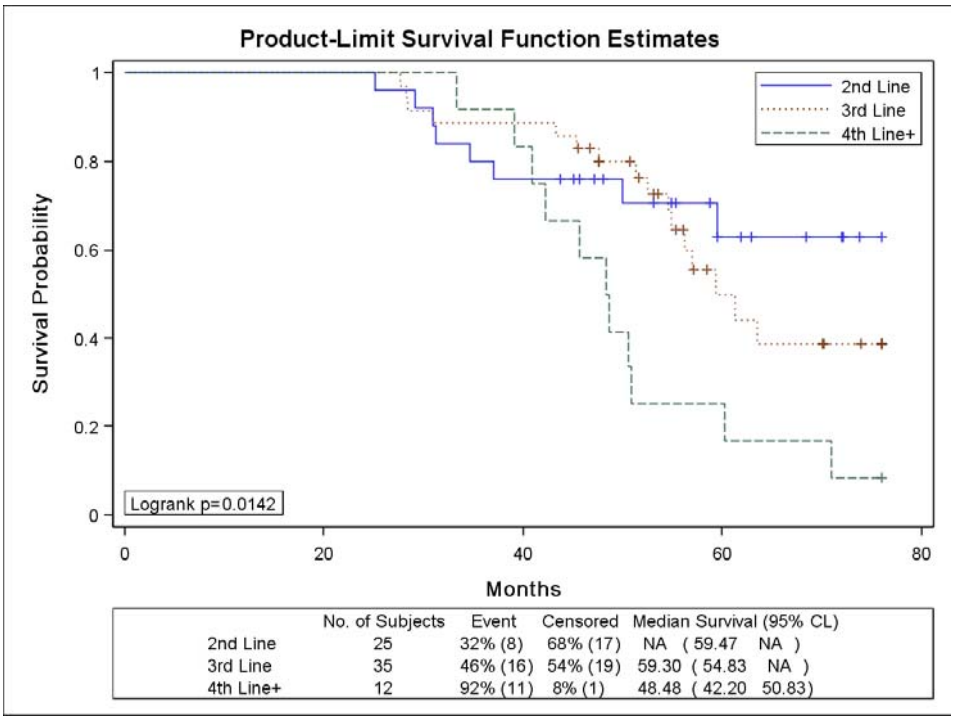
3.3.1 Clinical effectiveness for patients treated with bortezomib

To ensure equal follow-up between all four groups, OS estimates from diagnosis were censored after the last available follow-up estimate for the group of patients with the shortest total follow-up. The group of patients with the shortest available follow-up was the group of patients treated with bortezomib in second line because this group was still treated at the time data collection. Accordingly, patients in all four groups with follow-up available after 76 months were censored.

No adjustment

The unadjusted curves for the patient groups treated with bortezomib reveal that the median OS from diagnosis for patients exposed in the second line has not been reached, while the median OS from diagnosis for patients exposed in third line and fourth line or later is 59.3 and 48.5, respectively (Figure 3.13). Estimates of mean unadjusted estimates for such patient groups reveals that patients exposed in third line have the longest OS (mean OS = 55.5), followed by patients exposed in second line (mean OS = 52.2), while patients exposed in fourth line survive from diagnosis on average for the shortest duration (mean OS = 50.1). The logrank statistic is significant ($p = 0.01$), suggesting that the difference in survival between the three groups is statistically significant.

Figure 3.13: Kaplan-Meier curves for overall survival of patients treated with bortezomib stratified by line of treatment



Adjusted survival curves

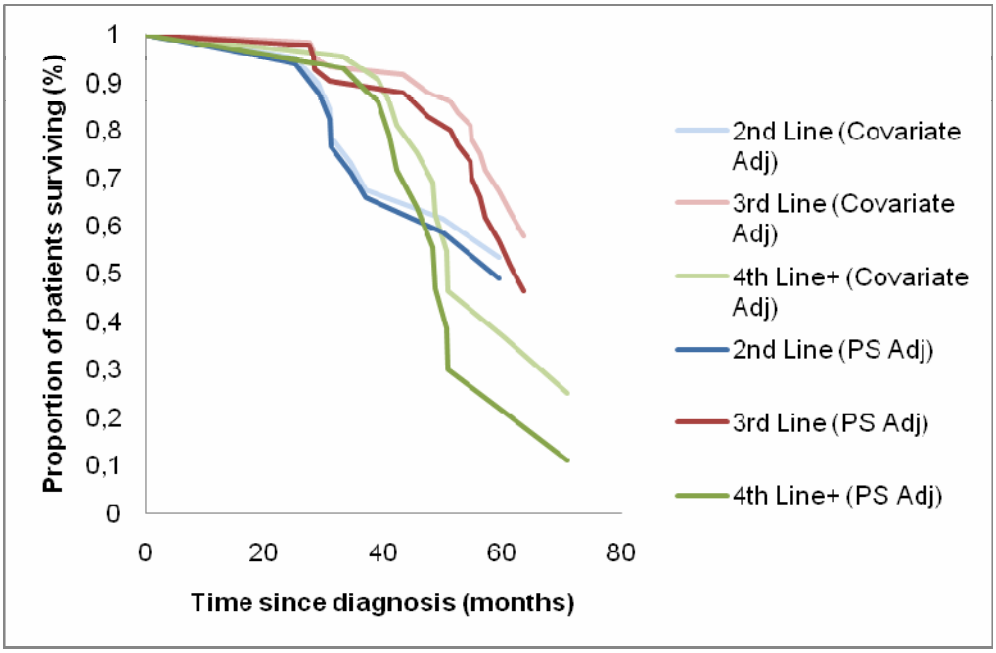
Adjusted OS curves reveal minor changes in the overall shape of the graph. However, with covariate adjustment, the survival estimates are slightly increased compared to estimates resulting with PS adjustment (Figure 3.14).

As a result of the increase, the median OS estimates for patients exposed in second or third line were not available, while patients exposed in fourth line or later survived from diagnosis at a median of 50.7 months. Comparison of the mean estimates of OS after covariate adjustment reveals a similar pattern as that of the unadjusted analysis, with patients exposed in third line having the longest OS (mean OS = 63.3), followed by patients exposed in second line (mean OS = 59.3), while patients exposed in fourth line survive from diagnosis on average for the shortest duration (mean OS = 52.1). The absolute difference between the mean OS estimates of all three groups is more spread out after covariate adjustment in comparison to the unadjusted estimates.

When comparing the mean OS estimates resulting after PS adjustment to the mean unadjusted and covariate adjusted estimates, again a similar pattern is revealed, with patients exposed in third line have the longest OS (mean = 58.8; median = 63.5), followed by patients exposed in second line (mean OS = 57.9; median = 59.9), while

patients exposed in fourth line survive from diagnosis on average for the shortest duration (mean OS = 44.1; median = 49). In contrast, the difference between mean OS estimates after PS adjustment for patients treated in second line to patients treated in third line is compressed to the largest degree out of all three analytical methods with the difference being less than 1 month. Lastly, the PS adjusted method produces the shortest mean estimate for survival from diagnosis for patients exposed in fourth line or later.

Figure 3.14: Adjusted overall survival for patients treated with bortezomib stratified by line of treatment



Comparison of estimates

Patients treated with bortezomib in second and third line in this pilot study appear to live the longest. It is interesting to note that the method of average PS adjustment results in a longer median OS compared to the mean OS for patients treated in fourth line or later, which is in contrast to a longer mean OS compared to the median as observed from the unadjusted and average covariate adjusted analyses.

Table 3.11: Comparison of mean and median OS estimated with and without adjustment in patients receiving bortezomib

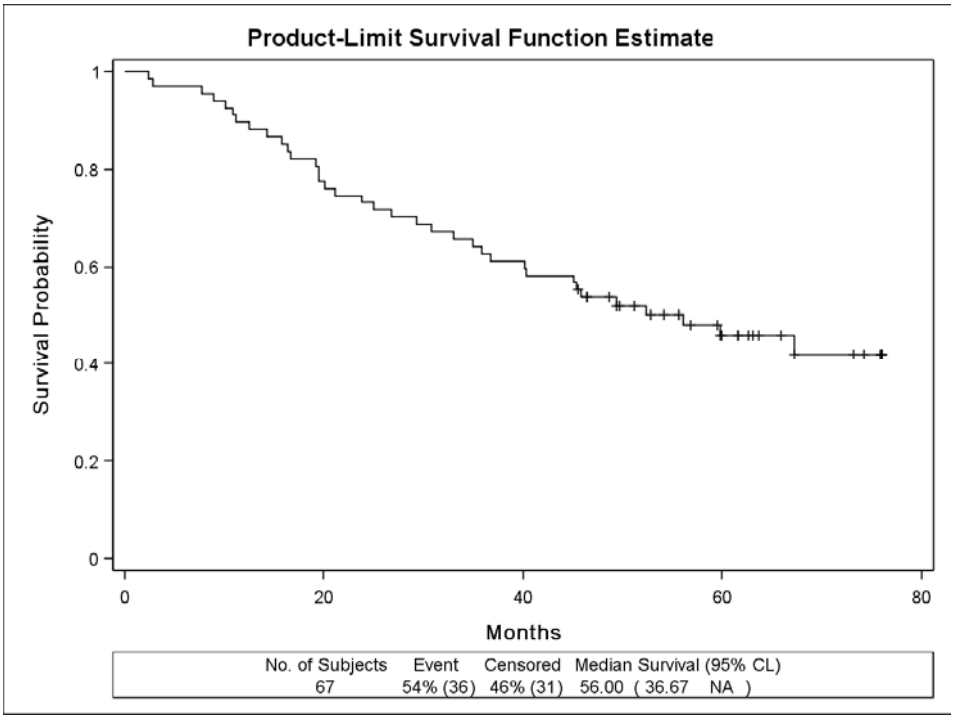
Bortezomib treatment status	% Censored	No Adjustment		Average covariate adjustment		Average PS adjustment	
		Mean	Median	Mean	Median	Mean	Median
2	68%	52.2	NA	59.3	NA	57.9	59.9
3	54%	55.5	59.3	63.3	NA	58.8	63.5
4+	8%	50.1	48.5	52.1	50.7	44.1	49.0

3.3.2 Clinical effectiveness for patients not treated with bortezomib

No adjustment

The unadjusted survival curve for patients never treated with bortezomib reveals a mean OS estimate of 45.9 months and a median of 56 months (Figure 3.15). When disregarding censoring patients with follow-up longer than 76 months, follow-up estimates for patients never receiving bortezomib ranged between 2.5 and 84.8 months, suggesting extensive variation in survival within this group.

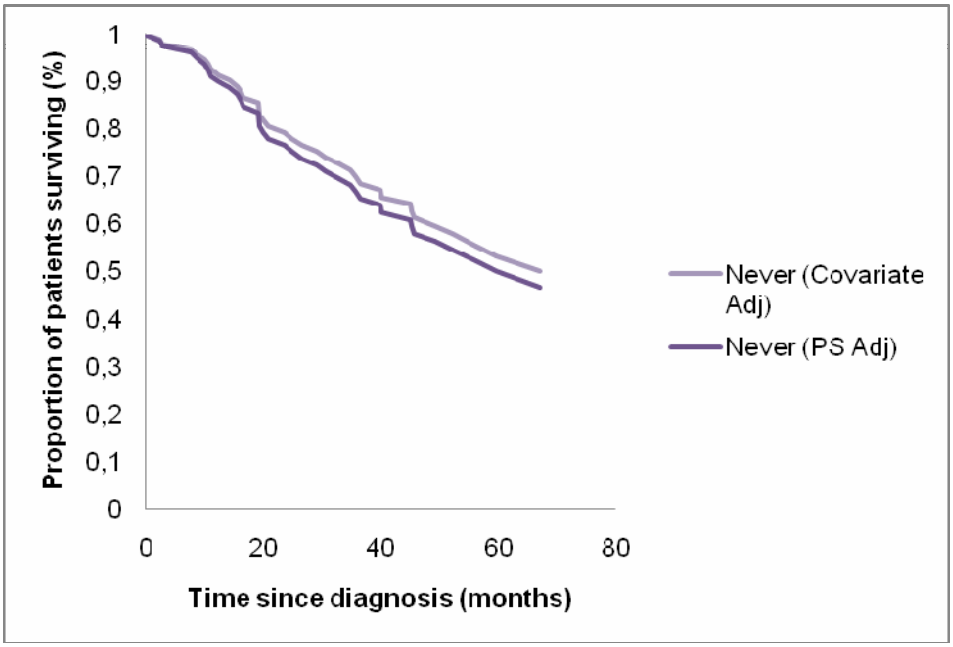
Figure 3.15: Kaplan-Meier curves for overall survival of patients never treated with bortezomib



Adjusted survival curves

Adjustment of the OS for patients never treated with bortezomib by means of the covariate adjustment method reveals an extended mean and median OS estimate of 59.3 and 67.1, respectively, compared to the unadjusted estimates (Figure 3.16). Mean and median OS estimates after PS adjustment were 57.6 and 60.1, respectively, which are similarly higher compared to the unadjusted estimates but lower than that after covariate adjustment.

Figure 3.16: Adjusted overall survival for patients never treated with bortezomib



Comparison of estimates

The OS for patients never receiving bortezomib is greatly extended by the average covariate method, regardless of reporting the mean or median (Table 3.12).

Table 3.12: Comparison of mean and median OS estimated with and without adjustment in patients never receiving bortezomib

Bortezomib treatment status	% Censored	No Adjustment		Average covariate adjustment		Average PS adjustment	
		Mean	Median	Mean	Median	Mean	Median
Never	46%	45.9	56.0	59.3	67.1	57.6	60.1

3.3.3 Summary of clinical effectiveness for all patient groups

Patients that appear to have the most survival gain from bortezomib treatment are those treated in second and third line. In general, the adjusted survival curves do not differ in overall shape from their unadjusted counterparts. Comparison of the adjusted OS estimates reveals two consistent results (Table 3.11 and 3.12): (1) both methods lead to extended mean and median OS estimates compared to the crude, with the exception of adjustment for the group exposed in fourth line or greater for which the OS estimates adjusted by means of the PS are reduced; (2) adjustment by means of covariates results in the most extended mean and median estimates of all three analyses.

3.4 Costs in clinical practice

3.4.1 Costs in clinical practice for patients treated with bortezomib

Table 3.13 presents the total mean treatment costs for all patients ever receiving bortezomib (n=72). These cost analyses were based on the resource use of the full patient sample including patients still treated at the end of the data collection.

The mean follow-up duration was 26 (SD 14.4) months. Total mean treatment costs amounted to €81,626 but varied widely between patients. Treatment costs ranged from €17,793 to €229,783, with the most expensive patient receiving lenalidomide in line 6 for approximately one year. Inpatient hospital days and active treatment were the most important cost drivers.

With total mean costs of €30,733 (SD 24,654), active treatment (excluding stem cell transplantation) was responsible for 38% of the total mean treatment costs. Bortezomib accounted for 57% and lenalidomide for 35% of the active treatment costs.

Inpatient hospital day costs amounted to a mean €12,294 (SD 13,769). Patients were admitted for an average of 23.4 (SD 26.7) inpatient days. As expected, inpatient hospital days were especially important in patients receiving stem cell transplantation.

Table 3.13 also presents the total mean treatment costs separately for patients receiving bortezomib in the second (n=25), third (n=35) and fourth+ (n=12) treatment line. Compared with patients receiving bortezomib in the second line, total costs were substantially higher for patients receiving bortezomib in the third line (€53,726 versus €95,962; Mann-Whitney U test: $p = 0.002$). A similar trend was observed when comparing

patients receiving bortezomib in second line to those receiving the drug in fourth line or later (€53,726versus €97,937; Mann-Whitney U test: p = 0.027). The significantly lower results for patients treated with bortezomib in second line are not surprising since the majority of patients (68%) treated in second line were still in follow-up at the time of data collection compared to 54% and 8% of patients in third line and fourth+ line, respectively.

Table 3.13: Total mean costs per patient treated with bortezomib

	All bmib patients (n=72)		Bmib 2nd line (n=25)		Bmib 3rd line (n=35)		Bmib 4th+ line (n=12)	
Resource Use (numbers)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Inpatient hospital days	23.4	26.7	13.4	18.7	26.2	30.4	36.1	23.5
Intensive care days	0.3	1.4	0.4	2.0	0.3	1.1	0.2	0.6
Outpatient visits	51.6	35.5	32.6	29.4	55.4	30.4	79.9	40.6
Consultations by telephone	3.9	5.0	3.3	4.5	4.0	2.9	5.1	9.5
Day-care treatments	28.7	17.9	23.3	14.4	30.1	17.2	36.1	24.0
Emergency room visits	1.5	2.0	1.2	2.1	1.4	1.7	2.3	2.3
Costs (Euro 2009)								
Inpatient hospital days	€ 12,294	€ 13,750	€ 6,708	€ 9,767	€ 14,115	€ 15,476	€ 18,619	€ 12,112
Intensive care unit days	€ 607	€ 2,909	€ 832	€ 4,160	€ 535	€ 2,219	€ 347	€ 1,201
Outpatient visits	€ 5,676	€ 3,902	€ 3,590	€ 3,234	€ 6,097	€ 3,343	€ 8,791	€ 4,461
Consultations by telephone	€ 51	€ 65	€ 43	€ 59	€ 52	€ 38	€ 66	€ 124
Day-care treatments	€ 4,799	€ 2,993	€ 3,894	€ 2,402	€ 5,024	€ 2,872	€ 6,026	€ 4,010
Emergency room visits	€ 160	€ 216	€ 131	€ 231	€ 153	€ 189	€ 245	€ 251
Radiotherapy	€ 1,971	€ 3,139	€ 398	€ 722	€ 2,511	€ 3,574	€ 3,675	€ 3,640
Surgical procedures	€ 766	€ 2,058	€ 262	€ 1,070	€ 905	€ 2,495	€ 1,407	€ 2,127
Other diagnostic procedures	€ 172	€ 286	€ 85	€ 166	€ 187	€ 301	€ 308	€ 387
Laboratory	€ 4,642	€ 3,466	€ 2,593	€ 1,963	€ 5,356	€ 3,773	€ 6,832	€ 2,955
Pathology	€ 114	€ 122	€ 47	€ 81	€ 140	€ 112	€ 182	€ 160
Bacterial cultures	€ 190	€ 288	€ 74	€ 119	€ 221	€ 343	€ 342	€ 285
Viral cultures	€ 71	€ 207	€ 11	€ 31	€ 80	€ 237	€ 171	€ 287
Xrays	€ 897	€ 584	€ 521	€ 486	€ 1,000	€ 528	€ 1,385	€ 455
CT scans	€ 277	€ 421	€ 158	€ 330	€ 338	€ 496	€ 346	€ 311
MRIs	€ 315	€ 441	€ 173	€ 290	€ 409	€ 521	€ 337	€ 401
Radionucleide scans	€ 10	€ 58	€ 0	€ 0	€ 10	€ 59	€ 29	€ 101
PET scans	€ 745	€ 2,009	€ 564	€ 1,822	€ 1,008	€ 2,385	€ 353	€ 877
Ultrasounds	€ 65	€ 140	€ 34	€ 66	€ 86	€ 177	€ 65	€ 128
Antibacterial medication (prophylaxis)	€ 2,560	€ 2,413	€ 1,793	€ 1,770	€ 2,505	€ 2,428	€ 4,320	€ 2,793
Antibacterial medication (acute infection)	€ 238	€ 213	€ 178	€ 180	€ 296	€ 236	€ 194	€ 168
Biphosphonates (prophylaxis)	€ 2,776	€ 2,044	€ 1,434	€ 1,454	€ 3,541	€ 2,017	€ 3,342	€ 1,867
Transfusion of ery's	€ 1,298	€ 3,141	€ 539	€ 1,702	€ 1,381	€ 3,628	€ 2,635	€ 3,660
Erythropoietin	€ 166	€ 388	€ 75	€ 183	€ 206	€ 449	€ 238	€ 496
Transfusion of platelets	€ 986	€ 2,553	€ 572	€ 1,990	€ 1,056	€ 2,998	€ 1,643	€ 2,187
Chronic neurotoxicity medication	€ 745	€ 1,915	€ 831	€ 1,615	€ 735	€ 2,104	€ 595	€ 2,061
Chronic gastro-intestinal medication	€ 3,670	€ 3,887	€ 1,929	€ 2,065	€ 4,513	€ 4,457	€ 4,838	€ 4,021
Chronic analgesics	€ 664	€ 671	€ 371	€ 376	€ 853	€ 767	€ 725	€ 684
Thalidomide	€ 514	€ 708	€ 84	€ 239	€ 776	€ 846	€ 643	€ 489
Bortezomib	€ 17,407	€ 11,143	€ 16,914	€ 9,563	€ 18,927	€ 12,536	€ 13,999	€ 9,779
Dexamethasone	€ 103	€ 127	€ 67	€ 88	€ 100	€ 89	€ 188	€ 228
Adriamycin	€ 133	€ 268	€ 101	€ 248	€ 92	€ 162	€ 320	€ 451
Vincristine	€ 25	€ 61	€ 12	€ 43	€ 18	€ 48	€ 75	€ 96
Lenalidomide	€ 10,769	€ 18,062	€ 7,550	€ 14,487	€ 15,629	€ 21,551	€ 3,298	€ 7,258
Melphalan	€ 76	€ 202	€ 0	€ 0	€ 65	€ 148	€ 266	€ 377
Prednisone	€ 21	€ 78	€ 2	€ 5	€ 32	€ 110	€ 29	€ 23
Cyclophosphamide	€ 17	€ 40	€ 6	€ 16	€ 23	€ 53	€ 24	€ 31
Donor leukocyte infusions	€ 1,594	€ 3,015	€ 1,124	€ 2,354	€ 1,941	€ 3,431	€ 1,561	€ 3,051
Interferon alpha	€ 22	€ 134	€ 27	€ 133	€ 27	€ 158	€ 0	€ 0
Stem cell transplantation	€ 3,969	€ 13,313	€ 0	€ 0	€ 4,960	€ 15,399	€ 9,345	€ 18,456
Other active treatment	€ 52	€ 269	€ 0	€ 0	€ 61	€ 278	€ 134	€ 462
Total global costs	€ 81,626	€ 47,246	€ 53,726	€ 27,956	€ 95,962	€ 51,484	€ 97,937	€ 42,382
Median	€ 72,182		€ 47,906		€ 78,788		€ 85,051	
Minimum	€ 17,793		€ 17,793		€ 37,567		€ 30,234	
Maximum	€ 229,783		€ 115,793		€ 229,783		€ 186,372	

Table 3.14 presents the proportion of the total costs for the most costly individual cost components that explain the majority of the total global costs for patients treated with bortezomib. The share of total global costs explained by costs for hospital days, concomitant medication, resource use and active treatment is also shown. The top three

individual cost components that explain the largest of proportion of total global costs include bortezomib treatment (21%), inpatient hospital stays (15%) and lenalidomide treatment (13%). Furthermore, costs for active treatment accounted for almost half of total global costs for bortezomib patients, followed by costs for all other resource use excluding costs for inpatient and intensive care unit hospital days, which accounted for one-fourth of total global costs.

Table 3.14 Proportion of total costs explained by cost components

Cost components (Euro 2009)	All bmib patients (n=72)
Inpatient hospital days	15%
Intensive care unit days	1%
Outpatient visits	7%
Day-care treatments	6%
Laboratory	6%
Bortezomib	21%
Lenalidomide	13%
Stem cell transplantation	5%
Total % explained by above components	***72%***
Total hospital day costs*	15%
Total concomitant medication costs	16%
Total resources use costs**	25%
Total active treatment costs	44%

*includes inpatient and intensive care unit days
**excludes hospital day costs

3.4.2 Costs in clinical practice for patients not treated with bortezomib

Table 3.15 presents the total mean treatment costs for patients never receiving bortezomib (n=67). These cost analyses were based on the resource use of the full patient sample including patients still treated at the end of the data collection. The mean follow up duration was 21.5 (SD 16) months. Total mean treatment costs amounted to €52,760 but varied widely between patients. Treatment costs ranged from €748 to €179,571, with the most expensive patients consuming substantial high proportions of their total costs for hospital stays, resource use and active treatment. Inpatient hospital days and cost of lenalidomide therapy were the most important cost drivers for the entire group.

With total costs of €10,409 (SD 24,340), active treatment (excluding stem cell transplantation) was responsible for 20% of the total mean treatment costs. Lenalidomide

accounted for 86% of the total active treatment costs and stem cell transplant accounted for 8% of total costs.

Inpatient hospital days amounted to €12,168 (SD 13,843) and stem cell transplantations to €4,412 (SD 10,937). Patients were admitted for an average of 23.6 (SD 26.8) inpatient days. Inpatient hospital days were especially important in patients receiving stem cell transplantation.

Table 3.15: Total mean costs for all patients never receiving bortezomib

	Never Bmib (n=67)	
Resource Use (numbers)	**Mean**	**SD**
Inpatient hospital days	23.6	26.8
Intensive care days	1.1	2.9
Outpatient visits	33.9	36.6
Consultations by telephone	2.3	4.0
Day-care treatments	6.8	9.9
Emergency room visits	0.6	1.0
Costs (Euro 2009)		
Inpatient hospital days	€ 12,168	€ 13,843
Intensive care unit days	€ 2,297	€ 6,071
Outpatient visits	€ 3,732	€ 4,023
Consultations by telephone	€ 30	€ 53
Day-care treatments	€ 1,132	€ 1,653
Emergency room visits	€ 65	€ 111
Radiotherapy	€ 1,698	€ 2,623
Surgical procedures	€ 1,383	€ 3,035
Other diagnostic procedures	€ 265	€ 1,255
Laboratory	€ 4,106	€ 4,899
Pathology	€ 97	€ 113
Bacterial cultures	€ 192	€ 276
Viral cultures	€ 91	€ 262
Xrays	€ 762	€ 789
CT scans	€ 245	€ 308
MRIs	€ 290	€ 459
Radionucleide scans	€ 21	€ 83
PET scans	€ 274	€ 894
Ultrasounds	€ 75	€ 113
Antibacterial medication (prophylaxis)	€ 1,869	€ 2,802
Antibacterial medication (acute infection)	€ 139	€ 120
Biphosponates (prophylaxis)	€ 2,440	€ 2,249
Transfusion of ery's	€ 368	€ 867
Erythropoietin	€ 296	€ 867
Transfusion of platelets	€ 294	€ 1,170
Chronic neurotoxicity medication	€ 118	€ 962
Chronic gastro-intestinal medication	€ 2,970	€ 3,960
Chronic analgesics	€ 522	€ 690
Thalidomide	€ 818	€ 957
Bortezomib	€ 0	€ 0
Dexamethasone	€ 67	€ 69
Adriamycin	€ 39	€ 105
Vincristine	€ 6	€ 20
Lenalidomide	€ 8,923	€ 24,282
Melphalan	€ 67	€ 124
Prednisone	€ 7	€ 15
Cyclophosphamide	€ 9	€ 23
Donor leukocyte infusions	€ 467	€ 1,310
Interferon alpha	€ 6	€ 49
Stem cell transplantation	€ 4,412	€ 10,937
Other active treatment	€ 0	€ 0
Total global costs	€ 52,760	€ 45,865
Median	€ 36,882	
Minimum	€ 748	
Maximum	€ 179,571	

Table 3.16 presents the proportion of the total costs for the most costly individual cost components that explain the majority of the total global costs for patient never treated with bortezomib. The share of total global costs explained by costs for hospital days, concomitant medication, resource use and active treatment is also shown. The individual cost components that explain the largest of proportion of total global costs include inpatient hospital stays (22%) and lenalidomide treatment (16%), followed by costs for laboratory tests (8%) and stem cell transplant (8%). Costs for active treatment costs consume nearly one-third of total global costs for patients never treated with bortezomib, followed by costs for all other resource use excluding costs for inpatient and intensive care unit hospital days and total hospital day costs, each accounting for 27% of total global costs.

Table 3.16: Proportion of total costs explained by cost components

Cost components (Euro 2009)	**Never Bmib (n=67)**
Inpatient hospital days	22%
Intensive care unit days	4%
Outpatient visits	7%
Day-care treatments	2%
Laboratory	8%
Bortezomib	0%
Lenalidomide	16%
Stem cell transplantation	8%
Total % explained by above components	***68%***
Total hospital day costs*	27%
Total concomitant medication costs	17%
Total resources use costs**	27%
Total active treatment costs	30%

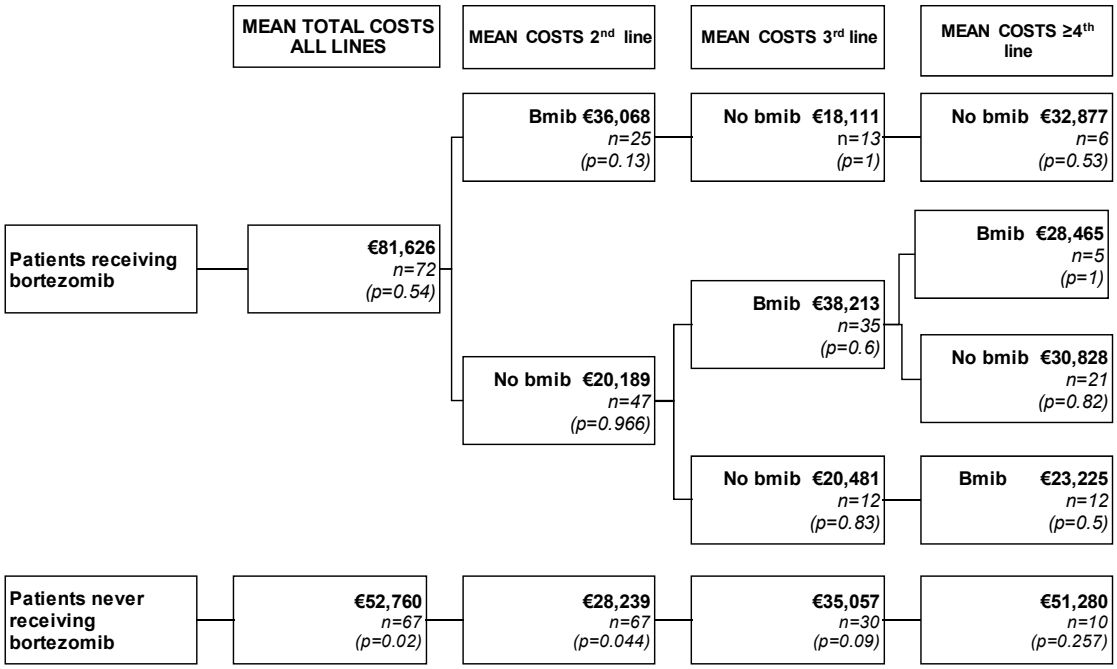
*includes inpatient and intensive care unit days
**excludes hospital day costs

3.4.3 Overview treatment costs within treatment lines

Figure 3.17 presents an overview of total mean costs and costs per treatment line for both patients receiving bortezomib and patients never treated with bortezomib. These cost analyses were based on the resource use of the full patient sample including patients still treated at the end of the data collection. In order to determine whether the inclusion of these patients influenced our cost estimates, cost analyses were additionally conducted solely for patients whose resource use was collected until the end of treatment. P-values

shown are for comparison of the differences between total costs when including versus excluding patients still treated at the end of the data collection.

Figure 3.17: Overview treatment costs (including patients still treated at the end of data collection)



P-values shown for comparison of the differences between total costs when including versus excluding patients still treated at the end of the data collection.

For patients treated with bortezomib, the cost difference between patients whose resource use was collected until the end of treatment and patients still treated at the end of the data collection was not significant (Mann-Whitney U test: p = 0.54). For patients never receiving bortezomib, this cost difference was significantly greater (Mann-Whitney U test: p = 0.02). This cost differences was predominantly owing to the substantially higher costs for lenalidomide (Mann-Whitney U test: p = 0.004), donor leukocyte infusions (Mann-Whitney U test: p = 0.02) and stem cell transplants (Mann-Whitney U test: p = 0.056) among patients who were still treated at the end of data collection.

Figure 3.17 presents the by-line line treatment costs for patients ever receiving bortezomib (n=72) including patients still being treated at follow-up. The mean follow-up duration was 10.4 (SD 5.33) months versus 13.3 (SD 9.6) months for bortezomib patients receiving bortezomib in second line versus those receiving other. Mean costs were €15,879 higher for patients receiving bortezomib (n=25/72) compared with patients not receiving bortezomib (n=47/72; Mann-Whitney U test: p = 0.000).

Figure 3.17 presents the third line treatment costs for patients ever receiving bortezomib (n=60). The mean total costs of third line and follow up duration for all bortezomib patients receiving third line was €30,311 (SD 25,831) and 7.6 (SD 4.9) months. Twelve of the 25 patients receiving bortezomib in the second line did not receive any treatment in the third line because they were either still treated in the second line at the end of the data collection (8/12), experienced no further benefit from treatment (3/12) or died (1/12). The remaining 13/25 patients received any treatment in the third line at a total cost of third line treatment equal to €18,111 (SD 16,521) and a mean total follow-up of 6.2 (SD 5.1) months.

All of the 47 patients who did not receive bortezomib in the second line treatment received some sort of treatment in the third line, with 35 receiving bortezomib. Mean total follow-up for the 35 bortezomib patients was 7.3 (SD 4.3) months compared to 10.1 (SD 5.9) among patients not receiving bortezomib (n=12). Third line costs were €18,964 higher for patients receiving bortezomib (n=35/47) compared with all patients not receiving bortezomib in third line irrespective of receiving bortezomib in second line (n=25/47; Mann-Whitney U test: p = 0.01).

Figure 3.17 presents the fourth+ line treatment costs for patients ever receiving bortezomib (n=44). Seven of the 13 patients receiving bortezomib in the second line but not in the third line did not receive any treatment in the fourth+ line because they were either still treated in the third line at the end of the data collection (5/7) or died (2/7). The remaining 6/13 patients received some sort of treatment in the fourth+ line at a total mean cost for fourth+ line equal to €32,877 (SD 12,915) and a total mean follow-up of 9.25 (SD 4.6) months. None of these patients received bortezomib.

Nine of the 35 patients receiving bortezomib in the third line but not in the second line did not receive any treatment in the fourth+ line because they were either still treated in the third line at the end of the data collection (5/9) or died (4/9). The remaining 26/35 patients received some sort of treatment in the fourth+ line, with 5 receiving bortezomib. Mean total costs for fourth+ line for patients receiving bortezomib (n=5/26) compared with patients not receiving bortezomib were not found to be significantly different (n=21/26; Mann-Whitney U test: p = 0.18). Mean total follow-up in fourth+ line was 20.8 (SD 18.2) and 11.8 (SD 9) for patients receiving bortezomib compared to those not receiving bortezomib. The longer follow-up in patients receiving bortezomib in third and fourth line or later contributes greatly to the higher costs in fourth+ line seen in these patients. The higher costs are also attributable to two unique patients: one patient who received

bortezomib in third, fifth and sixth line and to a second patient who received bortezomib in third, fourth, fifth and sixth line.

Twelve of the 12 patients who neither received bortezomib in the second nor third line treatment received bortezomib in the fourth line or later. Mean total costs for fourth+ line for these patients amounted to €23,225 (SD 21,312) and a total mean follow of 11.7 (SD 6) months.

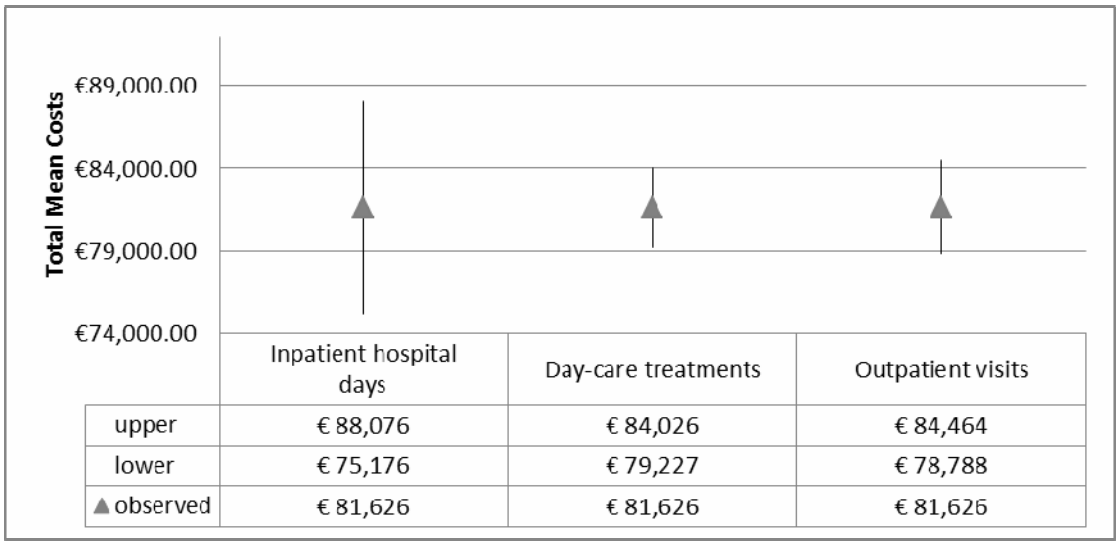
Finally, Figure 3.17 also presents the mean total costs by-line for patients never treated with bortezomib. The mean total costs for second, third and fourth+ line were €28,239 (SD 31,146), €35,057 (SD 36,263) and €51,280 (SD 45,541), respectively. Total mean follow-up for each respective line were 15.7 (SD 14.4), 10.6 (SD 10.4) and 7.3 (SD 5.5) months. The substantially higher costs in the fourth+ line were mainly attributable to costs of lenalidomide treatment, stem cell transplants and inpatient hospital stays.

3.4.4 Sensitivity analyses

Varying the unit costs of inpatient hospital days, day-care treatments and outpatient visits between 50% and 150% appeared to have a rather modest influence on the total mean costs with the greatest influence when varying the unit price for inpatient hospital days.

For patients treated with bortezomib, total mean costs varied from €75,176 to €88,076 when inpatient hospital day unit costs were varied, from €79,227 to €84,026 when day-care treatment unit costs were varied and from €78,788 to €84,464 when outpatient visit unit costs were varied. The results of the sensitivity analyses on total mean costs for patients treated with bortezomib are presented in Figure 3.18.

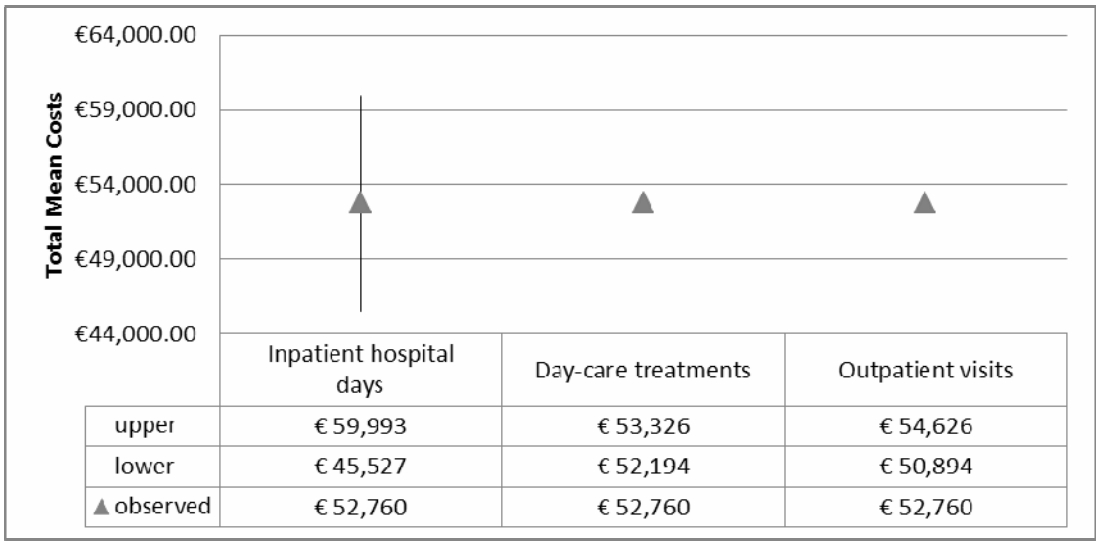
Figure 3.18: Results of sensitivity analysis on total mean costs for bortezomib patients



	Inpatient hospital days	Day-care treatments	Outpatient visits
upper	€ 88,076	€ 84,026	€ 84,464
lower	€ 75,176	€ 79,227	€ 78,788
▲observed	€ 81,626	€ 81,626	€ 81,626

For patients never treated with bortezomib, total mean costs varied from €45,527 to €59,993 when inpatient hospital day unit costs were varied, from €52,194 to €53,326 when day-care treatment unit costs were varied and from €50,894 to €54,626 when outpatient visit unit costs were varied. The results of the sensitivity analyses on total mean costs for patients never treated with bortezomib are presented in Figure 3.19.

Figure 3.19: Results of sensitivity analysis on total mean costs for patients never treated with bortezomib



	Inpatient hospital days	Day-care treatments	Outpatient visits
upper	€ 59,993	€ 53,326	€ 54,626
lower	€ 45,527	€ 52,194	€ 50,894
▲observed	€ 52,760	€ 52,760	€ 52,760

3.5 Clinical practice versus clinical trial

3.5.1 Effectiveness

Baseline characteristics

The majority of the baseline characteristics of patients treated with bortezomib in the pilot study do not differ significantly from those included in the APEX trials (Table 3.17). Slight differences were observed. For instance, the pilot patients were slightly younger than the APEX patients and presented on average with lower levels of serum β_2-microglobulin and higher levels of c-reactive protein. As a result of restricting the selection of patients for the pilot study to those relapsing from or becoming refractory to the HOVON50 trial, which restricts the eligible patient population to those aged less than 65, the pilot study patients were younger than the patients included in the APEX trial. However, valid comparisons of prognostic biomarkers were difficult due to the high frequency of missing values in the pilot study. From the baseline comparisons it is also revealed that receipt of combination treatment during the initial treatment was more common among the pilot patients in comparison to that of the patients included in the APEX trial, but this result is explained by the many combinations of treatment administered during the HOVON50 trial and subsequent treatment in daily practice.

Table 3.17: Comparison of baseline characteristics between pilot and APEX patients receiving bortezomib

Baseline Characteristic		Pilot (n=72)	APEX (n=333)
Male		56%	56%
Age*		59 (47, 67)	62 (48, 74)
Type of myeloma			
	IgG	63%	60%
	IgA	19%	23%
	IgD	1%	2%
	Light Chain	13%	12%
	Nonsecretory	NR	1%
	NR	4%	0%
Median time since diagnosis (yr)*		3 (1, 4)	3.5 (1.3, 7.8)
	NR	2.8%	0.6%
Median serum B2 (mg/liter)*		2.7 (1.7, 5.1)	3.7 (2.0, 8.8)
	NR	85%	3%
C-reactive protein (mg/liter)*		7 (1.5, 41)	4 (4, 23.1)
	NR	72%	10%
Hemoglobin (g/liter)*		119 (97, 143)	108 (86, 132)
	NR	67%	1%
Platelet count (cells/mm^3 x 10^5)*		1.76 (0.7, 2.86)	1.93 (0.88, 3.16)
	NR	65%	1%
Number of previous lines			
	1	35%	40%
	2 or 3	58%	56%
	≥4	7%	4%
Type of previous therapy			
	Corticosteriods	100%	98%
	Alkylating agents	100%	91%
	Anthracyclines	100%	77%
	Thalidomide	79%	48%
	Vinca alkaloids	100%	75%
	SCT or other high-dose therapy	93%	67%

*Estimates presented as the median (10th and 90th percentile)

Treatment-related outcomes

Comparisons of treatment-related outcomes between pilot and APEX patients receiving bortezomib are presented in Table 3.18. In support of previous results revealing pilot patients to be more likely to receive lower total doses of bortezomib compared to APEX patients (Table 3.8), pilot patients also discontinue treatment earlier compared to APEX patients, with a median total number of cycles equal to 4 and 6 in the pilot versus APEX patients, respectively. Despite these findings, the proportion of patients in both groups experiencing a favourable response (i.e., complete response (CR), very good partial response (VGPR), partial response (PR), and minor response (MR)) during bortezomib

treatment were similar. However, the pilot patients were less likely to experience a response of 'no change' and were more likely to experience 'progressive disease'. As for time-to-event outcomes, pilot patients treated with bortezomib were less likely to survive the first year following relapsed/refractory treatment compared to those in the APEX trial. This difference may be due to reduced sensitivity to bortezomib resulting from previous thalidomide treatment, as many pilot patients receiving bortezomib had previously received thalidomide. TTP is longer for the pilot patients, especially those treated with bortezomib as first refractory treatment. This is likely due to the more stringent criteria for progression used in clinical trials compared to that in daily practice.

Table 3.18: Comparison of treatment-related outcomes between pilot and APEX patients receiving bortezomib

Treatment-related outcomes	Bortezomib (Pilot)	Bortezomib (APEX)
Cycles of bortezomib		
≥5	40%	56%
≥8	15%	29% (39%*)
11	1%	9%
Median	4	6
Response to treatment		
Complete	8%	6%
VGPR/PR/MR	55%	41%
No change	3%	43%
Progressive disease	19%	7%
Not evaluated	15%	3%
1-year survival rate (%)	66%	80%
Median TTP (mos) All Pts		
All patients	6.8	6.22
One previous treatment	8.9	7
More than one previous treatment	4.7	4.9

All estimates were taken from Richardson, et al. (2005) unless denoted by (*).
*Estimate taken from extended follow-up reported by Richardson, et al. (2007b)

3.5.2 Costs

Annex VI describes the results of the systematic review carried out to provide, as comprehensive as possible, a retrieval of economic evaluations of bortezomib in the treatment of multiple myeloma. Only one publication was identified. Mehta, Duff, and Gupta (2004) compared bortezomib treatment to best supportive care and thalidomide in advanced multiple myeloma based on resource use of the SUMMIT trial based on the perspective of the United States healthcare payer (costs reported in 2003 US dollars).

Mehta, Duff, and Gupta (2004) found chemotherapy costs for patients receiving bortezomib to be fairly similar to those found in our cost analyses (mean costs of bortezomib per patient ever treated with bortezomib of $22,059 versus our estimate of €17,407). However, total mean costs were substantially lower than in our cost analyses ($65,222 per patient versus €81,626). This difference was predominantly explained by the difference in median overall survival from start of relapsed/refractory treatment (15.7 months versus our estimate of 33.2 months). The authors themselves commented that their unit costs based on (Medicare) reimbursement fees may not necessarily reflect the actual purchase price. They found an incremental cost-effectiveness ratio of $45,356 per additional life-year for bortezomib compared with best supportive care (Mehta, Duff, and Gupta 2004).

It should be mentioned that NICE (National Institute for Health and Clinical Excellence) conducted a single technology appraisal on bortezomib for multiple myeloma patients at first relapse in 2007. They estimated an incremental cost-effectiveness of bortezomib versus high dose dexamethason to be around £28,000 - £31,000 per life year gained (NICE 2007). Additionally they stated that using bortezomib in later lines reduces treatment benefits and thus results in a higher ICER.

4. Discussion

4.1 Dynamics in daily clinical practice

The pilot study shows that daily practice dynamics complicate outcomes research of bortezomib. In the last few years, there have been great advances in treatment for multiple myeloma which resulted in changes to the professional guidelines. Bortezomib was initially recommended as third line therapy but was subsequently shifted to use in second line. More recently, it was recommended for use as first line therapy. Current national guidelines for any relapsed or refractory disease advise two different treatment options: namely, bortezomib combined with dexamethasone or lenalidomide with dexamethasone. If thalidomide was not used upfront, the guidelines advise thalidomide with dexamethasone as a third option. However, most patients follow a relapsing disease course, implying that physicians must decide on new regimes after every subsequent relapse. Possibly as result of changes to the professional guidelines, our real-world data exposes large variation in treatment regimes and treatment order, creating significant hurdles in identifying a treatment comparator. It seems unfeasible with small patient numbers to compare bortezomib with many different comparators. Moreover, these treatments were often combined in various ways. Our data reveals that it is essential to select appropriate outcome measures since effects from previous treatment regimes cannot be ignored.

We illustrated that physicians needed several years before bortezomib administration was common practice. In addition, pilot patients received lower bortezomib dosages and fewer treatment cycles compared to the APEX trial, of which is unclear how it affects treatment effectiveness. It could indicate that pilot patients had lower tolerance or more frequently experienced side-effects of bortezomib treatment, especially when taking into account the fact that patients who are not eligible for trials receive it in daily practice. However, these results might also suggest that physicians are more cautious and reluctant to new novel pharmaceuticals. The results of these dynamics in daily practice underscore the need for refinement of practice and evidenced-based professional guidelines and the necessity of an active professional association advocating appropriate use.

Data for the pilot study was retrospectively collected from hospital medical records which restricted the availability of data compared to that collected in a clinical trial. In daily

practice, physicians do not have to follow a strict trial protocol. Patient files were often incomplete, suggestive of seemingly less strict criteria being used in maintaining patient charts. For example, clinical trials dictate response and outcome measures, whereas we often found that physicians used various outcome definitions and reported response in more subjective terms, such as “patient is responding well” or “patient has a good response on the treatment”. Furthermore, it was not always possible to determine via the physician’s notes the reason a patient progressed to a new treatment line or the reasons for selecting a specific treatment regime. The absence of such information limited the ability to analyse and interpret certain treatment outcomes. A prospective research design might tackle some of the above described drawbacks, but it cannot resolve all issues. However, it does signify the importance of active cooperation of physicians in outcomes research.

4.2 Clinical effectiveness

Interpretation of results

Patients treated with bortezomib

Regardless of adjustment, patients in second and third line appear to do better compared to patients treated in fourth line or later when examining OS from diagnosis. This also holds when examining OS from start of second line. Contradictory to what would be expected, patients receiving bortezomib in third line seem to do better compared to patients who receive it in second line. This is not surprising given that the median survival has yet to be reached for patients treated in second line, indicating that the patients treated in second line represent the later stages of diffusion of bortezomib use in daily practice and that patients in third line represent the early stages of diffusion. This difference is illustrated by the difference in the proportion of patients treated with bortezomib prior to 2007 for the group of patients treated in second line versus those treated in third line (44% and 86%, respectively; Table 3.2). Further, because the patients treated in second line were more likely to have been treated with thalidomide in the HOVON50 trial compared to patients treated with bortezomib in third line (56% and 29%, respectively; Table 3.2) and response to thalidomide is associated with reduced progression-free and overall survival after relapse treatment (Lokhorst et al. 2010; Vogl et al. 2009), the group of patients treated in second line selected for this pilot study may also have had a reduced capacity to benefit from bortezomib in terms of OS. An additional

reason for this difference may be due to the possibility that patients treated in third line were prognostically more favourable compared to the second line patients suggested by the fact that they lived long enough to receive three lines of therapy. The limitation in adequate follow-up reflects the well-known difficulty with assessing the effectiveness of new therapies for multiple myeloma during the current era of constant advances in treatment. In other words, the assessment of the effectiveness of one therapy is soon replaced and made less relevant by the need for an assessment of its successor, while the assessment of the successor is difficult due to incomplete follow-up. Given this limitation, the results presented here by this study demonstrate that third line usage of bortezomib is effective in daily practice and that its usage in second line is likely to be demonstrated as similarly effective once complete full follow-up is available for patients treated in second line.

Patients never treated with bortezomib

This group of patients is suspected to be a mixture of patients with extremely poor prognosis and patients with extremely favourable prognosis, as the OS in this group ranged from a few months to greater than the last available follow-up for patients in second line (i.e., 76 months). Therefore, the median and mean overall survival for this group as a whole is considerably long (mean = 45; median = 56). Due to such variation within this group, the mean OS should be assumed to most accurately reflect the average survival within this group, as the median does not take into account the distribution of survival estimates.

Adjustment methods

The use of adjustment by the propensity score and mean covariate methods did not result in strikingly different survival curves compared to the unadjusted curves. If prognostic factors fully explain the decision to administer bortezomib, one would expect that correction for such prognostic factors would result in curves that are more similar to one another with the remaining difference to be solely explained by the treatment effect instead of differences in prognosis. However, the curves appear to be of similar form with a slight extension of the mean and median estimates. Such results suggest that prognostic factors either do not fully explain the decision to receive bortezomib, i.e., no confounding by indication exists, or residual confounding by indication exists on account of missing information not available in the data.

Adjustment for the propensity to receive bortezomib in third line, fourth line or later could also have been used to adjust the survival curves for prognostic factors on the decision to receive bortezomib at different points in relapsed/refractory treatment. However, it is unlikely that the prognostic factors that are related to the decision to administer bortezomib in second line have a differential effect in later treatment lines. Therefore, one would expect correction of OS by the propensity to receive bortezomib in later lines to produce survival graphs similar to that of the unadjusted.

Comparison to previous studies

A number of studies have reported outcomes for bortezomib use in daily practice (Wu et al. 2005; Freimann et al. 2007; Onitilo et al. 2007; Knauf et al. 2009). Each of these studies report response rates and toxicity profiles comparable to that seen in large-scale clinical trials, which is also consistent with the response rates observed in the pilot patients. Only one study reported the median OS from start of bortezomib treatment (Wu et al. 2005). Wu et al. (2005) reported a median OS from start of bortezomib to be 15 months, which is slightly shorter compared to the estimate of 17.2 reported here for the pilot patients. Comparison of OS from diagnosis could not be evaluated because no studies reported the OS from diagnosis.

Strengths and weaknesses of the analysis

Adjustment methods

There are notable drawbacks to the chosen adjustment methods. Regarding the average covariate adjustment method, the obvious drawback is the use of the mean estimate for nominal variables, which is the situation for all variables included in the prediction model. The central issue is how to interpret the mean effect of a prognostic factor at the individual level (Chang, Gelman, and Pagano 1982). Furthermore, the adjusted regression model computes an average hazard rate, as opposed to the average survival. In other words, the method neither accounts for heterogeneity in survival within the group nor the effect of time-dependency on the individual's survival (Nieto and Coresh 1996).

Adjustment by means of the average PS is susceptible to the same drawbacks as that mentioned above for the average covariate method. In addition, the use of the average PS method is further limited by the drawbacks of using the logistic regression to identify factors that are predictive of getting a particular treatment, including missing predictors or confounders in the available data, selecting predictors solely on statistical

significance and the inappropriate inclusion/exclusion of interaction terms (Weitzen et al. 2004).

Despite the advantages of goodness of fit and good discrimination of the outcome (i.e., treatment with bortezomib in second line) for the predictive model in this study, the ability to define such a highly predictive model has in this case resulted in largely non-overlapping distributions of the PS within the groups. The overlap in distribution results in difficulty to apply the ideal PS adjustment method. The ideal method would be to stratify outcomes for patients groups by propensity score percentiles where the distribution of patients within each group is divided into equal groups (i.e., terciles, quartiles, quintiles, etc.). This would allow the more robust method of comparing across groups based on similar percentile groups. However, due to the low number of patients represented in each PS decile as a result of not only the small number of observations in the patient population but also a highly discriminative model, we were unable to use the more robust methods to incorporating the PS in the analysis.

A final drawback of using the PS method in this analysis was the correction for a propensity to receive a treatment at one point in time when in reality the patient is eligible to receive the treatment at multiple points in time. This method should further be applied separately for each line. Namely, a separate effectiveness outcome estimate should be adjusted for the propensity to receive bortezomib not only in second line, but also in third line, fourth line and later. This would require three different propensity estimates for each patient. Similarly, due to the small number of observations within each patient group, this method is not feasible.

The strength of the adjustment analyses is the added information regarding statistically significant factors that are predictive of receipt of bortezomib in daily practice. Greater overlap between the clinically and statistically significant factors would be expected; however, small numbers within patient groups may have resulted in rejected parameters due to statistical insignificance. Consequently, there remains the possibility of residual confounding not accounted for by the final prediction model. The method of selecting parameters for the predictive model as that employed here may have been inappropriate and could have been replaced by a more appropriate method. Unfortunately, many studies in the literature vary with regard to methods, indicating uncertainty in the guidelines/recommendations to estimation of a useful PS (Weitzen et al. 2004).

Choice of outcome

The choice of outcome here was restricted for many reasons. The availability of data in patient charts restricted the analysis to the use of OS, TTNT and TTP. The use of the outcome TTNT resulted in bortezomib patients receiving subsequent treatment lines earlier than patients receiving other therapies, suggesting that bortezomib is ineffective when using this outcome. Similar results were obtained when using the outcome TTP. The counterintuitive results seen with the outcome TTNT are suspected to be due to the diffusion phenomenon in daily practice, where patients given a new drug for which clinicians have little experience with are followed more carefully. The outcome TTNT, therefore, is not preferred when assessing the effective of a new drug in daily practice for multiple myeloma. The counterintuitive results for the outcome TTP is also suspected to be due to the diffusion phenomenon but additionally due to variation in either definitions or routine diagnostics for determining progression in daily practice. The outcome TTP, therefore, is not preferred for indications where the definition of progression is subjective and/or not defined by strict criteria used by all clinicians in daily practice, such as is the case for multiple myeloma.

The outcome OS was feasible within the restraints of the data. The most difficult decision was to determine the baseline from which OS would be computed due to confounding of initial therapy. Due to the inclusion of a 'control' arm consisting of patients who never received bortezomib, the largest confounder of the effect of bortezomib on the outcome OS, regardless of examining OS from diagnosis or start of relapsed/refractory treatment, was the HOVON50 treatment received in first line therapy. The reason for this is that treatment received by a patient at initial therapy is not only related to OS from diagnosis but also to the decision to receive bortezomib in subsequent lines. Treatment received in subsequent lines after HOVON50 is also related to OS from start of relapsed/refractory therapy. Most importantly, treatment with thalidomide is standard in many cases prior to receiving bortezomib. Therefore, the OS estimates should be further stratified by HOVON50 treatment arm, regardless of baseline being diagnosis or start of relapsed/refractory treatment. However, the differential effect of HOVON50 treatment on the treatment effect of bortezomib is concealed by the limitation of small numbers (Figure 3.12). This limitation is visible by the insignificant logrank and Wilcoxan statistic (refer to section 3.3) when further stratifying by HOVON50 treatment, as this created 8 comparator groups with small numbers of observations resulting in estimates lacking the precision to reveal a significant effect of HOVON50 treatment. If an adequate sample size were

available, the stratification of effectiveness results by initial therapy received would be necessary.

4.3 Clinical costs

To our knowledge, our cost analyses of multiple myeloma treatment are the first based on real-world resource use. For patients ever receiving bortezomib, total mean treatment costs amounted to €81,626. Treatment costs during bortezomib regimens were slightly more expensive in the third line (€ 38,213) than in the second line (€36,068). The average cost of a patient treated with bortezomib in third and fourth line or later was more expensive (€95,962 and €97,937) compared to patients treated during second line (€53,726) mainly due longer follow-up available for these patients which resulted in greater resource use and administration of further active or palliative treatment.

For patients never receiving bortezomib, total mean treatment costs amounted to €52,760. Although total mean treatment costs were lower for patients never receiving bortezomib, the treatment line costs were structurally higher for patients never receiving bortezomib compared with those for patients ever receiving bortezomib in another treatment line than the one under consideration. Treatment line costs for patients never receiving bortezomib were €28,239 (versus €20,189) in the second line, €35,057 (versus €18,111 and €20,481) in the third line and €51,280 (versus €32,877 and €30,828) in the fourth+ line.

The inclusion of patients still treated at the end of the data collection influenced our cost estimates only slightly. For patients treated with bortezomib, the cost difference between patients whose resource use was collected until the end of treatment and patients still treated at the end of the data collection was not significant (Mann-Whitney U test: $p = 0.54$). For patients never receiving bortezomib, the substantially higher costs of two of the four excluded patients who were mainly attributable to costs from fourth line onwards for lenalidomide treatment, stem cell transplant and inpatient hospital stays.

In general, it is known that treatment costs are skewed and few patients with high or expensive resource use may have a considerable impact on the average costs per patient. From our patient sample, it can be concluded that total mean treatment costs varied widely between patients, with the most expensive patients more likely to receive lenalidomide treatment and stem cell transplantations.

The robustness of our results was tested in sensitivity analyses. Our sensitivity analyses show that the total mean treatment costs are maintained over a wide variation in unit costs of inpatient hospital days, day-care treatments and outpatient visits. Furthermore, the conclusions drawn from our cost analyses still hold, even if unit costs were 0.5 or 1.5 times the current costs.

Costs are preferably determined from a societal perspective in which all relevant costs are included (Drummond et al. 2005). However, considering limited time and information, it was impossible to collect retrospective data on societal costs for our cost analyses. Therefore, our cost analyses were conducted from the hospital perspective. Disregarding productivity costs is expected to have influenced our results, as this study included younger (< 65 years of age) working multiple myeloma patients. Furthermore, disregarding patients' out of pocket expenses (e.g. expenses for travel, time and home modifications) may have influenced the treatment costs of patients who consumed more inpatient hospital days and day-care treatments.

4.4 Cost-effectiveness of bortezomib

Economic evaluations compare costs of a treatment with the effects of the treatment. Although safety and efficacy are still the primary research parameters used to assess the value of alternative treatment strategies, as illustrated by the high number of published articles in the effectiveness review, cost-effectiveness has become increasingly important in current health care decision making (Drummond et al. 2005; Moeremans and Annemans 2006). Nevertheless, only one study assessed the costs of bortezomib treatment in multiple myeloma. Mehta et al. (2004) concluded that bortezomib provides a cost-effective option in the treatment of relapsed multiple myeloma and provides the best value among currently available therapeutic options in terms of cost per life-year gained. However, the review of Moeremans et al. (2006) demonstrated that more evidence is required to confirm the cost-effectiveness of novel as well as established treatment strategies for multiple myeloma at different stages of the disease. Moreover, NICE concluded in their bortezomib technology appraisal that using bortezomib in later lines could reduce treatment benefits and thus result in a higher ICER (NICE 2007).

Estimating real-world cost-effectiveness of bortezomib in relapsed multiple myeloma requires comprehensive data on both treatment effects and costs. Generally, outcomes measures such as DOR, TTP, TTNT and OS are essential in determining cost-

effectiveness. However, as previously mentioned, our pilot data only allows the assessment of TTNT, OS and survival from start of a new treatment line, whereas the other outcomes are either frequently missing or the validity of which is questionable. The effectiveness outcome measures TTNT and OS are expected to be valid estimates of bortezomib in the selected patient group from daily clinical practice in the Netherlands. Nevertheless, it is not possible to compute cost-effectiveness from start of diagnosis, since we did not collect cost data from the first treatment regime. It is, however, feasible to assess cost-effectiveness of bortezomib for relapsed multiple myeloma.

We were able to estimate the real-world cost-effectiveness of bortezomib for relapsed multiple myeloma. In cost-effectiveness analyses, it is preferred to report costs per QALY. As no data was available regarding quality of life, we estimated cost-effectiveness by means of the outcomes OS from start of relapsed/refractory treatment for all patients treated with bortezomib and for OS from start of respective treatment lines when bortezomib was administered. The cost from the start of second line for all patients treated with bortezomib was €2,767 (mean costs: €81,626; mean OS: 29.5 months) per month of survival. Similarly, for patients treated in second line only, the cost-effectiveness of bortezomib from start of relapsed or refractory treatment was €2,858 (mean costs: €53,726; mean OS: 18.8 months) per month of survival. As for patients receiving bortezomib in third line and fourth line or later, the cost-effectiveness of bortezomib from the start of relapsed or refractory treatment was €3,096 (mean costs: €95,962; mean OS: 31 months) and €3,099 (mean costs: €97,937; mean OS: 31.6 months) per month of survival, respectively. It should be noted that these estimates must be interpreted cautiously since the costs are based on all patients including the patients still treated at the time of data collection and we ignored treatment costs and effects from the first treatment regime and disregarded effects from treatment combinations, which could bias the validity of these cost-effectiveness estimates as previously described.

4.5 Incremental analysis

The dynamics in daily clinical practice as described in this report compromise the ability to compute a valid and precise real-world incremental cost-effectiveness measure. Mainly as a result of the study design chosen for collecting the bortezomib pilot data, it is impossible to perform an incremental analysis. Firstly, prognosis varied greatly within the group of patients never receiving bortezomib as well as that between the patients receiving

bortezomib in second and third line, of which could not be differentiated merely on differences in baseline characteristics. The incomparability of the patient groups could not be corrected for due to missing values and other missing information on seemingly clinical significant important decision-making criteria that appeared to be absent in patient charts. Secondly, extensive treatment variation and different treatment combinations in daily practice of multiple myeloma complicate the identification of a treatment comparator. Finally, only 139 patients were included in the pilot study. It is impossible to overcome the majority of the limitations of the data with small patient numbers, whereas the availability of large numbers could have offered more opportunities to carry out incremental analysis by using comprehensive modelling techniques. Accordingly, incremental analyses were not performed since it was not expected that they would provide valid and precise estimates.

4.6 Pilot outcomes research of bortezomib

The Dutch policy regulations for expensive hospital medicines *("Beleidsregel dure geneesmiddelen"*) aim to relieve the financial burden of hospitals. However, it also stipulates that outcomes research needs to be conducted in order to be entitled to the continuation of financial compensation after three years. By order of CVZ, iMTA has researched methodological aspects of outcomes research to provide empirical experience additional to the Guidance for Outcomes Research *("Leidraad voor Uitkomstenonderzoek"*). Two pilot studies were at the core of this research. The results of the research regarding methodological issues related to outcomes research are reported separately. This report describes the results of the bortezomib pilot study, investigates how bortezomib is used in the Dutch daily practice and explores real-world treatment effects and costs of bortezomib in relapsed or refractory multiple myeloma. To our knowledge, this is the first study assessing both the effects and the costs of bortezomib in relapsed multiple myeloma using real-world patient level data in the Dutch setting.

Outcomes research: Knowledge at time T=0

In 2006, at time T=0 for this indication, bortezomib was assessed by CVZ and as a result was admitted to the Dutch policy list for expensive drugs based on the phase III APEX trial. The APEX trial showed that bortezomib was superior to high dose dexamethasone in terms of increased overall survival, response rates and response duration in relapsed multiple myeloma patients (Richardson et al. 2005). In the CVZ assessment report, the

expected costs for bortezomib treatment were based on the claim of the manufacturer, which was estimated at €27,432 per treated patient (Commissie Farmaceutische Hulp 2005). These costs were computed based on the price of bortezomib vials assuming that patients receive on average six cycles; no other costs were included in the T=0 assessment.

In the following years, outcomes research needs to be conducted in order to assess appropriate use and to evaluate real-world cost-effectiveness. The flowchart for pragmatic outcomes research design, available in the Guidance for Outcomes Research, advises collection of detailed patient data if there is no indication for a cost-effectiveness measure at T=0 (Delwel 2008). Additionally, if there would have been a T=0 model, a Value of Information (VOI) analysis would have been of limited use since treatment of multiple myeloma in the current era is known for constant advances in treatment and, thus, expected to reveal high variation in daily practice. Consequently, the flowchart would again advise collection of detailed data. In the following years, we retrospectively collected detailed patient level data from hospital medical records. In contrast to CVZ's recommendation in the Guidance for Outcomes Research, we did not collect data on disease- and treatment-related Quality of Life, since this was not possible with a retrospective study design. To date, there is no evidence in the literature for a significant difference in utilities between treatment strategies administered to relapsed/refractory multiple myeloma patients. One study did demonstrate a utility value for relapsed/refractory multiple myeloma patients while receiving bortezomib (Mujica-Mota et al. 2004).

Outcomes research: Knowledge from literature at time T=3

Only very limited information on costs of bortezomib became available in these years (see literature review in Annex VI). Mehta et al. published in 2004 information on costs for bortezomib therapy prior to T=0; however, their resource use data was partly derived from a clinical trial but also partly estimated by an expert panel. The manufacturer submitted in 2007 an application for bortezomib to the (outpatient) drug reimbursement system. The pharmaco-economic assessment and budget impact reports incorporated costs for the administration of bortezomib in an outpatient clinic (Commissie Farmaceutische Hulp 2007a; Commissie Farmaceutische Hulp 2007c). However, the calculations were based on the assumption that bortezomib would mainly be administered outside a hospital, which is not in accordance with our daily practice data.

On the contrary, many articles concerning the effectiveness of bortezomib were published (see literature review Annex III). These articles provide updated effectiveness information on bortezomib mono-therapy or combination therapy (e.g. dexamethasone, melphalan, adriamycin and thalidomide) from phase I, II and III studies on various outcome measures such as PFS, TTP, DOR and OS.

Outcomes research: Insight gained from the pilot study at time T=3

We investigated both the treatment effects and costs of bortezomib in relapsed multiple myeloma using real-world patient level data taken from daily clinical practice. The data collection challenged the feasibility of outcomes research for bortezomib since many patients were treated in more than one hospital, thereby requiring over 1700 hours for data collection in 42 different hospitals. This report illustrates the impact of daily practice dynamics for outcomes research. It is achievable with real-world data to investigate daily practice utilisation of bortezomib in relapsed multiple myeloma. The diffusion of bortezomib, the application of bortezomib regimes, dose modifications, actual received dosages and related toxicities were explored. Our data reveals that, in daily practice within the hospitals where data was collected, relapsed multiple myeloma patients are treated with many different drugs in various combinations and in a diverse treatment order.

However, analysing treatment effects with real-world data is far more challenging. Retrospective observational studies are susceptible to several limitations related to bias and validity. Patients are not randomised to a specific treatment and physicians decide which treatment to use based on patient characteristics. Based on our data, it was only possible to correct for available prognostic factors. However, prognostic factors were often not reported, resulting in missing values. Although we suspect that we collected insufficient information on other important clinical decision-making criteria, we do consider the possibility that it might be unachievable to reveal all medical decision making criteria by review of medical records. Consequently, outcomes research with retrospective observational data will always be challenged by residual confounding issues. Furthermore, selecting appropriate outcome measures is more complicated with real-world data. As illustrated in this report, it is not clear whether physicians use universal response criteria. In addition, physicians' notes seem to provide insufficient information on decision criteria for a specific treatment regime. Moreover, in any retrospective study, it is impossible to obtain quality of life information and thus establish a relationship between a treatment response and a quality of life measurement. These issues challenge the selection of

appropriate outcome measures, such as the preferred quality-adjusted survival for conducting cost-effectiveness analyses, and have an impact on the validity of estimated outcomes.

As previously mentioned, it was possible to compute real-world costs and estimate real-world cost-effectiveness of bortezomib for relapsed multiple myeloma. However, these estimates have to be interpreted cautiously in light of the fact that we were restricted to select outcomes measures, we ignored treatment costs and effects from the first treatment line and we disregarded the effects of treatment combinations, thereby resulting in potentially biased real-world cost-effectiveness estimates. Furthermore, only 72 patients who received bortezomib were included in the pilot study. Such small numbers hinders the ability to correct for differences and constrains the value of a cost-effectiveness measure, since small numbers will result in wide confidence intervals and, thus, challenge precision of the estimate.

On the contrary, it is impossible with this pilot data to estimate a valid and precise real-world incremental cost-effectiveness ratio for bortezomib in relapsed multiple myeloma. Extensive treatment variation, incomparability of the patient groups and small patient numbers severely complicate performing an incremental analysis.

4.7 Conclusion

Bortezomib was admitted under the policy regulations for expensive drugs based on the results of the APEX trial. This clinical trial compared bortezomib to dexamethasone and proved bortezomib to be effective, i.e., increased overall survival, response rates and response duration. We performed a pilot outcomes research study and assessed the appropriate use and explored real-world effects and costs of bortezomib in relapsed or refractory multiple myeloma. The generalisability of the pilot results to other expensive drugs and the conclusions regarding methodological issues related to outcomes research are described in a separate report.

In the last years, there have been many advances in treatment of multiple myeloma, which is reflected by the heterogeneity in our data. Consequently, our real-world data challenged the assessment of cost-effectiveness of bortezomib treatment in the indication of relapsed disease. We showed that the dynamics within daily practice resulted in incomparability of pilot patients. Additionally, restrictive appropriate outcome measures and small patient numbers compromised the ability to estimate a valid and precise

incremental outcome comparing patients treated with and not treated with bortezomib. Outcomes research with retrospective observational data will always be challenged by residual confounding issues, however, we believe that a prospective research design will not overcome all above described issues.

Nevertheless, we demonstrated that outcomes research provides valuable information on drug usage in daily practice. We explored the diffusion of bortezomib, application of treatment regimes, dose modifications, actual dosages received and treatment-related toxicities. Compiling different data sources, such as daily practice data on more patients, information from extended follow up and other research studies, might offer opportunities to estimate more valid outcomes by data synthesis using comprehensive and advanced modelling techniques. Outcomes research performed in areas with constant advances in treatment should take heterogeneity of patient level data into account as a result of the rapid developments in that specific medical field. It should be noted that these advances in treatment for multiple myeloma in the last few years have extended overall disease survival.

Furthermore, this pilot study underscores the need for refinement of practice and evidence-based professional guidelines for relapsed multiple myeloma advocated by an active professional association as a means to reduce practice variation, support appropriate clinical decision-making and, ultimately, improve the treatment of individual patients. Moreover, active physician participation and prospective observational data using national and/or international registries could facilitate closer follow-up of patients, ensure uniform response criteria, enable the selection of groups of similarly treated patients and thus contribute to enhanced value of outcomes research.

References

Alexander, D. D., P. J. Mink, H. O. Adami, P. Cole, J. S. Mandel, M. M. Oken, and D. Trichopoulos. 2007. Multiple myeloma: A review of the epidemiologic literature. *International Journal of Cancer* 120, (12): 40.

Blade, J., D. Samson, D. Reece, J. Apperley, B. Bjorkstrand, G. Gahrton, M. Gertz, S. Giralt, S. Jagannath, and D. Vesole. 1998. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. myeloma subcommittee of the EBMT. european group for blood and marrow transplant. *British Journal of Haematology* 102, (5) (Sep): 1115-23.

Chang, I. M., R. Gelman, and M. Pagano. 1982. Corrected group prognostic curves and summary statistics. *Journal of Chronic Diseases* 35, (8): 669-74.

Commissie Farmaceutische Hulp. 2007a. *Farmaco economisch rapport bortezomib (velcade®) bij de indicatie multipel myeloom.* Diemen: College voor Zorgverzekeringen, 27052098.

———. 2007b. *Farmacotherapeutisch rapport bortezomib (velcade®) bij de indicatie recidiverend en refractair multipel myeloom.* Diemen: College voor Zorgverzekeringen, 27052156.

———. 2007c. *Kostenconsequentieraming van opname van bortezomib (velcade®) en lenalidomide (revlimid®) in het geneesmiddelenvergoedingssysteem.* Diemen: College voor Zorgverzekeringen, 27053023.

———. 2005. *Farmacotherapeutisch rapport bortezomib (velcade®).* Diemen: College voor Zorgverzekeringen, 25060777.

Cox, D. R. 1972. Regression models and life tables (with discussion). *Journal of the Royal Statistical Society Series B (Methodological)* 34, (2): 187-220.

D'Agostino, R. B. 1998. Tutorial in biostatistics: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Statistics in Medicines* 17, (19): 2265–2281.

Delwel, G. O. 2008. *Leidraad voor uitkomstenonderzoek.* Diemen: College voor Zorgverzekeringen, 270.

Drummond, M. F., M. J. Sculpher, G. W. Torrance, B. J. O'Brien, and G. L. Stoddart. 2005. *Methods for the economic evaluation of health care programmes.* Oxford University Press, USA.

Durie, B. G. M., and S. E. Salmon. 1975. A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *A Cancer Journal for Clinicians* 36, (3): 842-54.

Freimann, H., A. Calderoni, P. Cornu, and R. Olie. 2007. Daily practice use of bortezomib in relapsed/refractory multiple myeloma. *Swiss Medical Weekly* 137, (21/22): 317.

Greipp, P. R., J. S. Miguel, B. G. M. Durie, J. J. Crowley, B. Barlogie, J. Blade, M. Boccadoro, J. A. Child, H. Avet-Loiseau, and R. A. Kyle. 2005. International staging system for multiple myeloma. *Journal of Clinical Oncology* 23, (15): 3412.

Gu, X. S., and P. R. Rosenbaum. 1993. Comparison of multivariate matching methods: Structures, distances, and algorithms. *Journal of Computational and Graphical Statistics* 2, (4): 405-20.

Jagannath, S., B. Barlogie, J. R. Berenson, D. S. Siegel, D. Irwin, P. G. Richardson, R. Niesvizky, et al. 2008. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. *British Journal of Haematology* 143, (4): 537-40.

Kane, R. C., A. T. Farrell, R. Sridhara, and R. Pazdur. 2006. United states food and drug administration approval summary: Bortezomib for the treatment of progressive multiple myeloma after one prior therapy. *Clinical Cancer Research* 12, (10): 2955.

Kaplan, E. L., and P. Meier. 1958. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*: 457-81.

Knauf, W. U., B. Otremba, F. Overkamp, and M. Kornacker. 2009. Bortezomib in relapsed multiple Myeloma–Results of a non-interventional study by office-based haematologists. *Onkologie* 32, (4): 175-80.

Lee, J., C. Yoshizawa, L. Wilkens, and H. P. Lee. 1992. Covariance adjustment of survival curves based on cox's proportional hazards regression model. *Bioinformatics* 8, (1): 23.

Lokhorst, H. M., I. Schmidt-Wolf, P. Sonneveld, B. van der Holt, H. Martin, R. Barge, U. Bertsch, J. Schlenzka, G. M. J. Bos, and S. Croockewit. 2008. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica* 93, (1): 124.

Lokhorst, H.M., B. van der Holt, S. Zweegman, E. Vellenga, S. Croockewit, M.H. van Oers, P. von dem Borne, P. Wijermans, R. Schaafsma, O. de Weerdt, S. Wittebol, M. Delforge, H. Berenschot, G.M. Bos, K.S. Jie, H. Sinnege, M. van Marwijk-Kooy, P. Joosten, M.C. Minnema, R. Ammerlaan, P. Sonneveld. 2010. A randomized phase III study on the effect of thalidomide combined with adriamycin, dexamethasone (TAD), and high-dose melphalan, followed by thalidomide maitenance in patients with multiple myeloma. *Blood* 115, (6): 1113-20.

Mehta, J., S. B. Duff, and S. Gupta. 2004. Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. *Managed Care Interface* 17, (9) (Sep): 52-61.

Moeremans, K., and L. Annemans. 2006. An update: Health economics of managing multiple myeloma. *European Journal of Cancer* 42, (11) (Jul): 1684-91.

Morgan, G. 2003. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the international myeloma working group. *British Journal of Haematology* 121, (5): 749-57.

Mujica-Mota, R., A. Bagust, A. Haycox, R. Dhawan, and D. Dubois. 2004. Mapping health-related quality of life (HRQoL) measurements into generic utility measures (EQ-5D): A case study with bortezomib (Velcade). *Value in Health* 7 (6): 683 Abs PCN43 7, (6): 683.

Multiple Myeloma Research Foundation. What is multiple myeloma. in Multiple Myeloma Research Foundation [online]. 2009 [cited November/18 2009]. Available from http://www.multiplemyeloma.org/living-with-multiple-myeloma/newly-diagnosed-patients/what-is-multiple-myeloma/definition.html.

Multiple Myeloma Working Group. 2009. Description of the field of work. HOVON [online]. 2009 [cited November/18 2009]. Available from http://www.hovon.nl/working-groups/working-groups/myeloma.html?setlanguage=en.

Myeloomwerkgroep HOVON. 2005. De moderne behandeling van het multipel myeloom: Een richtlijn van de stichting hemato-oncologie voor volwassenen Nederland (HOVON). *Nederlands Tijdschrift Voor Geneeskunde* 149, (15): 808-13.

NICE. 2007. *Bortezomib monotherapy for relapsed multiple myeloma.* London: National Institute for Health and Clinical Excellence, STA129.

Nieto, F. J., and J. Coresh. 1996. Adjusting survival curves for confounders: A review and a new method. *American Journal of Epidemiology* 143, (10): 1059.

Onitilo, A. A., J. Engel, B. Olatosi, and S. Fagbemi. 2007. Community experience with bortezomib in patients with multiple myeloma. *American Journal of Hematology* 82, (7): 637-9.

Richardson, P. G., C. Mitsiades, R. Schlossman, N. Munshi, and K. Anderson. 2007a. New drugs for myeloma. *The Oncologist* 12, (6): 664.

Richardson, P. G., P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, J. L. Harousseau, et al. 2007b. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: Final time-to-event results of the APEX trial. *Blood* 110, (10) (Nov 15): 3557-60.

Richardson, P. G., P. Sonneveld, M. W. Schuster, D. Irwin, E. A. Stadtmauer, T. Facon, J. L. Harousseau, et al. 2005. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *The New England journal of medicine* 352, (24) (Jun 16): 2487-98.

Rosenbaum, P. R., and D. B. Rubin. 1983. The central role of the propensity score in observational studies for causal effects. *Biometrika* 70, (1): 41.

Smith, A. J., and E. P. Todd. 2005. Does matching overcome LaLonde's critique of nonexperimental estimators? *Journal of Econometrics* 125, (1-2): 305-53.

Sonneveld, P., B. van der Holt, C. M. Segeren, E. Vellenga, A. J. Croockewit, G. E. Verhoe, J. J. Cornelissen, et al. 2007. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: Long-term follow-up of the dutch cooperative group HOVON 24 trial. *Haematologica* 92, (7) (Jul): 928-35.

Stichting Farmaceutische Kengetallen. 2009. *Monitor dure geneesmiddelen 2007: Kosten van dure- en weesgeneesmiddelen in het ziekenhuis.* Den Haag: Stichting Farmaceutische Kengetallen.

Tan, S. S., L. Hakkaart-van Roijen, M. J. Al, C. A. Bouwmans, M. E. Hoogendoorn, P. E. Spronk, and J. Bakker. 2008. A microcosting study of intensive care unit stay in the netherlands. *Journal of Intensive Care Med* 23, (4): 250-7.

Tan, S. S., C. W. M. van Gils, M. G. Franken, L. Hakkaart-van Roijen, and C. A. Uyl-de Groot. 2010. The unit costs of inpatient hospital days, outpatient visits and daycare treatments in the field of oncology and haematology. *Value in Health* [Forthcoming].

Van Agthoven, M., M. T. Groot, and C. A. Uyl-de Groot. 2001. *Kosten van allogene stamceltransplantaties.* Rotterdam: Institute for Medical Technology Assessment.

Van Agthoven, M., E. Vellenga, W. E. Fibbe, T. Kingma, and C. A. Uyl-de Groot. 2001. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-hodgkin's lymphoma or hodgkin's disease a prospective randomised trial. *European Journal of Cancer* 37, (14): 1781-9.

Vogl, D.T., E.A. Stadtmauer, P.G. Richardson, P. Sonneveld, M.W. Schuster, D. Irwin, T. Facon, J.L. Harousseau, A. Boral, R. Neuwirth, K.C. Anderson. 2009. Impact of prior therapies on the relative efficacy of bortezomib compared with dexamethasone in patients with relapsed refractory multiple myeloma. *British Journal of Haematology* 147, (4): 531-534.

Weitzen, S., K. L. Lapane, A. Y. Toledano, A. L. Hume, and V. Mor. 2004. Principles for modeling propensity scores in medical research: A systematic literature review. *Pharmacoepidemiology and Drug Safety* 13, (12) (Dec): 841-53.

Wu, K. L., W. Van Wieringen, E. Vellenga, S. Zweegman, H. M. Lokhorst, and P. Sonneveld. 2005. Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice. Haematologica 90, (7): 996.

ANNEX

Annex I: Disease staging systems

Durie & Salmon staging system

Myeloma Staging System*

Stage	Criteria	Measured myeloma cell mass (cells × $10^{12}/m^2$)†
I	*All* of the following: 1. Hemoglobin value > 10 g/100 ml 2. Serum calcium value normal (≤ 12 mg/100 ml) 3. On roentgenogram, normal bone structure (scale 0) or solitary bone plasmacytoma only 4. Low M-component production rates a. IgG value < 5 g/100 ml b. IgA value < 3 g/100 ml c. Urine light chain M-component on electrophoresis < 4 g/24 hours	<0.6 (Low)
II	Fitting neither Stage I nor Stage III	0.6–1.20 (Intermediate)
III	*One or more* of the following: 1. Hemoglobin value <8.5 g/100 ml 2. Serum calcium value >12 mg/100 ml 3. Advanced lytic bone lesions (scale 3) 4. High M-component production rates a. IgG value >7 g/100 ml b. IgA value > 5 g/100 ml c. Urine light chain M-component on electrophoresis > 12 g/24 hours	>1.20 (High)

Subclassification
A = Relatively normal renal function (serum creatinine value < 2.0 mg/100 ml)‡
B = Abnormal renal function (serum creatinine value ≥ 2.0 mg/100 ml)

Examples
Stage IA = low cell mass with normal renal function
Stage IIIB = high cell mass with abnormal renal function

* See text for discussion of statistical significance and importance of myeloma type (IgG/IgA/Bence Jones only) and subtype (κ/λ).

† 10^{12} cells = approximately 1 kg or 2.2 lbs; m^2 = square meter of body surface area.

‡ If the serum creatinine value is not available, the blood urea nitrogen (BUN) value may be used as an indicator of renal function. (A BUN value of 30 mg/100 ml is roughly equal to a serum creatinine value of 2 mg/100 ml. See text for discussion.)

Source: Durie and Salmon 1975

International Staging System

New International Staging System

Stage	Criteria	Median Survival (months)
I	Serum β2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III*	44
III	Serum β2-microglobulin ≥ 6.5 mg/L	29

** There are two categories for stage II: serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β2-microglobulin 3.5 to < 5.5 mg/L irrespectie of the serum albumin level*

*Source:*Greipp et al. 2005

Comparison between Durie & Salmon and International Staging System

Comparison between Durie & Salmon and ISS Staging System: survival duration by stage in months

Durie & Salmon			International Staging System		
Stage	% of patients*	Median survival (months)	Stage	% of patients*	Median survival (months)
IA	7.5	62	I	29	62
IB	0.5	22			
IIA	22	58	II	33	44
IIB	4	34			
IIIA	49	45	III	39	29
IIIB	17	24			

** Percentage of patients falling into each staging category*

Source: Greipp et al. 2005

Annex II: Response criteria for multiple myeloma

EBMT, IBMTR and ABMT criteria for definition of response, relapse and progression with multiple myeloma patients (Blade et al. 1998):

Complete response (CR) requires all of the following:

1. Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
2. < 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
3. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
4. Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial response (PR) requires all of the following:

1. ⩾50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
2. Reduction in 24 h urinary light chain excretion either by ⩾90% or to <200 mg, maintained for a minimum of 6 weeks.
3. For patients with non-secretory myeloma only, ⩾50% reduction in plasma cells in a bone marrow aspirate and on trephine biopy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. ⩾50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for MR.

Minimal response (MR) requires all of the following:

1. 25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
2. 50–89% reduction in 24 h urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.
3. For patients with non-secretory myeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. 25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in the size or number of lytic bone lesions lesions (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

No change (NC)

1. Not meeting the criteria of either minimal response or progressive disease.

Plateau

1. Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

Time point for assessing response

1. Response to the transplant procedure will be assessed by comparison with results immediately prior to conditioning.
2. If transplant is part of a treatment programme response to the whole treatment programme will be assessed by comparison with the results at the start of the programme.

Relapse from CR requires at least one of the following:

1. Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
2. ⩾5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
4. Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

Progressive disease (for patients not in CR) requires one or more of the following:

1. >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation.
2. >25% increase in the 24 h urinary light chain excretion excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation.
3. >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium >11·5 mg/dl or 2·8 mmol/l) not attributable to any other cause.

Annex III: Literature review of effectiveness of bortezomib

Identification of studies

The aim of the search was to provide, as comprehensive as possible, a retrieval of the available evidence concerning the clinical effectiveness of bortezomib in the treatment of previously treated multiple myeloma.

Sources searched

Three electronic databases were searched. The literature search was performed in March 2009 via the PubMed, Cochrane Library and EMBASE databases.

Keyword strategies

The following search strategies were used:

PubMed

("bortezomib" [Title/Abstract]) OR ("velcade" [Title/Abstract]) AND "multiple myeloma" [Title/Abstract] AND (English [lang] OR Dutch [lang])

Cochrane

(bortezomib):ti,ab,kw or (velcade):ti,ab,kw and (multiple myeloma):ti,ab,kw

Embase

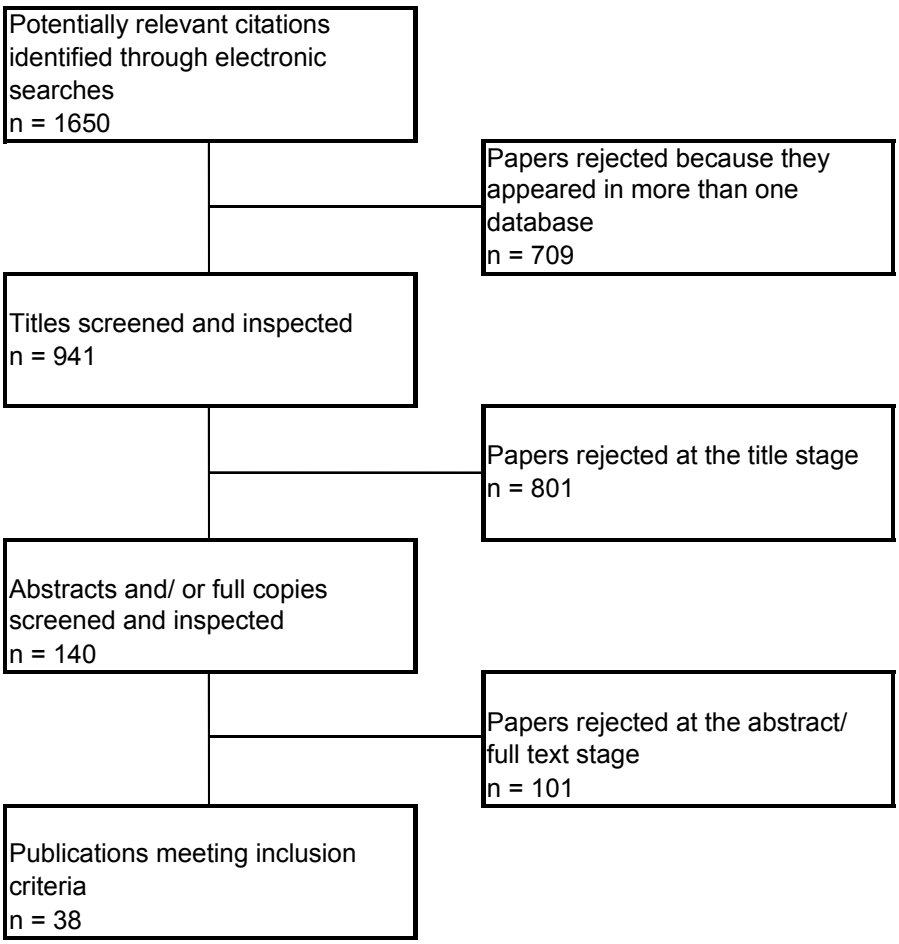
'bortezomib':ab,ti OR 'velcade':ab,ti AND 'multiple myeloma':ab,ti

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used: (1) articles were considered if they concern adult patients with multiple myeloma, (2) bortezomib in the first-, second- or third-line treatment was one of the main topics of the article (3) studies evaluated bortezomib as a single agent or in combination with other regimens, (4) the title contained a word or words referring to the effectiveness of bortezomib, such as response, length of remissions, survival or progression-free survival, articles should not primary deal with the adverse events of bortezomib, (5) only research articles were considered (editorials, letters, comments, guidelines, reviews, case reports etc. are excluded as well as phase I trials), (6) studies were considered if they included more than 20 patients and (7) only papers using the English or Dutch language were considered. Full papers were obtained for any titles or abstracts that were considered relevant or where the title or abstract information was not sufficient to make a decision.

Results of clinical effectiveness review

The database search identified 1650 articles, with 679 found via PubMed, 113 via the Cochrane Library and 858 via the EMBASE database. Out of the 1650 articles, 709 articles appeared in more than one database. After exclusion of redundant articles, a total of 941 unique articles were considered. Based on title alone, a total of 801 articles were excluded. The abstracts and/ or full texts of the remaining 140 articles were considered. Finally, 38 publications met the inclusion criteria, with a total of 25 focusing on bortezomib for the treatment refractory/relapsed multiple myeloma.



Results: bortezomib

A final total of 38 studies were suitable for inclusion in this systematic review. Studies of bortezomib for previously treated multiple myeloma were distinguished from studies of bortezomib in patients with previously untreated multiple myeloma. The first section of this review concerns studies of bortezomib for relapsed or refractory multiple myeloma. Table 1 presents the main characteristics of the study as well as the most important outcomes and toxicities. Table 2 presents the same data for studies concerning bortezomib in patients with previously untreated multiple myeloma.

The primary outcome for most studies was response rate. The majority of studies used the European Group for Blood and Marrow Transplantation (EBMT) criteria for defining response rate. The first criterion was based on reduction in serum M-protein by at least 50% from baseline (i.e., those patients who had a complete response or a partial response). Beside this criterion, the EBMT response criteria take additional clinically relevant information into account.

Evidence about the effectiveness of bortezomib in relapsed and/or refractory multiple myeloma

In May 2003, bortezomib received accelerated approval from the U.S. Food and Drug Administration (FDA) for the treatment of progressive multiple myeloma in patients who had received at least two prior therapies (Kane et al. 2006, 2955-2960). That approval was based on FDA analysis of evidence of durable responses, including complete responses, in heavily pretreated patients in two phase II studies. The first study is the Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy (SUMMIT), a multicenter, open-label, non-randomised trial. The second study is the Clinical Response and Efficacy study of bortezomib in the Treatment of relapsing multiple myeloma (CREST), which was a small, open-label, randomised phase II dose finding study.

A group of 202 patients with relapsed, refractory myeloma were enrolled in the SUMMIT. The mean age of the patient population was 60 years and 72% presented with Durie-Salmon stage III multiple myeloma. Of the 193 patients who could be evaluated, 178 had previously been treated with three or more of the major classes of agents for myeloma, with the median number of previous therapies being six (range: 2 - 15) (Richardson et al. 2003, 2609-2617).

The patients in the study received bortezomib (1.3 mg/m² on days 1, 4, 8 and 11) in a three-week cycle up to eight cycles. Of the 193 evaluable patients, 67 patients (35%)

had a complete, partial, or minimal response to bortezomib alone, 19 patients (10%) achieved complete or near-complete response. Only age and percentage of plasma cells in bone marrow were prognostic factors of responses to bortezomib. The median time to progression of disease was seven months compared to three months during the last treatment before enrolment. The median overall survival was 16 months (Richardson et al. 2003, 2609-2617).

The CREST evaluated two doses of bortezomib (1.0 and 1.3 mg/m²) in patients with relapsed or refractory multiple myeloma who had received only front-line therapy (Jagannath et al. 2004, 165-172). Patients were randomised to receive one of the two doses of bortezomib, on days 1, 4, 8 and 11 up to eight three-week cycles. A group of 54 patients with a median age of 63 years were enrolled. Fifty-six and sixty-two percent of patients in the 1.0 and 1.3 mg/m² dose groups, respectively, were Durie-Salmon stage III multiple myeloma at diagnosis. The median number of prior therapies was three (range: 1 - 7) in both groups. The ORR (CR/nCR + PR + MR) was 33% in the 1.0 mg/m² dose group and 50% in the 1.3 mg/m² dose group. Eleven and four percent of the patients, respectively, achieved a complete or near complete response. Dexamethasone (20 mg on the day of and the day following each bortezomib dose) was given to patients with progressive disease after two cycles or stable disease after the first four cycles. Forty-four percent of the patients who received bortezomib alone or in combination with dexamethasone in the 1.0 mg/m² dose group achieved ORR, 19% achieved complete or near-complete response. In the 1.3 mg/m² dose group 62% of the patients who received bortezomib alone or in combination with dexamethasone achieved ORR, 4% achieved complete or near-complete response. Updated survival analysis after prolonged survival showed a median overall survival of 26.8 months in the 1.0 mg/m² group and a median overall survival of 60.0 months in the 1.3 mg/m² group. Administration of bortezomib ± dexamethasone for first relapse has been associated with longer overall survival (Jagannath et al. 2008, 537-540).

The full approval in 2005 of bortezomib from the U.S. FDA for the treatment of patients who have received at least one prior therapy was based on findings of an international, randomised phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial (Kane et al. 2006, 2955-2960), in which single-agent bortezomib was compared to high-dose dexamethasone in patients with multiple myeloma progressing after at least one prior therapy. In this study, a total of 669 patients were randomly assigned to receive bortezomib (333) or high-dose dexamethasone (336) (Richardson et

al. 2005, 2487-2498). The median age was 62 and 61 years in the bortezomib group and dexamethasone group, respectively. The median number of previous therapies was two in both groups. Responses (CR + PR) were achieved in 38% of the patients in the bortezomib group and in 18% of the patients in the dexamethasone group. In 13% and 2% of the patients who received bortezomib or dexamethasone, respectively, complete or near-complete response was observed. Patients who received bortezomib as second-line therapy had a higher response rate than did those who received dexamethasone (45% vs. 26%), as did those who had received two or more previous treatments (34% vs. 13%) (Richardson et al. 2005, 2487-2498). In comparison with treatment with dexamethasone, treatment with bortezomib also resulted in a significantly longer time to progression and superior survival.

Extended follow-up of the patients in the phase III trial showed a median overall survival of 29.8 months in the bortezomib arm and a median overall survival of 23.7 months in the dexamethasone arm, despite more than 62% of dexamethasone patients crossing over to receive bortezomib (Richardson et al. 2007, 3557-3560). Responses in the bortezomib arm improved from 38% to 43% and the complete or near-complete response rate improved from 13% to 16%.

To summarize, two phase II studies showed the benefits of bortezomib. Moreover, the APEX trial demonstrated that bortezomib is superior to dexamethasone in the treatment of relapsed or refractory multiple myeloma. In addition to the SUMMIT, CREST and APEX trial, other clinical trials have evaluated bortezomib as single-agent for patients with multiple myeloma. Furthermore, clinical trials have also evaluated bortezomib in combination with other agents for relapsed or refractory multiple myeloma, such as dexamethasone, melphalan, doxorubicin, and thalidomide. The following section will review the evidence for the various regimens of bortezomib.

Single-agent bortezomib

In a multi-institutional analysis of the efficacy and toxicity of bortezomib in patients who were treated in community centers in a compassionate needs program, a total of 50 Dutch patients were enrolled with a median age of 59 years (Wu, Van Wieringen et al. 2005). The median number of prior treatments was three (range: 1-5). Forty-six percent responded to the bortezomib treatment (CR + PR + MR). Results of this study were comparable with the results of SUMMIT and CREST, which reported similarly defined response rates of 35-50%.

In a phase I/II trial, 34 Japanese patients with relapsed or refractory multiple myeloma received single-agent bortezomib (0.7, 1.0 or 1.3 mg/m²) (Ogawa, Tobinai et al. 2008). The median age of the patients was 60 years. Forty-four percent of the patients were Durie-Salmon stage II and 56% of the patients were Durie-Salmon stage III. The median number of lines of prior therapy was two (range: 1-8) The overall response rate was 30% (CR + PR). Of the ten responders, five patients had one line of prior therapy, two patients had three lines of prior therapy and three patients had four or more lines of prior therapy.

A phase II trial evaluated the efficacy and toxicity of bortezomib (1.6 mg/m²) in a total of 40 patients who had received either one or two previous treatment regimens (Hainsworth, Spigel et al. 2008). Median age of the patients was 69 years. An objective responses to treatment was achieved in 55% (CR + PR) of the patients.

A single institution, phase II study evaluated bortezomib as pre-auto-SCT and as maintenance therapy post auto-SCT in 40 patients (Uy, Goyal et al. 2008). The median age of these patients was 56 years. 68% and 30% of the patients had Durie-Salmon stage III and stage II multiple myeloma respectively. The median number of prior therapies was one (range: 0-3). Response evaluation immediately before stem cell mobilization showed a ORR of 70% (CR + VGPR + PR). Post transplant, the ORR was 78%.

Bortezomib and dexamethasone

The SUMMIT and CREST evaluated bortezomib alone and in combination with dexamethasone for patients with suboptimal response. The SUMMIT concluded that 18% of the patients had a minimal or partial response to this combination. However, just patients with progressive disease after two cycles or stable disease after four cycles received dexamethasone which also counted for CREST. CREST showed an ORR (CR + PR + MR) for patients who received a combination of bortezomib and dexamethasone of 11% in the 1.0 mg/m2 dose group and 12% in the 1.3 mg/m2 dose group (Jagannath, Barlogie et al. 2004).

Bruno and colleagues (2006) retrospectively evaluated bortezomib in 23 patients who had relapsed after allografting (Bruno, Patriarca et al. 2006). The median age of the patients at transplant was 53 years. The overall response rate (CR + EN-PR + PR + MR) was 61%. No significant differences in toxicity and response rates were seen between patients treated with bortezomib plus steroids and bortezomib alone.

Freimann and colleagues (2007) determined the safety and efficacy results of daily practice use of bortezomib in Switzerland (Freimann, Calderoni et al. 2007). Addition of oral dexamethasone (20 mg the day of and the day after bortezomib administration) was recommended after 2 or 4 cycles in case of progressive or stable disease, respectively. A total of 88 patients entered the program. The median age was 66 years and the median number of previous treatments was three (range: 2-6). Of the 83 evaluable patients, the overall intent-to-treat response rate (≥ MR) was 61%.

A retrospective study under 37 patients evaluated two different doses of bortezomib (1.0 or 1.3 mg/m²) following reduced intensity allogeneic stem-cell transplantation (El-Cheikh, Michallet et al. 2008). The median age of the patients was 49 years, which is relatively young compared to the median age of the patients in most trials. The myeloma stage at diagnosis according to the Durie-Salmon classification was III for 86% of the patients. The median time between allo-SCT and initiation of bortezomib was 20 (range: 1-65) months. Seventy-three percent (CR + VGPR + PR) of the patients achieved an objective disease response after bortezomib. Differences were not found in disease response among patients receiving prior thalidomide and/or donor lymphocyte. Moreover using bortezomib in combination or without dexamethasone did not influence the response rates.

In 2009, a multicenter, phase IIIb trial was conducted to assess the response rates of bortezomib (1.3 mg/m²) with or without dexamethasone in 635 patients (Mikhael, Belch et al. 2009). Dexamethasone (20 mg/d) was added to bortezomib for patients who experienced progressive disease after ≥ 2 cycles or for stable disease after ≥ 4 cycles. The median age of the patients was 63 years and the patients received a median number of three (range: 0-11) prior therapies. The best ORR (CR + VGPR + PR + MR) rate in 635 evaluable patients was 67%. Of the 141 patients who had progressive disease or stable disease before dexamethasone was added to their regimen, the ORR with added dexamethasone was 33%. A total of 169 (27%) patients received stem-cell transplantation prior to bortezomib ± dexamethasone. The ORR in this group was 63%. Among the 397 (63%) patients who had received prior thalidomide, 64% achieved ORR.

Bortezomib and melphalan combination regimens

Bortezomib has also been studied in combination with melphalan. In 2006, the results of a phase I/II trial assessing bortezomib (0.7 to 1.3 mg/m²) in a 4-wk cycle and melphalan (0.025 to 0.25 mg/kg) combination therapy were published (Berenson, Yang et al. 2006).

Thirty-five patients with a median age of 60 years were enrolled in this study. The median number of prior treatments was three (range: 2-7). Responses were observed in 23 of 34 (69%) evaluable patients. Fifty-eight percent of the patients receiving the higher dose of bortezomib (1.0 mg/m²) achieved ≥ PR, in comparison with 33% of the patients in the lower dose group (0.7 mg/m²). The results of this trial suggest that the combination of low-dose melphalan with a higher dose of bortezomib (1.3 mg/m²) could improve response rates while minimizing toxicities.

In 2008, updated results of the phase I/II trial after longer follow-up were published (Berenson, Yang et al. 2008). Forty-eight patients were enrolled with a median age of 62 years. Responses occurred in 32/46 (70%) evaluable patients. The CRs, nCRs and VGPRs were all observed in the higher dose cohorts (1.0 or 1.3 mg/m² bortezomib). This phase I/II study showed that the combination of lower doses of melphalan and a longer and more convenient 4-wk cycle of bortezomib results in high response rates.

The addition of prednisone and thalidomide to bortezomib and melphalan increased the activity of the combination regimen, with response rates (CR + VGPR + PR) of 67% (Palumbo, Ambrosini et al. 2007). Fourteen patients received bortezomib, melphalan, prednisone and thalidomide (VMPT) as second-line therapy. The response rate in this group was 79%. All of the patients who received VMPT as second-line therapy had a 1-year progression-free survival in comparison with 27% of the patients who received VMPT as third-line. However, subgroup analysis did not show any statistical or clinical difference between responses and either age, line of treatment or dosage of bortezomib.

In a phase I/II trial the ORR of bortezomib in combination with low-dose melphalan and dexamethasone was assessed (Popat, Oakervee et al. 2009). Fifty-three patients were included in this study with a median age of 61 years. The median number of prior therapies was three (range: 1-5). The ORR (CR + nCR + VGPR + PR) was 68% compared with an ORR of 64% prior to the addition of dexamethasone. In the 33 patients who were treated at the maximum tolerated dose (melphalan, 7.5 mg/m²), the ORR was 76%, which was significantly higher than for those not treated at the maximum tolerated dose.

Bortezomib, thalidomide and dexamethasone

In a phase I/II study clinical activity was determined for bortezomib (1.0 or 1.3 mg/m²) in combination with thalidomide and dexamethasone (Pineda-Roman, Zangari et al. 2008). Eighty-five patients participated in this study. The median age was 60 years and 27% of

the patients were older than 65. In total, 92% and 65% had received one or two prior autotransplants, respectively. Seventy-four percent of the patients had received prior thalidomide. For the intention-to-treat population, 79% (CR + nCR + PR + MR) responded to bortezomib. This study did not show a significant difference in highest response rates for patients who did or did not receive dexamethasone. Prior thalidomide seems to be significantly associated with lower PR and nCR rates.

Bortezomib and pegylated liposomal doxorubicin (PLD) or doxorubicin combination regimens

In a phase III study 646 patients were randomly assigned to receive either bortezomib (1.3 mg/m²) or bortezomib in combination with PLD (Orlowski, Nagler et al. 2007). The median age of the patients was 61 years. Thirty-four percent of the patients had one prior therapy and 66% had two or more prior therapies. The overall response rate (CR + PR) in the intention-to-treat population was 41% for the patients who received bortezomib and 44% for the patients who received bortezomib in combination with PLD. Moreover, the median time to progression was improved from 6.5 months to 9.3 months for patients who received bortezomib in combination with PLD instead of bortezomib alone. The improved efficacy of bortezomib in combination with PLD was also seen across a variety of subgroups, such as patients aged ≥ 65 years old. In addition, patients treated with prior immunomodulatory drugs, anthracycline-based therapies and stem-cell transplantation benefited from the combination. The results of the above phase III study were stratified on the basis of whether patients had received prior thalidomide/lenalidomide (Sonneveld, Hajek et al. 2008). The analysis showed no statistical difference with respect to the prolonged time to progression attributed to the combination of PLD and bortezomib, compared with bortezomib alone between the subgroups.

The addition of doxorubicin (20 mg/m²) or pegylated liposomal doxorubicin (30 mg/m²) and dexamethasone to bortezomib (PAD) was also investigated in a multicenter trial (Palumbo, Gay et al. 2008). Data was available of 64 patients with relapsed/ refractory myeloma. The median age of the patients was 65 years and the median number of prior therapy lines was two (range: 1-7). 67% of the patients achieved at least PR. Fifteen patients (23%) achieved PAD as second-line therapy, of which 80% had at least a PR compared to 63% and 64% of the patients who received PAD as third-line or fourth- to eight-line therapy. Thirty-four patients received doxorubicin, of which 79% achieved at least PR in comparison with 30 patients who received PLD, of which 53% had at least PR.

A retrospective study of 57 patients with relapsed/ refractory myeloma determined the efficacy of bortezomib in combination with conventional chemotherapeutic agents for multiple myeloma compared with bortezomib alone (Min, Lee et al. 2007). This study resulted in observable improvements in response when bortezomib was combined with common chemotherapeutic agents.

Bortezomib and other agents for multiple myeloma

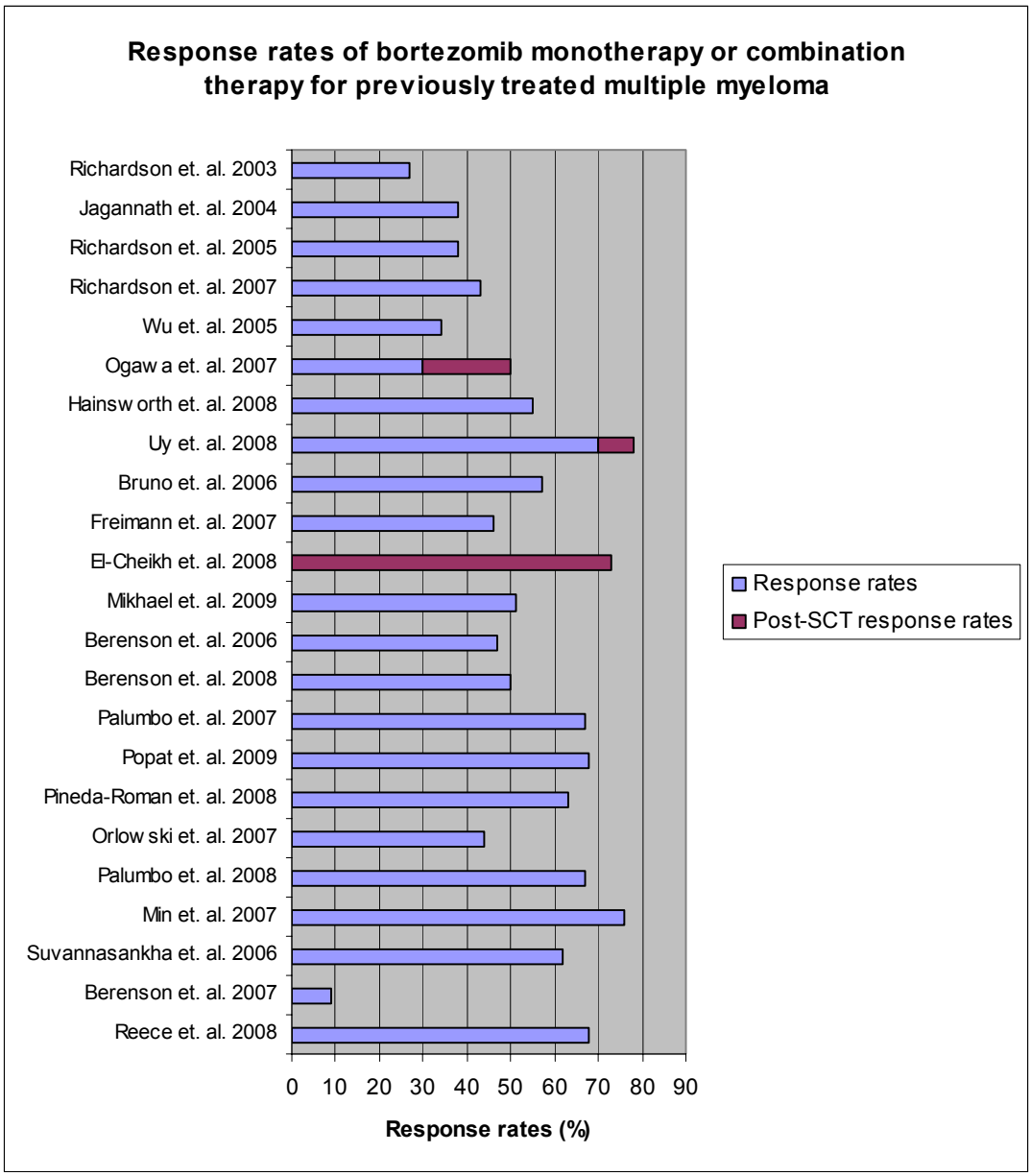
There are several other studies which evaluated bortezomib with other agents that are not mentioned above. Suvannasankha and colleagues reported a response rate (CR + nCR + PR) of 62% as a consequence of bortezomib in combination with methylprednisolone in the treatment of multiple myeloma (Suvannasankha, Smith et al. 2006).

A phase I/II study evaluated arsenic trioxide/ bortezomib/ ascorbic acid combination therapy (Berenson, Matous et al. 2007). In this study, 22 patients were enrolled with a median age of 63 years. The patients had received a median of four (range: 3-9) prior failed therapies. Objective responses (PR + MR) were observed in 27% of the patients.

Another phase I/II study tested bortezomib in combination with cyclophosphamide in combination with prednisone in relapsed/ refractory multiple myeloma (Reece, Rodriguez et al. 2008). Thirty-seven patients were enrolled in this trial. They had a median age of 60 years and their median number of prior regimens was two (range: 1-6). At the highest dose levels, the overall response rate was 95% (CR + PR + MR), with CR observed in more than 50% of patients.

The following figure presents the response rates of bortezomib monotherapy or bortezomib combination therapy that resulted from the different studies that are included in this review. The response rates include a partial response or higher.

Figure 1: Response rates of bortezomib monotherapy or combination therapy for previously treated multiple myeloma



Evidence about the effectiveness of bortezomib in previously untreated multiple myeloma

A number of studies showed that bortezomib in combination with other agents is also active in previously untreated multiple myeloma. These studies are discussed below.

Bortezomib and dexamethasone

SUMMIT and CREST showed improved outcomes after the addition of dexamethasone to bortezomib in relapsed or refractory multiple myeloma. A phase II study assessed the response of bortezomib therapy alone and in combination with dexamethasone for previously untreated multiple myeloma (Jagannath et al. 2005, 776-783). Thirty-two patients entered the trial with a median age of 60 years. Fifty-six percent of the patients had a diagnosis of Durie-Salmon stage IIIA and IIIB multiple myeloma. Dexamethasone was added to the regimen in 22 patients. The overall response (CR + nCR + PR) of bortezomib with or without dexamethasone was 88%.

A separate phase II study determined the CR rate achieved after four cycles of bortezomib plus dexamethasone combination therapy in patients with newly diagnosed multiple myeloma who were candidates for autologous stem-cell transplantation (ASCT) (Harousseau et al. 2006, 1498-1505). In total, 50 patients entered the trial of which 48 patients were evaluable. The median age of the patients was 55 years. The Durie-Salmon stage was I in 4 patients, II in 14 patients and III in 32 patients. The overall response was 66% (CR + VGPR + PR). No relationship was found between the CR or VGPR rate and the Durie-Salmon stage. Forty-two patients proceeded to stem-cell transplantation. After ASCT, the overall response was 90%.

The results of a phase II trial investigating the efficacy of bortezomib and dexamethasone as up-front therapy in multiple myeloma were comparable (Rosinol et al. 2007, 4452-4458). 40 patients entered the trial with a median age of 54 years. Twenty-six patients (65%) achieved at least PR (on an intent-to-treat basis). At the end of induction treatment 60% of the patients achieved at least PR. Of the 37 patients who underwent ASCT, 88% achieved at least PR (Rosinol et al. 2007, 4452-4458).

Bortezomib, melphalan and prednisone

A multicenter phase I/II study evaluated bortezomib in combination with melphalan and prednisone in elderly untreated patients with multiple myeloma (Mateos et al. 2006, 2165-2172). In total, 60 patients entered the trial and 53 patients were evaluable for response. The median age of the patients was 75 years. The response rate (CR + nCR + PR) was 89%. Updated time-to-events data evaluated the influence of known prognostic factors on the time to progression (Mateos et al. 2008, 560-565). A univariate analysis showed that the time to progression was not significantly influenced by advanced age.

A phase 3 study compared the use of melphalan and prednisone with or without bortezomib in previously untreated patients with multiple myeloma who were ineligible for high-dose therapy (San Miguel et. al. 2008, 906-917). A group of 682 patients entered the trial. Partial response or better were observed in 71% of the patients in the bortezomib group compared to 35% in the control group.

Bortezomib, thalidomide and dexamethasone

Bortezomib has also been studied in combination with thalidomide and dexamethasone. A study in 38 newly diagnosed patients with multiple myeloma showed rapid onset of remission in 33 patients (87%) including 6 patients with complete remission (16%) (Wang et. al. 2007, 235-239).

A large phase II study evaluated the addition of VTD (bortezomib, thalidomide and dexamethasone) to PACE (cisplatin, doxorubicin, cyclophosphamide and etoposide) combination chemotherapy as induction therapy prior to and as consolidation therapy after high-dose melphalan-based tandem transplants (Barlogie et al. 2007, 176-185). In total, 303 newly diagnosed patients with multiple myeloma were enrolled in total therapy 3 (TT3). The median age was 59 years. The cumulative frequency of nCR reached 83% at 24 months and CR reached 56% at 24 months (Barlogie et al. 2007, 176-185). Follow-up results were published of TT3, which were compared with TT2 outcomes in the context of both standard prognostic factors (SPF) and of gene expression profiling (GEP) data, available in 351 of 668 patients enrolled in TT2 and in 275 of 303 patients accrued to TT3 (Pineda-Roman et al. 2008, 625-634). The 2-year sustained CR rate with TT3 was 92% compared to 81% for TT2 with thalidomide and 79% for TT2 without thalidomide.

Bortezomib, doxorubicin and dexamethasone

A phase I/II trial tested PAD combination therapy which included bortezomib, doxorubicin and dexamethasone (Oakervee et al. 2005, 755-762). In total, 21 newly diagnosed multiple myeloma patients with a median age of 55 years entered the trial. The Durie-Salmon stage was IIA in 13 patients. The bortezomib dose was 1.3 mg/m² which was given on days 1, 4, 8 and 11. 95% of the patients achieved a PR or greater (all treatment levels included). After completion of PAD induction, patients underwent peripheral blood stem cell (PBSC) harvesting. Thereafter, high-dose melphalan was administered with forced diuresis. Eighteen patients received high-dose melphalan with stem-cell

transplantation. On the basis of an intent-to-treat analysis, the ORR rate was 95% (CR + nCR + VGPR + PR) at 3 months post-transplantation.

In 2007 updated results after long-term follow-up were published (Popat et al. 2008, 512-516). In this follow-up study a second cohort was evaluated. Patients in this cohort received bortezomib (1.0 mg/m²) and doxorubicin (9 mg/m²). In this cohort 89% achieved a PR or greater. The post-transplantation overall response rate was 89%. The CR and nCR rates appeared higher in the first cohort compared to the second cohort both pre- and post-HDT-PBSCT, however these differences were not statistically significant (Popat et al. 2008, 512-516).

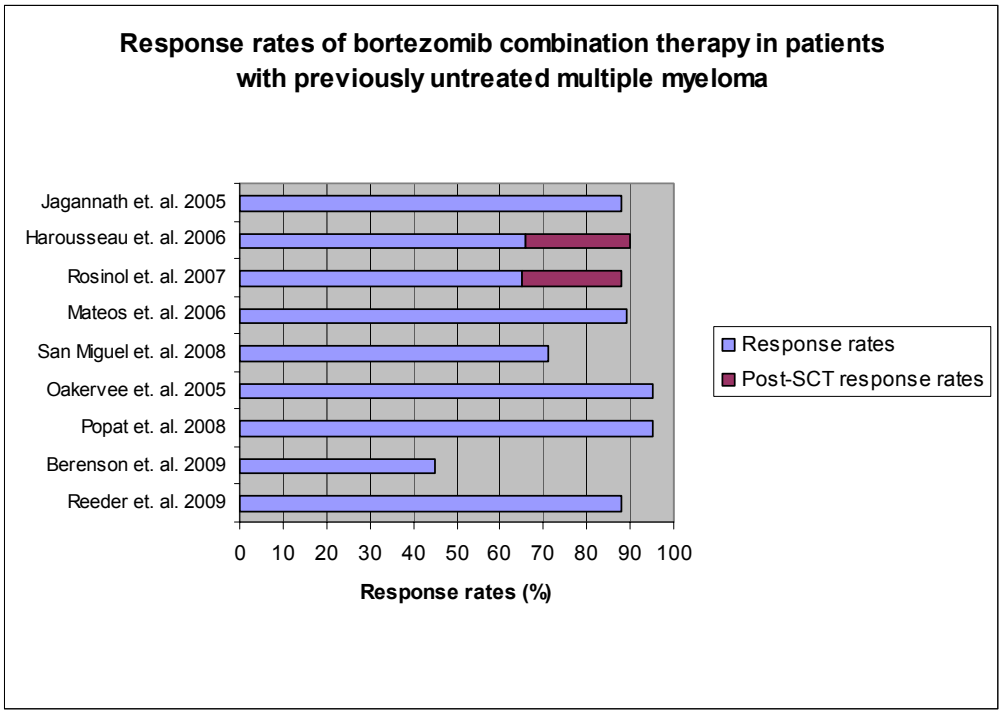
Bortezomib and other agents for multiple myeloma

Berenson and colleagues evaluated bortezomib in combination with ascorbic acid and melphalan in 35 patients with newly diagnosed multiple myeloma (Berenson et al. 2009). Median age was 70 years. In 23 of 31 evaluable patients (74%), responses (≥ MR) were observed.

A phase II clinical trial determined the response rates of bortezomib in combination with cyclophosphamide and dexamethasone (Reeder et al. 2009). In total, 33 newly diagnosed patients with multiple myeloma entered the trial. The mean age was 60 years. All patients had symptomatic disease (Durie-Salmon stage II or III). The overall intent-to-treat response rate in this study (≥ PR) was 88%.

The following figure presents the response rates of bortezomib combination therapy for patients with previously untreated multiple myeloma that resulted from the different studies that are included in this review.

Figure 2: Response rates of bortezomib combination therapy in patients with previously untreated multiple myeloma



Conclusion

The response rates for bortezomib in patients with relapsed or refractory multiple myeloma were greater compared to the response rates of dexamethasone alone (Richardson, Sonneveld et al. 2005). The response rates increased with the addition of dexamethasone to bortezomib treatment (Richardson, Barlogie et al. 2003; Jagannath, Barlogie et al. 2004). Chemotherapy agents that have been combined successfully with bortezomib include melphalan, doxorubicin and thalidomide.

Given the excellent efficacy and safety profile of bortezomib in relapsed and refractory multiple myeloma, questions were raised regarding use as a first-line treatment in newly diagnosed disease (Dicato et al. 2006, 474-482). The second section of this review gave an overview of the evidence of bortezomib in patients with previously untreated multiple myeloma. For this group of patients bortezomib is also promising, with primarily the bortezomib-based combinations resulting in high response rates. The optimal bortezomib-based combination has not been determined, as such depends in part on individual patient characteristics (Manochakian, Miller, and Chanan-Khan 2007, 978-990).

Table 1. Clinical studies of bortezomib for previously treated multiple myeloma (relapsed and/or refractory)									
Author, Year	**Design**	**Treatment**	**Regimen**	**N of patients enrolled/ evaluable**	**Response rate (CR + PR)**	**Time-to-event data**	**Post-SCT response rates**	**Post-SCT time-to-event data**	**Key toxicities**
SUMMIT, CREST and APEX trial									
Richardson et. al. 2003	Multicenter, phase II	Bortezomib ± dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11, up to eight 3-wk cycles; dexamethasone, 20 mg, on the day of and the day after each dose of bortezomib, for patients with progressive disease after two cycles or stable disease after four cycles	202/193	27%; CR/nCR rate, 10% (bortezomib alone)	TTP, 7 months; OS, 16 months	NA	NA	Grade 3/4: thrombocytopenia, 28%/3%; fatigue, 12%/0%; neuropathy, 12%;0% neutropenia, 11%/3%; vomiting, 8%/<1%; anemia, 8%/0%; diarrhea, 7%/1%; pain in limb, 7%/0%; dehydration, 7%/0%; nausea, 6%/0%; weakness, 5%/<1%
Richardson et. al. 2006	Multicenter, phase II (extended follow-up)	Bortezomib ± dexamethasone	As above	As above	As above	DOR, 12.7 months (bortezomib alone); TTP, 7 months; OS, 17.0 months	NA	NA	As above
Jagannath et. al. 2004	Phase II	Bortezomib ± dexamethasone	Bortezomib, 1.0 mg/m², on days 1, 4, 8, and 11, up to eight 3-wk cycles; dexamethasone, 20 mg, may be added on the day of and the day following each bortezomib dose for patients with progressive after two cycles or stable disease after the first four cycles	28/27	30% (37%); CR/nCR rate, 11% (19%)	DOR, 9.5 months; TTP, 7 months; OS, 26.7 months	NA	NA	Grade 3/4: Peripheral neuropathy, 4%/4%; pain in limb, 11%/0%; thrombocytopenia, 29%/0%; neutropenia, 11%/0%; lymphopenia, 11%/0%; hyponatremia, 11%/0%

			Bortezomib, 1.3 mg/m², on days 1, 4, 8, and 11, up to eight 3-wk cycles; dexamethasone, 20 mg, may be added on the day of and the day following each bortezomib dose for patients with progressive after two cycles or stable disease after the first four cycles	26/26	38% (50%); CR/nCR rate, 4% (4%) (Within brackets the response rates of bortezomib alone or in combination with dexamethasone)	DOR, 13.7 months; TTP, 11 months; OS, not reached			Grade 3/4: Peripheral neuropathy, 15%/0%; pain in limb, 8%/0%; thrombocytopenia, 19%/4%; weakness, 12%/0%; neutropenia, 23%/0%; lymphopenia, 12%/0%; pneumonia, 15%/0%; hyponatremia, 8%/0%
Jagannath et. al. 2008	Phase II (follow-up, median > 5 years)	Bortezomib ± dexamethasone	As above	As above		OS, 26.8 months; 1-yr survival rate, 82%; 5-yr survival rate, 32% OS, 60.0 months 1-yr survival rate, 81%; 5-yr survival rate, 45%	NA	NA	
Richardson et. al. 2005	Multicenter, phase III	Bortezomib versus high-dose dexamethasone	Bortezomib, 1.3 mg/m², on days 1,4, 8 and 11 for up to eight 3-wk cycles and on days 1, 8, 15 and 22 of cycles 9 to 11 (5-wk cycles)	333/315	38%; CR rate, 6%	TTP, 6.2 months; DOR, 8 months; 1-yr OS, 80%	NA	NA	Grade 3/4: thrombocytopenia, 26%/4%; neutropenia, 12%/2%; anemia, 9%/1%; diarrhea, 7%/0%; peripheral neuropathy, 7%/1%; fatigue, 5%/<1%; dyspnea, 5%/<1%

			Dexamethasone, 40 mg, on days 1 to 4, 9 to 12, and 17 to 20 of cycles 1 through 4 (5-wk cycles) and on days 1 to 4 of cycles 5 through 9 (4-wk cycles)	336/312	18%; CR rate, 1%	TTP, 3.5 months; DOR, 5.6 months; 1-yr OS, 66%			Grade 3/4: anemia, 10%/1%; thrombocytopenia, 5%/1%
Richardson et. al. 2007	Multicenter, phase III (extended follow-up)	Bortezomib versus high-dose dexamethasone	As above	333/315	43%; CR rate, 9%	TTP, 6.2 months; DOR, 7.8 months; 1-yr survival, 80%; OS, 29.8 months;	NA	NA	Where they occurred, only slight differences were seen in incidences of commonly reported adverse events between updated and initial analyses.
Single-agent bortezomib									
Wu, 2005	Case research	Bortezomib	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11, up to eight 3-wk cycles	50	34%; CR rate, 4%	DOR, 9 months; PFS, 7 months; OS, 15 months	NA	NA	Grade 3/4: Peripheral neuropathy, ±20%; Thrombocytopenia, ±18%
Ogawa et. al. 2007	Phase I/II	Bortezomib	Bortezomib, 0.7 mg/m² or 1.0 mg/m² or 1.3 mg/m², on days 1, 4, 8 and 11, up to six 3-wk cycles	34/33	30%; nCR rate, 15%	NR	10 patients had received prior autologous hematopoietic SCT: 50%; nCR rate, 20%	NR	Grade 3/4: lymphopenia, 56%; neutropenia, 62%; leukopenia, 35%; thrombocytopenia, 32%; anemia, 32%
Hainsworth et. al. 2008	Phase II	Bortezomib	Bortezomib, 1.6mg/m², for 4 consecutive weeks; up to ten 5-wk cycles	40/40	55%; CR rate, 5%	PFS, 9.6 months; 1-yr OS, 75%; 2-yr OS, 51%	NA	NA	Grade 3/4: neutropenia. 13%; thrombocytopenia, 20%; fatigue, 15%; diarrhea, 13%; neuropathy, 10%
Uy et. al. 2008	Single institution, phase II	Bortezomib	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11, for two 4-wk cycles	40/40	70%; CR + VGPR rate, 15%	NR	78%; CR + VGPR rate, 43%	3-yr EFS, 32.3%; 3-yr OS, 62.2%	Grade 3/4: neuropathy, 13%

			Post transplant: Bortezomib, 1.3 mg/m², on days 1, 8, 15 and 22, up to six 5-wk cycles						
Bortezomib and dexamethasone									
Bruno et. al. 2006	Retrospective study	Bortezomib + dexamethasone versus bortezomib (after allogeneic hematopoietic cell transplantation)	Bortezomib, 1.0 mg/m² or 1.3 mg/m², on days 1, 4, 8, and 11 of each monthly course either alone or with dexamethasone, 20 mg or 40 mg, on days 1, 4, 15, and 18	23/23	57%; CR rate, 22%	PFS, 6 months (after a median follow-up of 6 months)	NA	NA	Grade 3/4: thrombocytopenia, 26%; peripheral neuropathy, 13%; neutropenia, 9%
Freimann et. al. 2007	Research in routine clinical practice	Bortezomib ± dexamethasone	While treatment modalities were basically at physician's discretion, the Program recommended bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11, up to six 3-wk cycles; dexamethasone, 20 mg, on the day of and the day after bortezomib administration for patients with progressive or stable disease after 2 or 4 cycles, respectively	91/83	46%; CR/ nCR rate, 17%	NR	NA	NA	Thrombocytopenia, 34%; peripheral neuropathy, 31%; diarrhoea, 20%; fatigue, 19%
El-Cheikh et. al. 2008	Retrospective study	Bortezomib (after reduced intensity conditioning allogeneic stem-cell transplantation	Bortezomib, 1.3 mg/m² or 1.0 mg/m², on days 1, 4, 8 and 11; Dexamethasone, 20 mg/ day, on days 1, 2, 4, 5, 8, 9, 11 and 12; up to eight 3-wk	37	NA	NA	73%; CR rate, 19%	OS at 18 months: 65%	Peripheral neuropathy, 35%; thrombocytopenia, 24%; fatigue, 19%

		) ± dexamethasone	cycles						
Mikhael et. al. 2009	Multicenter, phase IIIb	Bortezomib ± dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11, up to eight 3-wk cycles; dexamethasone, 20 mg/d, on the day of and on the day after bortezomib administration for patients who experienced progressive disease after completing at least cycle 2 or had no change from baseline (stable disease) after completing at least cycle 4	642/635	51%; CR rate, 11% Dexamethasone was added in 208 patients (33%), of whom 70 (34%) showed improved response.	NR	169 (27%) of the 635 patients had received prior SCT: 48%; CR rate, 9%	NR	Grade 3/4: thrombocytopenia, 39%; neutropenia, 16%; anaemia, 12%; diarrhoea, 7%; peripheral neuropathy, 6%
Bortezomib and melphalan combination regimens									
Berenson et. al. 2006	Phase I/II	Bortezomib + melphalan	Bortezomib, 0.7 to 1.0 mg/m², on days 1, 4, 8 and 11; melphalan, 0.025 to 0.25 mg/kg, on days 1 to 4; up to eight 4-wk cycles	35/34	47%; CR/ nCR rate, 15%	PFS, 8 months	NA	NA	Grade 3/4: neutropenia, 34%/6%; thrombocytopenia, 37%/3%; anemia, 23%/6%
Berenson et. al. 2008	Phase I/II (median follow-up of 28 months)	Bortezomib + melphalan	Bortezomib, 0.7, 1.0 or 1.3 mg/m2, on days 1, 4, 8, and 11; melphalan, 0.025 to 0.25 mg/kg, on days 1 to 4; up to eight 4-wk cycles	48/46	50%; CR/ nCR rate, 15%	PFS, 9 months; OS, 32 months	NA	NA	Grade 3/4: neutropenia, 31%/0%; thrombocytopenia, 25%/2%; anemia, 13%/0%
Palumbo et. al. 2007	Multicenter, phase I/II	Bortezomib + melphalan + prednisone + thalidomide	Bortezomib, 1.0 mg/m², 1.3 mg/m² or 1.6 mg/m², on days 1, 4, 15 and 22; melphalan, 6 mg/m²/d, for 5 days;	30/ 30	67%; CR rate, 17%	1-yr PFS, 61%; 1-yr OS, 84%	NA	NA	Grade 3/4: neutropenia, 23%/20%; thrombocytopenia, 20%/13%; anemia, 13%/3%; herpes

			prednisone, 60 mg/m²/d, for 5 days; thalidomide, 50 mg/d, for 35 days; up to six 5-wk cycles						zoster reactivation, 7%/0%; neuropathy, 7%/0%
Popat et. al. 2009	Multicenter, Phase I/II	Bortezomib + melphalan + dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11; IV melphalan, 2.5, 5.0, 7.5 or 10.0 mg/m², on day 2; up to eight 4-wk cycles; Dexamethasone, 20 mg, on the day of and the day after each bortezomib injection, for patients with progressive disease or stable disease/response plateau after 2 or 4 cycles, respectively	53/53	68%; CR rate, 19%	PFS, 10 months; OS, 28 months	NA	NA	Grade 3/4: thrombocytopenia, 62%; neutropenia, 57%; infection, 21%, neuropathy, 15%
Bortezomib, thalidomide and dexamethasone									
Pineda-Roman et. al. 2008	Phase I/II	Bortezomib + thalidomide + dexamethasone	Bortezomib, 1.0 mg/m² or 1.3 mg/m², on days 1, 4, 8 and 11, 3-wk cycle; thalidomide, 50 mg/day with increments to 100, 150 and 200 mg/day, T was added with the second cycle; dexamethasone, 20 mg, on the day of and after V administration, D was added with the forth cycle	85/82	63%; CR/nCR rate, 22%	OS, 22 months; EFS, 6 months; 1-yr OS, 68%; 1-yr EFS, 30%	NA	NA	Grade 4: thrombocytopenia, 7%; neutropenia, 7%
Bortezomib and pegylated liposomal doxorubicin or doxorubicin combination regimens									
Orlowski et. al. 2007	Phase III	Bortezomib + pegylated	Bortezomib, 1.3 mg/m², on days 1, 4,	324/324 (221	44%; CR rate, 4%	For the intention-to-treat	NA	NA	Grade 3/4: neutropenia, 30%;

		liposomal doxorubicin versus bortezomib	8 and 11; pegylated liposomal doxorubicin, 30 mg/m², on day 4; up to eight 3-wk cycles	patients discontinued treatment)		population: TTP, 9.3 months; PFS, 9.0 months; 15-month survival rate, 76%; DOR, 10.2 months			thrombocytopenia, 22%; anemia, 9%; diarrhea, 7%; asthenia, 6%; fatigue, 5%; hand-foot syndrome, 5%
			Bortezomib, as above, up to eight 3-wk cycles	322/322 (236 patients discontinued treatment)	41%; CR rate, 2%	TTP, 6.5 months; PFS, 6.5 months; 15-month survival rate, 65%; DOR, 7.0 months			Grade 3/4: thrombocytopenia, 15%; neutropenia, 14%; anemia, 9%; neuralgia, 5%
Palumbo et. al. 2008	Multicenter trial	Bortezomib + doxorubicin + dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11; doxorubicin, 20 mg/m², on days 1 and 4 or PLD, 30 mg/m², on day 1; Dexamethasone, 40 mg/day, on days 1 through 4; up to six 4-wk cycles	64/64	67%; CR rate, 9%	1-yr EFS, 34%; 1-yr OS, 66%	NA	NA	Grade 3/4: thrombocytopenia, 23%/25%; neutropenia, 20%/16%; anemia, 11%/2%; peripheral neuropathy, 10%/0%; pneumonia, 9%/3%
Min et. al. 2007	Retrospective study	Bortezomib versus bortezomib + chemotherapeutic agents	Bortezomib, 1.3 mg/m²; 3-wk cycle	32	38%; CR rate, 19%	TTP, 365 days	NA	NA	Grade ≥ 3: thrombocytopenia, 71.9%; neutropenia, 25%; peripheral neuropathy, 15.6%
			Bortezomib, 1.3 mg/m²; dexamethasone, 20 mg, on the day and day after bortezomib administration; 3-wk cycle	25	76%; CR rate, 32%	TTP, 359 days			Grade ≥ 3: thrombocytopenia, 40%; neutropenia, 24%; peripheral neuropathy, 32%

			Bortezomib, 1.3 mg/m²; dexamethasone, 20 mg, on the day and day after bortezomib administration; doxorubicin, 4.5 mg/m2, on days 1–4 of the first cycle or thalidomide, 100 mg on days 1–28 of the second cycle; 3-wk cycle or 4-wk cycle						
Bortezomib and other agents for multiple myeloma									
Suvannasankha et. al. 2006	Phase II	Bortezomib + methylprednisolone	Bortezomib, 1.3 mg/m², on days 1, 8 and 25; methylprednisolone, 500-2000 mg, on days 1, 8 and 25; 4-wk cycles	29	62%; CR/nCR rate, 7%	TTP, 6.6 months; OS, 20.2 months	NA	NA	Grade 3: peripheral neuropathy, 7%
Berenson et al. 2007	Multicenter, phase I/II	Bortezomib + arsenic trioxide + ascorbic acid	Bortezomib, 0.7, 1.0 or 1.3 mg/m², on days 1, 4, 8 and 11; arsenic trioxide, 0.125 or 0.25 mg/kg, on days 1, 4, 8 and 11; ascorbic acid, 1 g, on days 1, 4, 8, and 11; up to eight 3-wk cycles	22/22	9%; CR rate, 0%	PFS, 5 months; OS, not reached; 1-yr PFS, 34%; 1-yr OS, 74%	NA	NA	Grade 4: thrombocytopenia, 5%
Reece et. al. 2008	Phase I/II	Bortezomib + cyclophosphamide + prednisone	Bortezomib, 0.7-1.5 mg/m², on days 1, 8 and 15, or days 1, 4, 8 and 11; cyclophosphamide, 150 or 300 mg/m², on days 1,8, 15 and 22; prednisone, 100 mg, every 2 days; 4-wk cycles	37/37	68%; CR rate, 32%	1-yr PFS, 56%; PFS, 15 months; 1-yr OS, 89%; OS, 24.3 months	NA	NA	Grade 3/4 (during cycles 2-8): hyperglycemia, 29%/0%; neutropenia, 24%/5%; hypophosphatemia, 19%/10%; thrombocytopenia, 14%/5%

Table 2. Clinical studies of bortezomib in patients with previously untreated multiple myeloma

Author, Year	Design	Treatment	Regimen	N of patients enrolled/ evaluable	Response rates	Time-to-event data	Post-SCT response rates	Post-SCT time-to-event data	Key toxicities
Bortezomib and dexamethasone									
Jagannath et. al. 2005	Multicenter, phase II	Bortezomib + dexamethasone versus bortezomib	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11, up to six 3-wk cycles; dexamethasone, 40 mg, on the day of and the day after bortezomib administration for patients who did not achieve PR after cycle 2 or CR after cycle 4	32/32	88%; CR/ nCR rate, 25%	1-yr survival rate, 87%	NA	NA	Grade 3/4: Sensory neuropathy, 16%; neutropenia, 16%; myalgia, 13%; diarrhoea, 9%; bone pain, 9%; fatigue, 6%; abdominal pain/ cramping, 6%
Harousseau et. al. 2006	IFM Phase II	Bortezomib + dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11; dexamethasone, 40 mg, on days 1-4 and 9-12 for the first two cycles, and on days 1-4 for the following two cycles; up to four 3-wk cycles	52/48	66%; CR rate, 21%	NR	90%; CR rate, 33% (in 42 of 48 patients who could proceed to ASCT)	NR	Grade 3: Infection, 10%; peripheral neuropathy, 6% (in 50 patients who received study drugs)
Rosinol et. al. 2007	Multicenter, phase II (PETHEMA)	Bortezomib + dexamethasone	Bortezomib, 1.3 mg/m², on days 1 ,4, 8 and 11 of a 3-wk cycle in cycles 1, 3 and 5; dexamethasone, 40 mg/d, on days 1 through 4, 9 through 12, and 17 through 20 of a 4-wk cycle in cycles 2, 4 and 6.	40/40	65%; CR rate, 13%	NR	88%; CR rate, 33% (n=37)	NR	Grade 3: neutropenia, 15%
Bortezomib, melphalan and prednisone									
Mateos et. al. 2006	Multicenter, phase I/II	Bortezomib + melphalan +	Bortezomib, 1.0 mg/m² or 1.3 mg/m²,	60/53	89%; CR/ nCR rate, 43%	16-months PFS, 91%; 16-months	NA	NA	Grade 3/4: thrombocytopenia,

	(GEM/PETH EMA)	prednisone	on days 1, 4, 8, 11, 22, 25, 29 and 32; melphalan, 9 mg/m², on days 1 to 4; prednisone, 60 mg/m² on days 1 to 4; for four 6-wk cycles followed by 1.0 mg/m² or 1.3 mg/m², on days 1, 8, 15, and 22 in combination with melphalan and prednisone as above; for five 5-wk cycles			EFS, 83%; projected 2-yr survival rate, 86%			51%; neutropenia, 43%; peripheral neuropathy, 17%; diarrhea, 16%; infection, 16%; anemia, 10%; constipation, 8%; asthenia, 5%
Mateos et. al. 2008	Multicenter, phase I/II (median follow-up of 26 months)	Bortezomib + melphalan + prednisone	As above	As above		TTP, 27.2 months; EFS, 25.0 months; OS, not reached; OS rate, 85% (at 38 months)	NA	NA	As above
San Miguel et. al. 2008	Multicenter, phase III (VISTA)	Bortezomib + melphalan + prednisone versus melphalan + prednisone	Melphalan, 9 mg/m², on days 1 to 4; Prednisone, 60 mg/m², on days 1 to 4; up to nine 6-wk cycles; bortezomib, 1.3 mg/m², on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1 to 4 and on days 1, 8, 22 and 29 during cycles 5 to 9 Melphalan + prednisone as above	344/337 338/331	71%; CR rate, 30% 35%; CR rate, 4%	TTP, 24 months; DOR, 19.9 months; OS, not reached TTP, 16.6 months; DOR, 13.1 months; OS, not reached	NA	NA	Grade 3/4: neutropenia, 30%/10%; thrombocytopenia, 20%/17%; leukopenia, 20%/3%; anemia, 16%/3%; lymphopenia, 14%/5%; peripheral sensory neuropathy, 13%/ <1%; neuralgia, 8%/1%, diarrhea, 7%/1%; pneumonia, 5%/2% Grade 3/4: neutropenia, 23%/15%; anemia, 20%/8%; thrombocytopenia,

									16%/14%; leukopenia, 16%/4%; lymphopenia, 9%/2%;
Bortezomib, thalidomide and dexamethasone									
Wang et. al. 2007	Single-center	Bortezomib + thalidomide + dexamethasone	Bortezomib, 1.3 mg/m²; dexamethasone, 20 mg/m², for 4 days beginning on days 1, 9 and 17; thalidomide, 100 mg daily increasing to a max. of 200 mg; up to three 4-wk cycles	38	87%; CR rate, 16%		NA	NA	Grade ≥ 3: myelosuppression, 11%; neuropathy, 5%; DVT/PE, 5%
Barlogie et. al. 2007	Phase II	Bortezomib + thalidomide + dexamethasone +cisplatin + doxorubicin + cyclophosphamide + etoposide (VDT-PACE in Total Therapy 3)	Bortezomib, 1.0 mg/m², on days 1, 4, 8 and 11; thalidomide, 200 mg/day, on days 4-7 or 1-4; dexamethasone, 40 mg/day, on days 4-7 or 1-4; cisplatin, 10 mg/m²/day or 7,5 mg/m²/day, on days 4-7 or 1-4; doxorubicin, 10 mg/m²/day or 7,5 mg/m²/day, on days 4-7 or 1-4; cyclophosphamide, 400 mg/m²/day or 300 mg/m²/day, on days 4-7 or 1-4; etoposide, 40 mg/m²/day or 30 mg/m²/day, on days 4-7 or 1-4 VTD-PACE was administered in the dose schedule delineated for two cycles prior to and after completion of tandem	303/303	NR	NR	24-month CR/nCR rate, 83%; 24-month CR rate, 56%	24-month EFS rate: 84% 24-month OS rate: 86%	Grade > 2: thrombo-embolic events in, 27%; peripheral neuropathy, 12%

			transplants. 3-year maintenance comprised monthly cycles of VTD in the first and TD in the remaining years.						
Pineda-Roman et. al. 2008	(follow-up)	VDT-PACE in Total Therapy 3 versus Total therapy 2 with or without thalidomide	As above	303/275 668/351	NR	NR	24-months CR rate, 92% 24-Months CR rate, 81%/79%	24-months EFS rate, 84%; 24-month OS rate, 87% 24-months EFS rate, 77%/73%; 24-month OS rate, 83%/87%	NR
Bortezomib, doxorubicin and dexamethasone									
Oakervee et. al. 2005	Phase I/II	Bortezomib + Doxorubicin + dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8, and 11, up to four 3-wk cycles; dexamethasone, 40 mg, on days 1-4, 8-11 and 15-18 of cycle 1 and on days 1-4 of cycles 2-4; doxorubicin, 0, 4.5 or 9 mg/m², on days 1-4 of each cycle	21/21	95%; CR rate, 24%	NR	18 of 21 patients received high-dose melphalan with SCT: 95%; CR rate, 43%;	NR	Grade ≥ 3: Infection, 19%; shingles, 14%; line infection, 14%; peripheral neuropathy, 5%; postural hypotension, 5%; nausea and vomiting, 5%; atrial fibrillation, 5%; hyperglycemia,5%
Popat et. al. 2008	Phase I/II (follow-up)	Bortezomib + Doxorubicin + dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8, and 11, up to four 3-wk cycles; dexamethasone, 40 mg, on days 1-4, 8-11 and 15-18 of cycle 1 and on days 1-4 of cycles 2-4; doxorubicin, 0, 4.5 or 9 mg/m², on days 1-4 of each cycle The second cohort received bortezomib	21/21 20/19	95%; CR/ nCR rate, 29% 89%; CR/ nCR rate, 16%	PFS, 29 months; OS, not reached; 1-yr OS, 100%; 2-yr OS, 95% PFS, 24 months; OS, not	95%; CR/ nCR rate, 57% 89%; CR/ nCR rate, 42%	NR NR	See above Grade 3/4: liver function tests, 15%;

			1.0 mg/m² and doxorubicin 9 mg/m²			reached; 1-yr OS, 95%; 2-yr OS, 73%			psychiatric, 10%; thrombocytopenia, 5%; neutropenia, 5%; infection, 5%
Bortezomib and other agents for multiple myeloma									
Berenson et. al. 2009	Multicenter, phase II	Bortezomib + ascorbic acid + melphalan	Bortezomib, 1.0 mg/m², on days 1, 4, 8 and 11; ascorbic acid, 1 g, on days 1-4; melphalan, 0.1 mg/kg, on days 1-4; up to eight 4-wk cycles	35/31	45%; CR rate, 16%	DOR, 17 months; TTP, 19 months; PFS, 13 months; OS, not reached	NA	NA	Grade 3/4: thrombocytopenia, 10%; neutropenia, 10%; peripheral neuropathy, 10%
Reeder et. al. 2009	Phase II	Bortezomib + cyclophosphamide + dexamethasone	Bortezomib, 1.3 mg/m², on days 1, 4, 8 and 11; cyclophosphamide, 300 mg/m², on days 1, 8, 15 and 22; dexamethasone, 40 mg, on days 1-4, 9-12 and 17-20; up to four 4-wk cycles	33/33	88%; CR/ nCR rate, 39%	NR	100%; CR/ nCR rate, 70% (N=23)	NR	Grade 3/4: thrombocytopenia, 25%; neutropenia, 13%; hyperglycemia, 13%; anemia, 12%; hypokalemia, 9%; neuropathy, 7%; thrombosis, 7%; diarrhea, 6%

Abbreviations: CR, complete response; DOR, duration of response; EFS, event-free survival; MR, minor response; NA, not applicable; nCR, near complete response; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response; SCT, stem-cell transplantation; TTP, time to progression.

References: Literature review of effectiveness of bortezomib

Barlogie, B., E. Anaissie, F. van Rhee, J. Haessler, K. Hollmig, M. Pineda-Roman, M. Cottler-Fox, et al. 2007. Incorporating bortezomib into upfront treatment for multiple myeloma: Early results of total therapy 3. British Journal of Haematology 138, (2) (Jul): 176-85.

Berenson, J. R., J. Matous, R. A. Swift, R. Mapes, B. Morrison, and H. S. Yeh. 2007. A phase I/II study of arsenic trioxide/bortezomib/ascorbic acid combination therapy for the treatment of relapsed or refractory multiple myeloma. Clinical Cancer Research : An Official Journal of the American Association for Cancer Research 13, (6) (Mar 15): 1762-8.

Berenson, J. R., H. H. Yang, K. Sadler, S. G. Jarutirasarn, R. A. Vescio, R. Mapes, M. Purner, et al. 2006. Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 24, (6) (Feb 20): 937-44.

Berenson, J. R., H. H. Yang, R. A. Vescio, Y. Nassir, R. Mapes, S. P. Lee, J. Wilson, et al. 2008. Safety and efficacy of bortezomib and melphalan combination in patients with relapsed or refractory multiple myeloma: Updated results of a phase 1/2 study after longer follow-up. Annals of Hematology 87, (8) (Aug): 623-31.

Berenson, J. R., O. Yellin, D. Woytowitz, M. S. Flam, A. Cartmell, R. Patel, H. Duvivier, et al. 2009. Bortezomib, ascorbic acid and melphalan (BAM) therapy for patients with newly diagnosed multiple myeloma: An effective and well-tolerated frontline regimen. European Journal of Haematology (Feb 17).

Bruno, B., F. Patriarca, R. Sorasio, D. Mattei, V. Montefusco, J. Peccatori, F. Bonifazi, et al. 2006. Bortezomib with or without dexamethasone in relapsed multiple myeloma following allogeneic hematopoietic cell transplantation. Haematologica 91, (6): 837-9.

Dicato, M., M. Boccadoro, J. Cavenagh, J. L. Harousseau, H. Ludwig, J. San Miguel, and P. Sonneveld. 2006. Management of multiple myeloma with bortezomib: Experts review the data and debate the issues. Oncology 70, (6): 474-82.

El-Cheikh, J., M. Michallet, A. Nagler, H. de Lavallade, F. E. Nicolini, A. Shimoni, C. Faucher, et al. 2008. High response rate and improved graft-versus-host disease following bortezomib as salvage therapy after reduced intensity conditioning allogeneic stem cell transplantation for multiple myeloma. Haematologica 93, (3) (Mar): 455-8.

Freimann, H., A. Calderoni, P. Cornu, and R. Olie. 2007. Daily practice use of bortezomib in relapsed/refractory multiple myeloma. Safety/efficacy results of a compassionate use program in switzerland. Swiss Medical Weekly : Official Journal of the Swiss Society of Infectious Diseases, the Swiss Society of Internal Medicine, the Swiss Society of Pneumology 137, (21-22) (Jun 2): 317-22.

Hainsworth, J. D., D. R. Spigel, J. Barton, C. Farley, M. Schreeder, J. Hon, and F. A. Greco. 2008. Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma: A phase 2 trial of the minnie pearl cancer research network. Cancer 113, (4) (Aug 15): 765-71.

Harousseau, J. L., M. Attal, X. Leleu, J. Troncy, B. Pegourie, A. M. Stoppa, C. Hulin, et al. 2006. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: Results of an IFM phase II study. Haematologica 91, (11) (Nov): 1498-505.

Jagannath, S., B. Barlogie, J. Berenson, D. Siegel, D. Irwin, P. G. Richardson, R. Niesvizky, et al. 2004. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. British Journal of Haematology 127, (2) (Oct): 165-72.

Jagannath, S., B. G. M. Durie, J. Wolf, E. Camacho, D. Irwin, J. Lutzky, M. McKinley, et al. 2005. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. British Journal of Haematology 129, (6): 776-83.

Jagannath, S., B. Barlogie, J. R. Berenson, D. S. Siegel, D. Irwin, P. G. Richardson, R. Niesvizky, et al. 2008. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. British Journal of Haematology 143, (4) (Nov): 537-40.

Kane, R. C., A. T. Farrell, R. Sridhara, and R. Pazdur. 2006. United states food and drug administration approval summary: Bortezomib for the treatment of progressive multiple myeloma after one prior therapy. Clinical Cancer Research : An Official Journal of the American Association for Cancer Research 12, (10) (May 15): 2955-60.

Manochakian, R., K. C. Miller, and A. A. Chanan-Khan. 2007. Clinical impact of bortezomib in frontline regimens for patients with multiple myeloma. The Oncologist 12, (8) (Aug): 978-90.

Mateos, M. V., J. M. Hernandez, M. T. Hernandez, N. C. Gutierrez, L. Palomera, M. Fuertes, J. Diaz-Mediavilla, et al. 2006. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Results of a multicenter phase 1/2 study. Blood 108, (7) (Oct 1): 2165-72.

Mateos, M. V., J. M. Hernandez, M. T. Hernandez, N. C. Gutierrez, L. Palomera, M. Fuertes, P. Garcia-Sanchez, et al. 2008. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Updated time-to-events results and prognostic factors for time to progression. Haematologica 93, (4) (Apr): 560-5.

Mikhael, J. R., A. R. Belch, H. M. Prince, M. N. Lucio, A. Maiolino, A. Corso, M. T. Petrucci, P. Musto, M. Komarnicki, and A. K. Stewart. 2009. High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: Results of a global phase 3b expanded access program. British Journal of Haematology 144, (2) (Jan): 169-75.

Min, C. K., M. J. Lee, K. S. Eom, S. Lee, J. W. Lee, W. S. Min, C. C. Kim, et al. 2007. Bortezomib in combination with conventional chemotherapeutic agents for multiple myeloma compared with bortezomib alone. Japanese Journal of Clinical Oncology 37, (12) (Dec): 961-8.

Oakervee, H. E., R. Popat, N. Curry, P. Smith, C. Morris, M. Drake, S. Agrawal, et al. 2005. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. British Journal of Haematology 129, (6) (Jun): 755-62.

Ogawa, Y., K. Tobinai, M. Ogura, K. Ando, T. Tsuchiya, Y. Kobayashi, T. Watanabe, et al. 2008. Phase I and II pharmacokinetic and pharmacodynamic study of the proteasome inhibitor bortezomib in japanese patients with relapsed or refractory multiple myeloma. Cancer Science 99, (1) (Jan): 140-4.

Orlowski, R. Z., A. Nagler, P. Sonneveld, J. Blade, R. Hajek, A. Spencer, J. San Miguel, et al. 2007. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 25, (25) (Sep 1): 3892-901.

Palumbo, A., M. T. Ambrosini, G. Benevolo, P. Pregno, N. Pescosta, V. Callea, C. Cangialosi, et al. 2007. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. Blood 109, (7) (Apr 1): 2767-72.

Palumbo, A., F. Gay, S. Bringhen, A. Falcone, N. Pescosta, V. Callea, T. Caravita, et al. 2008. Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO 19, (6) (Jun): 1160-5.

Pineda-Roman, M., M. Zangari, F. van Rhee, E. Anaissie, J. Szymonifka, A. Hoering, N. Petty, et al. 2008. VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. Leukemia : Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K 22, (7) (Jul): 1419-27.

Pineda-Roman, M., M. Zangari, J. Haessler, E. Anaissie, G. Tricot, F. van Rhee, J. Crowley, J. D. Shaughnessy Jr, and B. Barlogie. 2008. Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: Comparison with total therapy 2. British Journal of Haematology 140, (6) (Mar): 625-34.

Popat, R., H. E. Oakervee, S. Hallam, N. Curry, L. Odeh, N. Foot, D. L. Esseltine, M. Drake, C. Morris, and J. D. Cavenagh. 2008. Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: Updated results after long-term follow-up. British Journal of Haematology 141, (4) (May): 512-6.

Popat, R., H. Oakervee, C. Williams, M. Cook, C. Craddock, S. Basu, C. Singer, et al. 2009. Bortezomib, low-dose intravenous melphalan, and dexamethasone for patients with relapsed multiple myeloma. British Journal of Haematology (Jan 12).

Prince, H. M., M. Adena, D. K. Smith, and J. Hertel. 2007. Efficacy of single-agent bortezomib vs. single-agent thalidomide in patients with relapsed or refractory multiple myeloma: A systematic comparison. European Journal of Haematology 79, (2) (Aug): 93-9.

Reece, D. E., G. P. Rodriguez, C. Chen, S. Trudel, V. Kukreti, J. Mikhael, M. Pantoja, W. Xu, and A. K. Stewart. 2008. Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 26, (29) (Oct 10): 4777-83.

Reeder, C. B., D. E. Reece, V. Kukreti, C. Chen, S. Trudel, J. Hentz, B. Noble, et al. 2009. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: High response rates in a phase II clinical trial. Leukemia : Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K (Feb 19).

Richardson, P. G., B. Barlogie, J. Berenson, S. Singhal, S. Jagannath, D. Irwin, S. V. Rajkumar, et al. 2003. A phase 2 study of bortezomib in relapsed, refractory myeloma. The New England Journal of Medicine 348, (26) (Jun 26): 2609-17.

Richardson, P. G., B. Barlogie, J. Berenson, S. Singhal, S. Jagannath, D. Irwin, S. V. Rajkumar, et al. 2003. A phase 2 study of bortezomib in relapsed, refractory myeloma. The New England Journal of Medicine 348, (26) (Jun 26): 2609-17.

Richardson, P. G., P. Sonneveld, M. Schuster, D. Irwin, E. Stadtmauer, T. Facon, J. L. Harousseau, et al. 2007. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: Final time-to-event results of the APEX trial. Blood 110, (10) (Nov 15): 3557-60.

Richardson, P. G., P. Sonneveld, M. W. Schuster, D. Irwin, E. A. Stadtmauer, T. Facon, J. L. Harousseau, et al. 2005. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. The New England Journal of Medicine 352, (24) (Jun 16): 2487-98.

Rosinol, L., A. Oriol, M. V. Mateos, A. Sureda, P. Garcia-Sanchez, N. Gutierrez, A. Alegre, et al. 2007. Phase II PETHEMA trial of alternating bortezomib and dexamethasone as induction regimen before autologous stem-cell transplantation in younger patients with multiple myeloma: Efficacy and clinical implications of tumor response kinetics. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 25, (28) (Oct 1): 4452-8.

San Miguel, J.F. Schlag, R. Khuageva, N.K. Dimopoulos, M.A. Shpilberg, O. Kropff, M. Spicka, I. Petrucci, M.T. Palumbo, A. Samoilova, O.S. Dmoszynska, A. Abdulkadyrov, K.M. Schots, R. Jiang, B. Mateos, M.V. Anderson, K.C. Esseltine, D.L. Liu, K. Cakana, A. Van De Velde, H. Richardson, P.G. 2008. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. The New England Journal of Medicine 359, (9): 906-917.

Sonneveld, P., R. Hajek, A. Nagler, A. Spencer, J. Blade, T. Robak, S. H. Zhuang, J. L. Harousseau, R. Z. Orlowski, and DOXIL-MMY-3001 Study Investigators. 2008. Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomide/lenalidomide therapy. Cancer 112, (7) (Apr 1): 1529-37.

Suvannasankha, A., G. G. Smith, B. E. Juliar, and R. Abonour. 2006. Weekly bortezomib/ methylprednisolone is effective and well tolerated in relapsed multiple myeloma. Clinical Lymphoma & Myeloma 7, (2) (Sep): 131-4.

Uy, G. L., S. D. Goyal, N. M. Fisher, A. Y. Oza, M. H. Tomasson, K. Stockerl-Goldstein, J. F. Dipersio, and R. Vij. 2008. Bortezomib administered pre-auto-SCT and as maintenance therapy post transplant for multiple myeloma: A single institution phase II study. Bone Marrow Transplantation (Nov 24).

Wang, M. Giralt, S. Delasalle, K. Handy, B. Alexanian, R. Bortezomib in combination with thalidomide-dexamethasone for previously untreated multiple myeloma. Hematology 12, (3): 235-239.

Wu, K. L., W. van Wieringen, E. Vellenga, S. Zweegman, H. M. Lokhorst, and P. Sonneveld. 2005. Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice. Haematologica 90, (7) (Jul): 996-7.

Annex IV: Minimal Case Report Form

Minimal CRF

On Study Form

Patient namecode: ..... Hospital: ..... Patient study number: |__|__|__|__|

Referred from/to hospital.....
Name physician.....

Patient characteristics

Date of birth..... [dd/mm/yyyy]	11 |___|___|_____|
Sex.....	12 |___| 1=male 2=female
Date of randomisation..... [dd/mm/yyyy]	14|___|___|_____|
Treatment arm allocated.....	13|___| 1= A: chemotherapy without Thalidomide 2= B: chemotherapy with Thalidomide
WHO performance status.....	5 |___|
Stage of disease at inclusion.....	6 |___| 0=I A/B 1=IIA 2=IIB 3=IIIA 4=IIIB
Albumin..... [g/l]	30 |__|__|.|__| 999 = 'not done'
Serum β-2 microglobulin..... [mg/l]	33 |__|.|__|__| 999 = 'not done'

Comments

.....
.....
.....
.....
.....
.....
.....
.....
.....

Off Treatment Form

Patient namecode: ..... Hospital: ..... Patient study number:|__|__|__|__|

Date when taken off protocol treatment.....[dd/mm/yyyy]	2	|___|___|_____|
Number of (V)AD cycles given.....	3	|___|
CAD given.....	4	|___| 0=no 1=yes
Stem cells collected.....	5	|___| 0=no 1=yes
Number of HDM cycles given.....	6	|___|
Number of HDM cycles given according to Hospital policy.....	7	|___| 0=no* 1=yes 2=not applicable
If no, specify reason..... *Specify	8	.....
Thalidomide given during AD chemotherapy.....	9	|___| 0=no 1=yes
Thrombosis prophylaxis given during AD+Thalidomide.....	10	|___| 0=no 1=yes 2=not applicable
Thalidomide maintenance started.....	11	|___| 0=no 1=yes
Interferon maintenance started.....	12	|___| 0=no 1=yes
Bisphosphonates given.....	13	|___| 0=no 1=yes
Allogenic transplantation given.....	19	|___| 0=no 1=myeloblative 2=non-myeloblative
Type of NMA AlloSCT (if applicable).....	21	|___| 1=inclusion in HO54 2=according to HO54 8=other, specify*
*Specify	22	.....
Date stem cell infusion Allo transplant.....[dd/mm/yyyy]	20	|___|___|_____|
Best response on protocol.....	14	|___| 1=CR 2=PR 3=MR 4=NC 5=progressive disease
Reason for going off protocol treatment.....	15	|___| 0=normal completion (in case of AlloSCT) 1=not eligible for CAD, no further VAD 2=not eligible for HDM, no further VAD 3=not eligible for IFN maintenance 4=not at least PR 3 months after start IFN maintenance (arm A) 5=not at least PR 3 months after last course of HDM (arm B) 6=excessive toxicity (including toxic death) 7=progression/relapse (not after VAD I-III or SC collection) 8=intercurrent death 9=no compliance of the patient (especially refusal) 10=major protocol violation* 88=other*
*Specify	16	.....
Neurotoxicity present.....		|___| 0=no 1=yes

Follow-Up Form

Patient namecode: ..... Hospital: ..... Patient study number: |__|__|__|__|

Survival Status

Date last known to be alive or date of death	[dd/mm/yyyy]	2 |___|___|_____|
Date response evaluation	[dd/mm/yyyy]	26 |___|___|_____|
Survival status		3 |__| 0=alive 1=dead
Cause of death		4 |__| 1=multiple myeloma 2=toxicity* 3=infection* 4=combination* 8=other* 9=unknown
	*Specify	5 .....

Remission Status

Remission status at present		6 |__| 0=SD (never CR/PR/MR and no PD) 1=1st CR 2=1st PR* 3=1st MR 4=1st relapse from CR 5=1st progression after PR/MR 6=PD(progressive disease without prior response) 8=other, specify*
	*Specify	7 .....
Date of diagnosis relapse/progression (not reported previously)	[dd/mm/yyyy]	8 |___|___|_____|
Secondary malignancy (not reported previously)		9 |__| 0=no 1=yes*
	*Specify	10 .....
Date of diagnosis secondary malignancy	[dd/mm/yyyy]	11 |___|___|_____|

Treatment off Protocol (after previous Follow/Off Treatment and before date last contact present Follow Up)

Treatment given off protocol		12 |__| 0=no 1=chemotherapy only 2=AutoSCT 3=AlloSCT 4=radiotherapy 5=Thalidomide 6=combination 8=other
	*Specify	13 .....
Reason for this treatment		14 |__| 1=reinduction 2=consolidation 8=other*
	*Specify	15 .....
Date of start of this treatment	[dd/mm/yyyy]	16 |___|___|_____|
Date evaluation of this treatment	[dd/mm/yyyy]	17 |___|___|_____|
Response to this treatment		18 |__| 1=CR 2=PR 3=MR 4=NC 5=progressive disease 6=relapse from CR 7=progression after PR/MR

Annex V: Maximal Case Report Form

Erasmus MC

iMTA

SUMMARY FORM

Patient study number	Patient name code	Hospital
_____	___	.....

HOVON 50 STUDY

Date of randomization/start date line 1 ..... |____||____||_____|

Type of maintenance therapy given (0 = none 1 = INFα 2 = Thalidomide) ..... |__|

Inclusion in HOVON 54(or ALLOSCT) (0 = no 1 = yes) ..... |__|

Date of progression from 1st line therapy ..... |____||____||_____|

DLI (0 = no 1 = yes) ..... |__|

2nd LINE

Date start chemotherapy line 2 ..... |____||____||_____|

Type of chemotherapy given* ..... |__|+|__|+|__|

Specify drug (If applicable) .....

Date progression from line 2 ..... |____||____||_____|

Albumin (g/l) ..... |___|__|.|__|...Recording date ..... |____||____||_____|

Serum β_2-microglobulin (mg/l) ..... |__|.|__|...Recording date ..... |____||____||_____|

Present neurotoxicity (0=no; 1=yes) ..... |__|

3rd LINE

Date start chemotherapy line 3 ..... |____||____||_____|

Type of chemotherapy given* ..... |__|+|__|+|__|

Specify drug (If applicable) .....

Date progression from line 3 ..... |____||____||_____|

Albumin (g/l) ..... |___|__|.|__|...Recording date ..... |____||____||_____|

Serum β_2-microglobulin (mg/l) ..... |__|.|__|...Recording date ..... |____||____||_____|

Present neurotoxicity (0=no; 1=yes) ..... |__|

4rd LINE

Date start chemotherapy line 4 ..... |____||____||_____|

Type of chemotherapy given* ..... |__|+|__|+|__|

Specify drug (If applicable) .....

Date progression from line 4 ..... |____||____||_____|

Albumin (g/l) ..... |___|__|.|__|...Recording date ..... |____||____||_____|

Serum β_2-microglobulin (mg/l) ..... |__|.|__|...Recording date ..... |____||____||_____|

Present neurotoxicity (0=no; 1=yes) ..... |__|

* Type of chemotherapy given/ more options possible

1 = Interferon Alpha
2 = Thalidomide
3 = Bortezomib/Velcade
4 = Dexamethasone
5 = Doxorubicin (adriamycin)
6 = Vincristine
7 = Lenalidomide/Revlimid
8 = experimental/study (specify)
9 = Melfalan
10 = Prednison
88 = other (specify)
99 = unknown

Erasmus MC Czaring iMTA

SUMMARY FORM

Patient study number	Patient name code	Hospital
|__|__|__|__|	|__|__|__|	.....

5th LINE

Date start chemotherapy line 5 .....|____||____||_ _____|

Type of chemotherapy given* .....|__|+|__|+|__|

Specify drug (If applicable) .....

Date progression from line 5 .....|____||____||_ _____|

Albumin *(g/l)*.....|__|_|_|.|__|…Recording date .....|____||____||_ _____|

Serum β_2-microglobulin*(mg/l)*..... .....|__|_|_|.|__|…Recording date .....|____||____||_ _____|

Present neurotoxicity *(0=no; 1=yes)* .....|__|

6th LINE

Date start chemotherapy line 6 .....|____||____||_ _____|

Type of chemotherapy given* .....|__|+|__|+|__|

Specify drug (If applicable) .....

Date progression from line 6 .....|____||____||_ _____|

Albumin *(g/l)*.....|__|_|_|.|__|…Recording date .....|____||____||_ _____|

Serum β_2-microglobulin*(mg/l)*..... .....|__|_|_|.|__|…Recording date .....|____||____||_ _____|

Present neurotoxicity *(0=no; 1=yes)* .....|__|

FOLLOW-UP

Date start palliative care .....|____||____||_ _____|

Date of death .....|____||____||_ _____|

* Type of chemotherapy given/ more options possible

1 = Interferon Alpha
2 = Thalidomide
3 = Bortezomib/Velcade
4 = Dexamethasone
5 = Doxorubicin (adriamycin)
6 = Vincristine
7 = Lenalidomide/Revlimid
8 = experimental/study (specify)
9 = Melfalan
10 = Prednison
88 = other (specify)
99 = unknown

NB: de serum B2microglobuline en albumine dienen als prognostische factoren en moeten dus geregistreerd worden voor start chemotherapie, dus ten laatste de datum die er boven staat: " date start chemotherapy line …."

MaxCRF

ON-STUDY FORM (1)

Patient study number	Patient name code	Hospital
|_|_|_|_|_|	|_|_|_|	.....

CONSENT LETTER

2nd Hospital.....

Physician .....

Address.....

GENERAL PATIENT INFORMATION

Weight *(kg)*.....|__|__|__|

Height *(cm)*.....|__|__|__|

STRATIFICATION

Myeloma type (1=IgA; 2=IgG; 3=IgD; 4=IgE; 5=light chain) .....|__|

Plasma-cell infiltration in bone marrow (%).....|__|__|__|

Date progression from first-line therapy ..... |__|__||__|__||__|__|__|__|

Present neurotoxicity *(0=no; 1=yes)*.....|__|

COMMENTS

.....

.....

.....

.....

.....

.....

.....

Erasmus MC

iMTA Institute for Medical Technology Assessment

MaxCRF

TREATMENT FORM (2)

Patient study number	Patient name code	Hospital
|__|__|__|__|	|__|__|__|	....

Hospital in which this treatment cycle was given ....

Line number .... |__|

Cycle number ....|__|__|

PATIENT'S CHARACTERISTICS

Weight (kg)...|__|__|__|

Body surface area (m^2)... |__|.|__|__|

ADMINISTRATION of TREATMENT

Date start of this cycle......... .... |__|__||__|__||__|__|__|__|

Date last chemotherapy given .... |__|__||__|__||__|__|__|__|

Drug *(1)*	Theoretical full dose/day	Unit *(2)*	Route *(3)*	Theoretical nr of days	Total dose given	Unit *(2)*	Dosage *(4)*	Reason *(5)*
|__|	|__|__|__|__|.|__|	|__|	|__|	|__|__|	|__|__|__|__|.|__|	|__|	|__|	|__|
|__|	|__|__|__|__|.|__|	|__|	|__|	|__|__|	|__|__|__|__|.|__|	|__|	|__|	|__|
|__|	|__|__|__|__|.|__|	|__|	|__|	|__|__|	|__|__|__|__|.|__|	|__|	|__|	|__|

Specify drug and unit (if applicable)..

Specify dose modification and reason (if applicable)..

....

(1) Drug	*(2) Unit*	*(3) Route*
1 – Interferon Alpha 2 – Thalidomide 3 – Bortezomib/Velcade 4 – Dexamethasone 5 – Doxorubicin (adriamycin) 6 – Vincristine 7 – Lenalidomide/Revlimid 8 – experimental/study (specify) 9 – Mephalan 10 – Prednison 11 – other (specify) 99 – unknown	1 – mg 2 – mg/m^2 3 – $\times 10^6$ IU/m^2 4 – $\times 10^6$ IU 5 – other (specify)	1 – oral 2 – intravenous 3 – subcutaneous 4 – rectal 5 – transdermal (patch) 6 – cutaneous 7 – Tracheal 8 – Intramuscular 9 – other 99 – unknown

(4) Dosage	*(5) Reason*
1 – full dose according to schedule 2 – full dose given but delayed 3 – dose reduced 4 – dose reduced and delayed 5 – not given 6 – interrupted & resumed 7 – Thalidomide dose escalation 8 – other (specify)	1 – hematologic toxicity (specify) 2 – neurotoxicity (specify) 3 – gastrointestinal toxicity (specify) 4 – other toxicity (specify) 5 – combination (specify) 6 – patients condition (specify) 7 – renal insufficiency (specify) 8 – other (specify)

MaxCRF

END OF TREATMENT- LINE FORM (3)

Patient study number	Patient name code	Hospital
|_|_|_|_|_|	|_|_|_|	.....

Line number ..... |__|

Total number of cycles given ..... |__|__|

Major reason for discontinuation of this chemotherapy treatment ..... |__|

1 = progression of disease / relapse / death due to PD
2 = toxicity *(+ toxic death), specify:* .....
3 = patient's refusal (not related to toxicity)
4 = intercurrent death (not due to malignant disease or toxicity)
5 = stable disease or end of treatment protocol
6 = lost to follow-up
7 = other, *specify:* .....
99 = unknown

STRATIFICATION

WHO performance status at start chemotherapy ..... |__|

0 = asymptomatic; 1 = symptomatic fully ambulatory; 2 = in bed < 50%; 3 = in bed > 50%; 4 = bedridden

	Level before start this chemotherapy	Recording Date
Hemoglobin concentration *(mmol/l)*	|__|__|.|__|__|	|__|__|-|__|__|-|__|__|__|__|
Platelet count (*10^9/l)	|__|__|__|__|	|__|__|-|__|__|-|__|__|__|__|
C-reactive protein CRP *(mg/l)*	|__|__|__|.|__|__|	|__|__|-|__|__|-|__|__|__|__|
Creatinine clearance *(ml/min)*	|__|__|__|	|__|__|-|__|__|-|__|__|__|__|
Of *(mmol/l) beiden in UV*	|__|__|.|__|	|__|__|-|__|__|-|__|__|__|__|
Plasma-cell infiltration in bone marrow (0 if ≤ 50%; 1 if > 50%	|__|	|__|__|-|__|__|-|__|__|__|__|

RESPONSE

Response recorded *(0=no; 1=yes)* ..... |__|

Date of response evaluation ..... |__|__|-\|__|__|-\|__|__|__|__|

Response to this treatment ..... |__|

1 = CR; 2 = VGPR; 3 = PR; 4 = MR; 5 = NC/SD; 6 = PD;
7 = relapse from CR; 8 = progression after VGPR/PR/MR;

Date of progression from this treatment line ..... |__|__|-\|__|__|-\|__|__|__|__|

NEXT TREATMENT LINE

Start of another treatment line after progression *(0=no; 1=yes)* ..... |__|

If not, reason: ..... |__|

1 = no other treatment options
2 = patient refusal
3 = no further benefit/poor Performance State
4 = death
5 = other, *specify* .....
99 = unknown

RESOURCE USE FORM (4)

Patient study number	Patient name code	Hospital
_____	____	.....

Hospital.....

Line number..... |__||__|

Start date of this line (=date progression from previous line)..... |__|__||__|__||__|__|__|__|

End date of this line (=day before progression from this line)..... |__|__||__|__||__|__|__|__|

VISITS TO OUTPATIENT CLINIC

Number of visits during this line ..... |__||__|

Number of telephone consults during this line ..... |__||__|

Number of day wards visits during this line..... |__||__|

Number of emergency room visits during this line ..... |__||__|

RADIOTHERAPY

If yes, specify site(s).....

Total number of days/fractions ..... |__||__|

Total dose (GY) ..... |__|__|.|__|

SURGERY

If yes, specify .....

LABORATORY

Number during this line..... |__||__||__|

Pathology (cytology) number during this line ..... |__||__||__|

RADIOLOGY

X-ray, number during this line ..... |__||__|

CT-scan, number during this line ..... |__||__|

Skelet stat, number during this line ..... |__||__|

MRI, number during this line..... |__||__|

Radionucleide/Bone scan, number during this line..... |__||__|

PET scan, number during this line ..... |__||__|

Ultrasound (echo), number during this line ..... |__||__|

Other, specify .....

BACTERIOLOGY/VIROLOGY

Bacterial cultures, number during this line ..... |__||__|

Viral cultures, number during this line ..... |__||__|

OTHER PROCEDURES

Other, specify .....

.....

.....

RESOURCE USE FORM (4)

Patient study number	Patient name code	Hospital
_____	___	.....

Hospital.....

Line number.....|____|

HOSPITALISATIONS

Date of admission *(dd,mm,yy)*	Date of discharge *(dd,mm,yy)*	Days in Intensive Care Unit *(*)*	Department *(**)*	Major Reason *(***)*
_____	_____	____	____	____
_____	_____	____	____	____
_____	_____	____	____	____
_____	_____	____	____	____
_____	_____	____	____	____

Specify (if applicable).....

.....

(*) Days in ICU: if patient did not stay at all in ICU, indicate 0
(**) Department: if patient moved between different departments indicate the department where the patient stayed most of his time.

Days in ICU *(*)*
0 = none
99 = unknown

Department *(**)*
1 = haematology/internal medicine ward
2 = surgery ward
3 = other
99 = unknown

Major reason for admission/visit *(***)*
1 = administration of chemotherapy
2 = surgery (specify)
3 = surgery complications (specify)
4 = toxicity/adverse events from chemotherapy (specify)
5 = progression of disease
6 = observation/routine follow-up
7 = social problems
8 = palliative care
9 = other
99 = unknown

CONCOMITANT MEDICATION FORM (5)

Patient study number	Patient name code	Hospital
|__|__|__|__|	|__|__|__|	....

Line number ....\|__\|\|__\|

Hospital ....

CONCOMITANT MEDICATION

Only drugs related to treatment of Multiple Myeloma

Generic drug name	Type (*)	Route (**)	Dose of unit	Dose/day	Unit	Total nr of days	Indication for use (***)
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|
....	|____|	|____|	|____|	|__________|	|_____|	|_____|	|__|

*Type: 1= Biphosphonates, 2= Analgesic, 3= Antibiotic, 4= Anti-emetic (except steroid), 5= Anti-diarrhea, 6= Lactative, 7= Diuretic, 8= Steroid, 9= Sedative, 10= Anti-coagulant, 11= anti-hypertensiva, 12= Anti-allergic, 13= Antacidum, 14= Growth factors, 15= Transfusion of ery's, 16= Transfusion of platelets, 17 = antiviral, 18 = antifungal, 88= other, specify:..] 99 = unknown

**Route: 1= Per os, 2= Intravenous, 3= subcutaneous, 4= Rectal, 5= Transdermal (patch), 6= Cutaneous, 7= Tracheal, 8= Intramuscular, 88=Other, 99= Unknown

***Indication for use 1= Toxicity (chemotherapy related), 2= Prophylaxis, 3= Disease related, 88= other, 99 = unknown

CONCOMITANT MEDICATION & ADVERSE EVENTS FORM (5)

Patient study number	Patient name code	Hospital
_____	____	.....

Hospital (one form should be used for all hospitals) .....
Line number ..... |__||__|

CONCOMITANT MEDICATION

Antibacterial/ Antifungal/ Antiviral

(e.g. Amoxicillin, Azitromycine, Ciprofloxacine, Co-Trimaxol, Diflucan, Erythromycine, Feniticilline, Flucloxacilline, Fluconazol, Gentamicine, Norfloxacine, Noroxin, Tobramycine, Valaciclovir, Zelitrex, Zithromax)

Given as **Prophylaxis**: |___| 0=no; 1=yes

Given as treatment for **acute infection**: |___| 0=no; 1=yes

Biphosponates

(e.g. APD, Zeledronine acid, Clodronine acid, Ostac, Didrokit)

Given (as Prophylaxis): |___| 0=no; 1=yes

ADVERSE EVENTS

Anaemia:

|___| (0=no; 1=yes) requiring |__||__| (number of bags) GEs/ PCs (Transfusion of ery's)

|___| (0=no; 1=yes) requiring Erythropoietin (e.g. EPO, Eprex, Epoëtine, Aranesp, Darbepoëtine)

Thrombocytopenia:

|___| (0=no; 1=yes) requiring |__||__| (number of bags) transfusion of platelets

Neurotoxicity: |___| 0=no; 1=yes

|___| (0=no; 1=yes) requiring *chronic and ongoing* treatment (e.g. Neurontin, Gabapentine)

Gastro-intestinal: (e.g. nausea, constipation, diarrhea) |___| 0=no; 1=yes

|___| (0=no; 1=yes) requiring *chronic and ongoing* treatment
(e.g. Nexium, Omeprazol, Losec, Esomeprazol, Pantoprazol, Imodium, Loperamide, Lactulose, Duphalac)

Analgesics: |___| 0=no; 1=yes

|___| (0=no; 1=yes) requiring *chronic and ongoing* treatment
(e.g. Paracetamol, Panadol, Tramadol, Morfine, Kapanol, MS-Contin, Oramorph)

MaxCRF

END OF FOLLOW-UP FORM (6)

Patient study number	Patient name code	Hospital
____	___	.....

Date of evaluation* ..... |__|__||__|__||__|__|__|__|

* Date of evaluation/present date or date of death

SURVIVAL

Survival status at this moment (0= alive, 1 = dead)..... |__|

In case of death: Main cause of death ..... |__|

1 = progression of disease/ multiple myeloma
2 = toxicity*
3 = infection*
4 = combination*
8 = other*
99 = unknown

* Specify.....]

Annex VI: Literature review of cost-effectiveness of bortezomib

Identification of studies

The aim of the search was to provide, as comprehensive as possible, a retrieval of economic evaluations of bortezomib in the treatment of multiple myeloma.

Sources searched

Three electronic databases were searched. The literature search was performed in March 2009 via the PubMed, Cochrane Library and EMBASE databases.

Keyword strategies

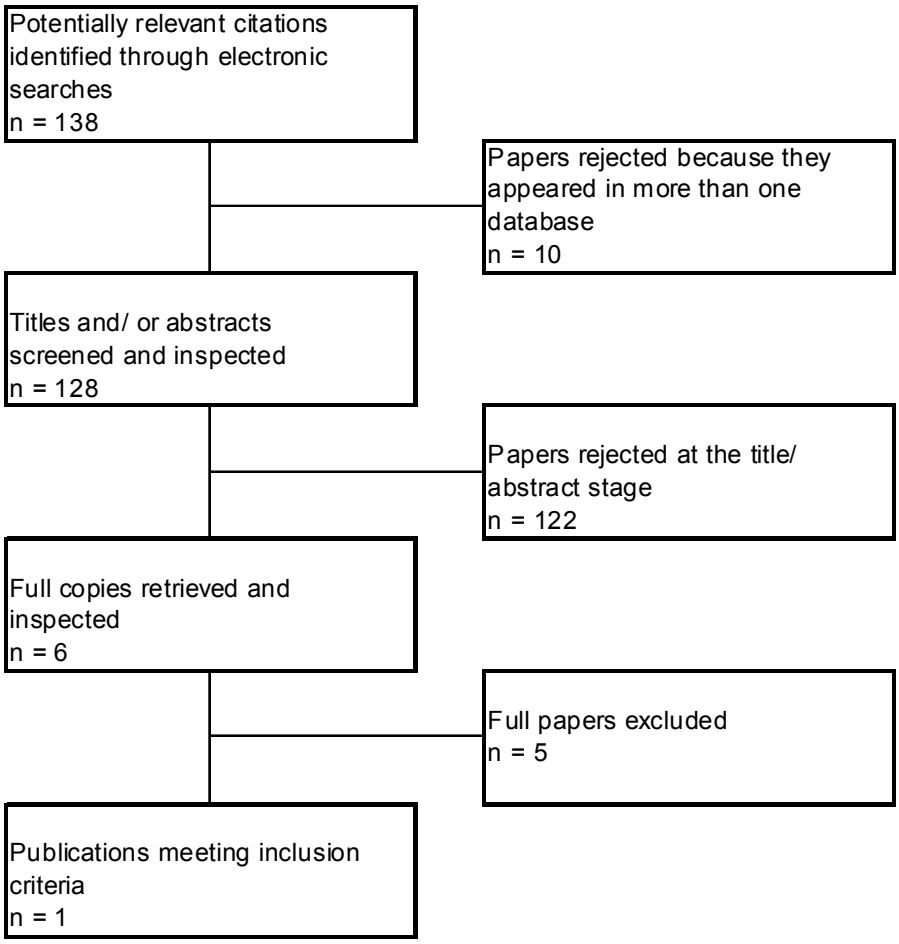
The queries used for the review were “bortezomib or velcade” and “cost or costs or economic”.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used: (1) articles were included if ‘costs’ or ‘cost-effectiveness’ of bortezomib for multiple myeloma was one of the main topics of the article, (2) only research articles were considered, reviews were excluded with the exception of hand-screening reference lists for additional publications, and (3) only articles using the English or Dutch language were considered. Full papers were obtained for any titles or abstracts that were considered relevant or where the title or abstract information was not sufficient to make a decision.

Results of cost-effectiveness review

The database-search identified 138 articles for potential inclusion in the review. Ten articles were excluded because they appeared more than once. A total of 122 articles were further rejected based on the title or abstract stage. Full copies were retrieved and inspected from a final selection of six articles. Of these, four articles were not research articles. One article included a review of recent health economic evidence in published literature relating to the management of multiple myeloma. In total, one publication met the inclusion criteria (Mehta, Duff, and Gupta 2004, 52-61).



Cost-effectiveness review

Mehta and colleagues (2004) report a cost-effectiveness study of bortezomib in the treatment of advanced multiple myeloma in comparison to best supportive care (BSC) and thalidomide. The economic analysis was undertaken from a payer's perspective.

Summary of effectiveness data

Evidence on the effectiveness of bortezomib was obtained from the Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy (SUMMIT), a single-arm, multicenter, phase II pivotal study (Richardson et. al. 2003). Decision analysis was employed to make three comparisons: (1) the full-cohort model that included all bortezomib patients from the SUMMIT versus BSC patients; (2) the first of two stratified models comparing bortezomib patients who were previous thalidomide users versus BSC

patients; and (3) the second stratified model comparing bortezomib patients who had not used thalidomide versus thalidomide patients.

The published data available from the SUMMIT did not include direct comparisons with the other treatment options (BSC and thalidomide). Therefore, a Delphi panel composed of six experts in MM was surveyed to obtain demographic, clinical, and medical resource-utilisation estimates. The median overall survival served as the measure of efficacy to evaluate cost-effectiveness.

Cost analysis

Only the direct medical costs associated with each therapy were included in the analyses. The total medical costs were a combination of costs related to three primary medical resource-utilisation components: (1) pharmacotherapy (i.e., primary therapy used to delay disease progression); (2) disease management (i.e., concomitant medications, office/clinic visits, diagnostic tests), and (3) adverse events. The resource use data were derived from the SUMMIT and the Delphi panel. Cost estimates obtained from objective, published sources were used to retrospectively assign unit costs to medical resource-utilisation. The price year was 2003.

Sensitivity analysis

Sensitivity analysis was performed by allowing the estimates for a number of key variables within a range of plus/minus 25%. The following variables were varied: (1) the prices of bortezomib and thalidomide, (2) the proportion of patients using bisphosphonates, (3) the frequency of chronic events, (4) the frequency of skeletal complications and (5) median survival.

Summary

The median overall survival for the bortezomib group was 16.0 months and 2.5 months in the BSC cohort. An estimated 62% and 7% of the patients in the bortezomib and BSC cohort, respectively, were assumed to survive for one year. In the first stratified model, the median overall survival for bortezomib patients with previous thalidomide use was 15.7 months compared to 2.5 months for the BSC cohort. One-year survival was 60% and 7%, respectively. In the second stratified model, bortezomib patients (without previous thalidomide use) had a median overall survival of 26.0 months, whereas the thalidomide

patients had an estimated median survival of 8.6 months. The one-year survival rates were 83% and 46%, respectively.

For the base-case analysis, the total costs of bortezomib therapy for multiple myeloma were $65.220 (€51.025) per patient, compared with $14.423 (€11.284) for BSC therapy. The total costs were based on the median duration of survival. The total costs of thalidomide therapy were $37.265 (€29.154) per patient.

The base-case scenario of the full-cohort model revealed an ICER of $45.356 (€35.484) per additional life-year for treatment with bortezomib compared with BSC. The ICER for treatment with bortezomib among patients previously treated with thalidomide relative to those managed with BSC resulted in an additional $49.797 (€38.959) per life-year gained. Conversely, the ICER for treatment with bortezomib among those without previous thalidomide use relative to those treated with thalidomide resulted in an additional $21.483 (€16.807) per life-year gained. The modified estimates used in the sensitivity analysis did not alter the direction of the results. The authors concluded that bortezomib provides a cost-effective option in the treatment of multiple myeloma and provides the best value among the currently available therapeutic options in terms of cost per life-year gained.

This study was associated with a few limitations. Firstly, only direct costs were included in the economic analysis, whereas the societal perspective is preferred in economic evaluations, of which requires the incorporation of all costs and effects. Secondly, the unit cost estimates may not be identical to the true costs. Finally, the ideal data source would have been a randomised clinical trial as opposed to the combination of clinical trial data, expert judgment and published data.

Conclusion

This systematic review contains just one cost-effectiveness analysis. Due to the weakness of the underlying data, it is too early to draw conclusions from this one assessment. Further research is necessary to assess the cost-effectiveness of bortezomib.

References: Literature review of cost-effectiveness of bortezomib

Mehta, J., S. B. Duff, and S. Gupta. 2004. Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. Managed Care Interface 17, (9) (Sep): 52-61.

Richardson, P. G., B. Barlogie, J. Berenson, S. Singhal, S. Jagannath, D. Irwin, S. V. Rajkumar, et al. 2003. A phase 2 study of bortezomib in relapsed, refractory myeloma. The New England Journal of Medicine 348, (26) (Jun 26): 2609-17.

Annex VII: Overview participating hospitals

The following hospitals participated in the pilot study:

Participating hospitals
Alkmaar, Medisch Centrum Alkmaar
Almere, Flevo ziekenhuis
Amersfoort, Meander Medisch Centrum
Amstelveen, Ziekenhuis Amstelland
Amsterdam, Academisch medisch centrum
Amsterdam, VU Medisch Centrum
Apeldoorn, Gelre ziekenhuis, locatie Apeldoorn
Arnhem, Alysis Zorggroep, locatie Rijnstate
Beverwijk, Rode Kruis Ziekenhuis
Capelle aan den IJssel, IJsselland ziekenhuis
Delft, Reinier de Graaf Gasthuis
Den Bosch, Jeroen Bosch Ziekenhuis, locatie Groot Ziekengasthuis
Den Haag, Haga ziekenhuis, locatie Leyweg
Den Helder, Gemini ziekenhuis
Deventer, Deventer ziekenhuis
Dirksland, Dirskland ziekenhuis
Dordrecht, Albert Schweitzer ziekenhuis
Ede, Ziekenhuis Gelderse Vallei
Enschede, Medisch Spectrum Twente
Goes, Oosterschelde ziekenhuis
Gorinchem, Rivas Zorggroep, locatie Beatrix ziekenhuis
Groningen, Universitair Medisch Centrum Groningen
Heemstede, Spaarne ziekenhuis, locatie Heemstede
Heerlen, Atrium Medisch Centrum, locatie Heerlen
Hoorn, Westfriesgasthuis
Leiden, Leids Universitair Medisch Centrum
Lelystad, IJsselmeerziekenhuizen, Zuiderzeeziekenhuis, locatie Lelystad
Nieuwegein, St Antonius ziekenhuis
Nijmegen, Universitair Medisch Centrum Sint Radboud
Roosendaal, Franciscus Ziekenhuis Roosendaal
Rotterdam, Erasmus MC, centrum locatie
Rotterdam, Erasmus MC, Daniel den Hoed
Rotterdam, Maasstad Ziekenhuis, locatie Clara
Rotterdam, Sint Franciscus Gasthuis
Terneuzen, ZorgSaam Ziekenhuis Terneuzen
Tilburg, Sint Elisabeth Ziekenhuis
Tilburg, TweeSteden Ziekenhuis, locatie Tilburg
Utrecht, Universitair Medisch Centrum Utrecht
Vlissingen, Ziekenhuis Walcheren
Woerden, Zuwe Hofpoort Ziekenhuis
Zutphen, Gelre Ziekenhuizen, locatie Het Spittaal
Zwolle, Isala Klinieken, locatie Sophia

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

Pilot outcomes research: costs and effects of oxaliplatin in stage III and metastatic colorectal cancer

C.W.M. van Gils[1]

W. Redekop[1]

L. Mol[3]

S. de Groot[1]

S.S. Tan[1]

M. Koopman[2]

J. Gaultney[1]

M.G. Franken[1]

C.J.A. Punt[4]

C.A. Uyl-de Groot[1]

1 Institute for Medical Technology Assessment, Erasmus University Rotterdam,

2 Department of Medical Oncology, University Medical Centre Utrecht,

3 Comprehensive Cancer Centre East Netherlands (IKO),

4. Department of Medical Oncology, Radboud University Nijmegen Medical Centre, The Netherlands.

July 2010

Acknowledgements

The authors would like to thank all the hospitals that participated, all hospital data managers involved and the Dutch Cancer Registry. The authors would also like to thank Anneke Spreij, Sangeeta Lachman, Ilse van Manen, Willem Lock, Tessa Jansen, Eva de Vries and Naomi van der Linden for their contributions to this study. This study was financed by the *College voor zorgverzekeringen* (CVZ, Health Care Insurance Board).

Contents

Abbreviations

5FU/LV	5-fluorouracil and leucovorin
AE	Adverse events
ANOVA	Analyses Of Variance
CAPOX	combinationtherapy of capecitabine and oxaliplatin
CBS	Centraal Bureau voor de Statistiek (Statistics Netherlands)
CEA	carcinoembryonic antigen
CFH	Commissie Farmacotherapeutische Hulp
CI	confidence interval
CRC	Colorectal cancer
CRF	Case Report Form
CVZ	College voor zorgverzekeringen (Health Care Insurance Board)
DCCG	Dutch Colorectal Cancer Group
DFS	Disease free survival
EORTC	European Organisation for Research and Treatment of Cancer
FL	fluoropyrimidines
FOLFOX	combinationtherapy of infusional 5FU/LV and oxaliplatin
FOLFIRI	combinationtherapy of infusional 5FU/LV and irinotecan
HR	Hazard Ratio
ICD-O	International Classification of Diseases for Oncology
IFL	combinationtherapy of bolus 5FU/LV and irinotecan
iMTA	institute for Medical Technology Assessment
mCRC	Metastatic colorecal cancer
MOSAIC trial	RCT comparing FOLFOX to 5FU/LV
NKR	Nederlandse Kanker registratie (Netherlands Cancer Registry)
NSABP C-07 trial	RCT comparing FOLFOX to 5FU/LV
NVMO	Nederlandse Vereniging voor Medische Oncologie (Dutch Society of Medical Oncology)
NZa	Nederlandse Zorg autoriteit (The Dutch Healthcare Authority)
OR	Odds Ratio
OS	Overall survival
QALY	Quality-adjusted life year
RCT	Randomized Controlled Trial
TNM	classification of malignant tumours; T = direct extent of the primary tumor; N = degree of spread to regional lymph nodes; M = presence of metastasis
UFT	uracil/tegafur
WHO PS	World Health Organization Performance Status
X-ACT trial	RCT comparing capecitabine to 5FU/LV

Summary

Introduction

Colorectal cancer is one of the most common causes of cancer in the western world with more than 200,000 deaths in Europe in 2006. Over the past decade, significant progress has been achieved in the treatment of colorectal cancer by advances in, among others, systemic chemotherapy. Oxaliplatin, a third-generation chemotherapeutic agent, became available for the palliative treatment of metastatic colorectal cancer in 2000 and was subsequently approved for the adjuvant treatment of stage III colon cancer in 2005. Oxaliplatin is an expensive medicine and was admitted under the Dutch 'expensive medicines' policy regulation in order to allow hospitals to obtain additional funding for this drug. Since 2006, the Dutch policy regulation for expensive hospital medicines requires evidence about the real world utilization, effectiveness and cost-effectiveness after three years of temporary supplemental funding. Outcomes research in this particular context is new in Dutch policymaking and experience in the application of outcomes research is therefore lacking. This paper investigates how oxaliplatin is used in daily practice and explores its real-world treatment effects and costs in stage III colon and metastatic colorectal cancer in Dutch daily practice. This pilot outcomes research study was conducted as part of a comprehensive study of methodological issues related to outcomes research.

Methods

The oxaliplatin pilot study examined the appropriate use and cost-effectiveness of oxaliplatin by exploring how it was used in Dutch daily practice for a) the treatment of stage III colon cancer; and b) the treatment of metastatic colorectal cancer. Real-world effects and costs of oxaliplatin treatment were investigated. The pilot study population was identified via the database of the Dutch Cancer Registry and comprised patients diagnosed with stage III colon or stage IV colorectal cancer. Of note, stage IV concerns patients who present with distant metastases (synchronous disease), as opposed to patients who develop distant metastases during follow-up (metachronous disease). Since patients with metachronous disease are not registered by the Dutch Cancer registry, this analysis is restricted to stage IV synchronous patients. First, minimal Case Report Forms were retrospectively completed using hospital medical records. Second, maximal Case Report Forms were used to collect additional detailed data for a representative sub-group.

We investigated how oxaliplatin was used in daily practice and analysed application of treatment regimes, dose modifications and treatment-related toxicities. Survival curves were visualised using Kaplan-Meier methods to analyse the effect of oxaliplatin on disease-free survival (stage III) and overall survival (stage IV). Treatment costs were calculated using the hospital perspective and resource use was assessed per individual patient by means of micro-costing estimates. Results of stage III colon cancer were compared to the pivotal clinical registration trial (MOSAIC trial). Results of stage IV colorectal cancer were compared to the post-registration trial (CAIRO trial) that took place in the Netherlands during the same time period used in the pilot study. Our retrospective study design made it impossible to collect data on Health Related Quality of Life (HRQOL). However, the CAIRO study measured the disease specific quality of life using the QLQ-C30 questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC). We used a recently developed model to convert these QLQ-C30 values into health utilities to allow comparisons of Quality adjusted life years (QALYs) between the treatment groups in metastatic colorectal cancer. Lastly, the incremental cost-effectiveness of oxaliplatin in stage III colon cancer was determined using a probabilistic Markov model, synthesising evidence from the pilot study and the pivotal clinical registration trial (MOSAIC).

Results

Oxaliplatin in stage III colon cancer

In total 463 patients were treated in 19 selected hospitals. 391 of these patients were included. The most frequently used treatment regimens in the Netherlands during the study period were capecitabine combined with oxaliplatin (CAPOX, 37%), 5FU/LV combined with oxaliplatin (FOLFOX, 35%), capecitabine monotherapy (24%), and different 5-FU/LV regimens (4%). There was a quick diffusion of oxaliplatin in the time period examined in the pilot study. The planned dose for each regimen was equal to the dosing recommendations found in the Dutch guidelines. The mean administered dosage per week across all cycles was only slightly lower than the planned dosage. However, oxaliplatin seemed to be less well tolerated when given in the CAPOX schedule than in the FOLFOX schedule. Patients who did not receive oxaliplatin were significantly older and more often had comorbidities than patients who received oxaliplatin. There were clear reasons why patients did not receive oxaliplatin. These observations provided evidence to conclude that the prognosis of patients who received oxaliplatin was not comparable with the prognosis

of other patients, and that a direct comparison of disease-free survival was not justified. However we were able to compare our findings to the results of the MOSAIC trial. In total 82% of the pilot patients who received oxaliplatin fulfilled the inclusion criteria of the MOSAIC trial. Baseline characteristics, FOLFOX schedules, total cumulative dosages and disease free survival outcomes were comparable between the MOSAIC trial patients and the pilot study patients who fulfilled the eligibility criteria used in the MOSAIC study and also received oxaliplatin. The average costs per patient were € 9,114 for 5FU/LV, € 9,220 for capecitabine monotherapy, € 30,873 for FOLFOX and € 17,212 for CAPOX. Differences in baseline characteristics did not seem to be associated with total costs. The incremental cost-effectiveness per QALY gained varied between € 15,491 and € 22,836, depending on the chosen population and scenario.

Oxaliplatin in metastatic colorectal cancer

In total 433 patients diagnosed with stage IV colorectal cancer were treated in 29 selected hospitals; 312 of these patients were included for further analyses. Sixty-three percent of the patients received first-line monotherapy with fluoropyrimidines, and 37% received combination therapy with either oxaliplatin or irinotecan. When the CAIRO eligibility criteria were applied to the pilot study population, 71% (224/314) of them fulfilled all criteria. Most patients with metastatic colorectal cancer received several treatment lines. At least half of the patients receiving monotherapy as first-line treatment received combination therapy with either oxaliplatin or irinotecan in the second line. In the third line 22% of the patients still received chemotherapy. The types of second-line and third-line therapy given to patients receiving first-line combination therapy were very similar to these results, although a larger proportion of these patients received both oxaliplatin and irinotecan during the course of their disease compared to patients receiving first-line monotherapy. In general, our findings were in line with the recommendations found in the Dutch guidelines. The prognosis of the pilot study patients who fulfilled the CAIRO study eligibility criteria was comparable with the prognosis of the patients in the CAIRO study. This was reflected in the overall survival outcomes. Among eligible pilot patients, median overall survival was 15.1 (95% CI 12.8 – 19.0) months for the patients who received first-line combination therapy and 11.2 (95% CI 9.5 – 13.3) months for patients receiving first-line monotherapy. In the CAIRO study, the median overall survival was 15.9 (95% CI 14.3 – 18.0) months for patients receiving first-line combination therapy and 13.4 (95% CI 11.5 – 15.2) months for the patients who received first-line monotherapy. No significant differences were found

between the CAIRO study and the pilot patients treated in Dutch clinical practice. However, patients receiving monotherapy in the pilot study tended to have a slightly worse outcome compared to the CAIRO patients receiving first-line monotherapy and compared to patients receiving combination therapy. This can be explained by the non-random assignment of treatments in the pilot population. The proportion of patients older than 70 years of age was greater amongst the pilot study patients receiving monotherapy than amongst the pilot study patients receiving combination therapy and the CAIRO patients. Besides this we found that these patients were significantly less often treated with a third-line therapy than patients in the CAIRO sequential (first-line monotherapy) treatment arm. This may reflect a tendency towards a higher motivation for treatment in trial versus non-trial patients. Regarding quality of life, the CAIRO study found that patients randomised to first-line monotherapy and patients receiving combination therapy had a comparable overall mean utility (0.77 vs. 0.76). Total mean costs in eligible pilot patients amounted to € 19,812 for monotherapy, € 28,200 for oxaliplatin combination therapy and € 44,664 for irinotecan combination therapy. Mean costs for monotherapy and oxaliplatin combination therapy were significantly different. A substantial cost variation was found in the total costs obtained for individual patients within treatment groups as well as in each individual cost component. Inpatient hospital days and chemotherapy (leucovorin, capecitabine, oxaliplatin and irinotecan) were the most important cost drivers.

Discussion

Outcomes research provides valuable information on the utilisation of oxaliplatin in daily practice. In stage III colon cancer, insight into patient baseline characteristics, use of oxaliplatin, toxicities and effectiveness demonstrated that treatment with oxaliplatin in clinical practice corresponds well with the requirements for registering oxaliplatin at T = 0.
However, a valid comparison between patients who did and did not receive oxaliplatin was not possible. As a result, MOSAIC patients randomised to receive the control treatment without oxaliplatin were used as a comparator group in the cost-effectiveness model to calculate the incremental cost-effectiveness of oxaliplatin. In our opinion, this approach led to a sufficiently precise and valid estimate of the cost-effectiveness of oxaliplatin in daily clinical practice. In conclusion, both the cost-effectiveness and the appropriate use of oxaliplatin in the treatment of stage III colon cancer in daily practice could be sufficiently substantiated. In metastatic colorectal cancer we were able to make use of the CAIRO post-registration trial and the pilot patients were selected from the same underlying source

population as part of the CAIRO patients. This allowed valid comparisons to be made between the eligible pilot population and the CAIRO patients. The results of the studies were comparable and led us to conclude that it was feasible to make a sufficiently precise and valid estimate of the cost-effectiveness of oxaliplatin. Also, the appropriate use of oxaliplatin for the indication of metastatic colorectal cancer could be sufficiently substantiated.

However it is important to realise that a crucial factor in this pilot study was the ability to use data and results from trials such as the MOSAIC and CAIRO, combined with a limited dynamics in daily practice (i.e., a limited amount of treatment variation). The combination of data sources used in this study is a cogent reminder that the assessment of the real-world effectiveness and cost-effectiveness of a medicine will make use of all available data. The actual approach to be taken will have to depend on the types of data and evidence available at the time of the final assessment (i.e., 3-4 years of use in daily practice).

Samenvatting

Introductie

Colorectaal kanker is één van de meest voorkomende vormen van kanker in de westerse wereld. Er stierven meer dan 200.000 personen ten gevolge van colorectaal kanker in Europa in 2006. De afgelopen tien jaar is er belangrijke vooruitgang geboekt in de behandeling van colorectaal kanker door verbetering van onder andere systemische chemotherapie. Oxaliplatin is sinds 2000 beschikbaar voor het palliatief behandelen van gemetastaseerd colorectaal kanker en werd in 2005 goedgekeurd voor de adjuvante behandeling van stadium III colon kanker. Oxaliplatin is een duur medicijn en is daarom op de beleidsregel 'Dure geneesmiddelen' geplaatst, zodat ziekenhuizen aanvullende financiering krijgen. Uit deze beleidsregel vloeit sinds 2006 voort dat na drie jaar tijdelijke aanvullende financiering, bewijs over het gebruik, het effect en de kosten-effectiviteit van de dure geneesmiddelen in de dagelijkse, klinische praktijk verzameld wordt. Uitkomstenonderzoek voor dit doeleinde is nieuw in Nederland. Er is daarom weinig ervaring met de toepassing ervan. Het doel van deze studie is onderzoeken hoe oxaliplatin wordt gebruikt in dagelijkse, klinische praktijk. Daarnaast worden de werkelijke behandeleffecten en kosten in stadium III colon kanker en gemetastaseerd colorectaal kanker in de dagelijkse, klinische praktijk onderzocht. Deze pilot studie is uitgevoerd als onderdeel van een uitgebreide studie naar methodologische aspecten bij uitkomstenonderzoek.

Methoden

De oxaliplatin pilot studie onderzoekt hoe oxaliplatin in de dagelijkse, klinische praktijk gebruikt wordt. Tevens wordt de kosteneffectiviteit van oxaliplatin onderzocht voor a) de behandeling van stadium III colon kanker; en b) de behandeling van gemetastaseerd colorectaal kanker. De onderzoekspopulatie is vastgesteld door middel van de database van de Nederlandse Kankerregistratie (NKR) en bestaat uit patiënten die gediagnosticeerd zijn met stadium III colon kanker of stadium IV colorectaal kanker. Stadium IV colorectaal kanker patiënten betreft patiënten die zich presenteerden met afstandsmetastasen (synchrone metastasen), in tegenstelling tot patiënten die afstandsmetastasen ontwikkelden gedurende follow-up (metachrone metastasen). Omdat patiënten met metachrone metastasen niet geregistreerd zijn door de NKR is deze studie alleen gericht op patiënten met stadium IV colorectaal kanker (synchrone metastasen). Eerst werden

minimale Case Report Forms retrospectief ingevuld met behulp van de medische dossiers van de patiënten. Daarna werden maximale Case Report Forms gebruikt om aanvullende informatie te verzamelen over een representatieve subgroep. Om het gebuik van oxaliplatin in de dagelijkse, klinische praktijk te onderzoeken werden de toepassing van behandelschema's, dosis aanpassingen en behandelinggerelateerde toxiciteiten bestudeerd. Overlevingscurves werden ontwikkeld met behulp van de Kaplan-Meier methode om de effecten van oxaliplatin op ziektevrije overleving (stadium III) en totale overleving (stadium IV) te analyseren. Behandelkosten werden berekend vanuit het ziekenhuisperspectief. Kosten werden per individuele patiënt bepaald met behulp van van micro-costing. Resultaten van de stadium III colon kanker pilot studie werden vergeleken met de klinische registratie trial (MOSAIC trial). Resultaten van de stadium IV colorectaal kanker pilot studie werden vergeleken met de post-registratie trial (CAIRO trial) die plaats vond in Nederland gedurende dezelfde periode als de pilot studie. Het retrospectieve onderzoeksdesign maakte het onmogelijk om data te verzamelen over de gezondheidsgerelateerde kwaliteit van leven. Echter, de CAIRO trial onderzocht de ziektespecifieke kwaliteit van leven gebruikmakend van de QLQ-C30 vragenlijst van de Europese Organisatie voor Onderzoek en Behandeling van Kanker (EORTC). Met behulp van een recent ontworpen model zijn de QLQ-C30 waarden omgezet in utiliteiten om een vergelijking te kunnen maken in voor kwaliteit van leven gecorrigeerde levensjaren (QALYs) tussen verschillende behandelingen voor gemetastaseerd colorectaal kanker. Tot slot is de incrementele kosten-effectiviteit van oxaliplatin in stadium III colon kanker vastgesteld met behulp van een probabilistisch Markov model, waarin resultaten van de pilot studie en MOSAIC trial werden samengevoegd.

Resultaten

Oxaliplatin in stadium III colon kanker

In totaal werden 463 patiënten behandeld in 19 geselecteerde ziekenhuizen. Van deze patiënten werden er 391 geïncludeerd. De meest frequent toegepaste behandelschema's in Nederland gedurende de studie waren capecitabine gecombineerd met oxaliplatin (CAPOX, 37%), 5FU/LV gecombineerd met oxaliplatin (FOLFOX, 35%), capecitabine monotherapie (24%) en verschillende 5-FU/LV schema's (4%). Er was een snelle verspreiding van oxaliplatin in de bestudeerde tijdsperiode van de pilot studie. De geplande dosering voor elk schema was gelijk aan de doseringsaanbevelingen in de Nederlandse richtlijnen. De gemiddelde toegediende dosering per week gedurende alle

kuren was slechts iets lager dan de geplande dosering. Oxaliplatin lijkt echter minder goed getolereerd te worden in het CAPOX schema dan in het FOLFOX schema. Patiënten die geen oxaliplatin kregen waren significant ouder en hadden meer comorbiditeiten dan de patiënten die wel behandeld werden met oxaliplatin. Er waren duidelijke redenen waarom patiënten niet met oxaliplatin behandeld werden. Het bleek dat de prognose van patiënten die met oxaliplatin behandeld werden niet vergelijkbaar was met de prognose van andere patiënten, en dat directe vergelijking met betrekking tot ziektevrije overleving niet mogelijk was. Daarentegen was het wel mogelijk om de bevindingen te vergelijkingen met de resultaten van de MOSAIC trial. In totaal voldeden 82% van de pilot patiënten die met oxaliplatin behandeld werden aan de inclusiecriteria van de MOSAIC trial. Basiskarakteristieken, FOLFOX schema's, totale cumulatieve doseringen en uitkomsten met betrekking tot ziektevrije overleving waren vergelijkbaar tussen de MOSAIC trial patiënten en de pilot studie patiënten die behandeld werden met oxaliplatin en voldeden aan de inclusiecriteria van de MOSAIC trial. De gemiddelde kosten per patiënt waren €9.114 voor 5FU/LV, €9.220 voor capecitabine monotherapie, €30.873 voor FOLFOX en €17.212 voor CAPOX. Verschillen in basiskarakteristieken leken niet in verband te staan met de totale kosten. De incrementele kosten-effectiviteit per gewonnen QALY varieerde van €15.491 tot €22.836, afhankelijk van de gekozen populatie en het scenario.

Oxaliplatin in gemetastaseerd colorectaal kanker

In totaal werden 433 patiënten met stadium IV colorectaal kanker behandeld in 29 geselecteerde ziekenhuizen; 312 patiënten werden geïncludeerd voor verdere analyse. Drieënzestig procent van deze patiënten kreeg eerstelijns monotherapie met fluoropyrimidines en 37% kreeg combinatietherapie met oxaliplatin of irinotecan. Eenenzeventig procent (224/314) van de pilot studie populatie vervulde de inclusiecriteria van de CAIRO trial. Minstens de helft van de patiënten die monotherapie als eerstelijns behandeling kreeg, kreeg combinatietherapie met oxaliplatin of irinotecan in de tweede lijn. In de derde lijn werd 22% van de patiënten nog steeds met chemotherapie behandeld. Deze resultaten kwamen overeen met het type tweedelijns en derdelijns behandeling dat aan patiënten werd gegeven die in de eerste lijn met combinatietherapie behandeld werden, alhoewel een groter deel van deze patiënten oxaliplatin en irinotecan kregen gedurende hun ziekte in vergelijking met patiënten die monotherapie kregen als eerstelijns behandeling. Over het algemeen komen de bevindingen overeen met de aanbevelingen in de Nederlandse richtlijnen. De prognose van de pilot studie patiënten die voldeden aan de

inclusiecriteria van de CAIRO trial was vergelijkbaar met de prognose van de patiënten in de CAIRO trial. Dit werd ook zichtbaar in resultaten met betrekking tot totale overleving. De mediane totale overleving van de 'eligible' pilot studie patiënten; i.e. de patiënten die voldeden aan de inclusiecriteria was 15,1 (95% BI 12,8 – 19,0) maanden voor de patiënten die combinatietherapie in de eerste lijn kregen en 11,2 (95% BI 9,5 – 13,3) maanden voor patiënten die monotherapie in de eerste lijn kregen. In de CAIRO studie was de mediane totale overleving 15,9 (95% BI 14,3 – 18,0) maanden voor patiënten die combinatietherapie in de eerste lijn kregen en 13,4 (95% BI 11,5 – 15,2) maanden voor patiënten die monotherapie in de eerste lijn kregen. Er werd geen significant verschil gevonden in de totale overleving van de patiënten in de CAIRO trial en de pilot patiënten die werden behandeld in dagelijkse, klinische praktijk. Echter, patiënten die monotherapie kregen in de pilot studie leken een iets slechtere uitkomst te hebben vergeleken met de CAIRO patiënten die eerstelijns monotherapie kregen en vergeleken met patiënten die combinatietherapie kregen. Dit verschil kan worden verklaard door de niet-random toewijzing van behandelingen in de pilot populatie. Het aantal patiënten dat ouder was dan 70 jaar was groter bij de patiënten in de pilot studie die monotherapie kregen dan bij de patiënten in de pilot studie die combinatietherapie kregen en bij de CAIRO trial patiënten. Ook kregen deze patiënten significant minder vaak een derdelijns behandeling dan patiënten in de CAIRO studie (eerstelijns monotherapie). Dit wijst wellicht op een neiging tot een grotere motivatie voor het behandelen van trial versus non-trial patiënten. Betreffende kwaliteit van leven was één van de conclusies van de CAIRO trial dat patiënten die eerstelijns monotherapie kregen en patiënten die combinatietherapie kregen een vergelijkbare gemiddelde utiliteit hadden (0,77 vs. 0,76). De gemiddelde totale kosten voor de 'eligible' pilot patiënten bedroegen € 19.812 voor monotherapie, € 28.200 voor oxaliplatin combinatietherapie en € 44.664 voor irinotecan combinatietherapie. De gemiddelde totale kosten voor monotherapie en oxaliplatin combinatietherapie waren significant verschillend. Een substantiële variatie in kosten werd gevonden in de totale kosten van individuele patiënten binnen behandelgroepen, als ook voor individuele kostencomponenten. Kosten van verpleegdagen en chemotherapie (leucovorin, capecitabine, oxaliplatine en irinotecan) waren de belangrijkste kostenposten.

Discussie

Uitkomstenonderzoek voorziet in belangrijke informatie over het gebruik van oxaliplatin in de dagelijkse, klinische praktijk. In stadium III colon kanker, inzicht in de

basiskarakteristieken van patiënten, het gebruik van oxaliplatin, de effectiviteit en toxiciteiten liet zien dat de behandeling met oxaliplatin in de praktijk overeenkomt met de vereisten voor de registratie van oxaliplatin op T = 0. Een goede vergelijking tussen patiënten die wel en niet met oxaliplatin behandeld werden was echter onmogelijk. Ter vergelijking werden daarom MOSAIC patiënten gebruikt die de controlebehandeling kregen voor het berekenen van de incrementele kosteneffectiviteit van oxaliplatin. Naar onze mening heeft deze benadering geleid tot een voldoende precieze en valide schatting van de kosteneffectiviteit van oxaliplatin in de dagelijkse, klinische praktijk.

Zowel de kosteneffectiviteit als het juiste gebruik van oxaliplatin bij de behandeling van stadium III colon kanker in de dagelijkse, klinische praktijk is voldoende onderbouwd. Bij gemetastaseerd colorectaal kanker kon gebruik gemaakt worden van de CAIRO post-registratie trial. De pilot studie patiënten werden geselecteerd uit dezelfde populatie, waardoor valide vergelijkingen gemaakt konden worden tussen de 'eligible' pilot studie patiënten en de CAIRO trial patiënten. De resultaten van de studies waren vergelijkbaar, waaruit bleek dat het mogelijk was om een voldoende precieze en valide schatting te maken van de kosten-effectiviteit van oxaliplatin. Bovendien kon het juiste gebruik van oxaliplatin voor de indicatie gemetastaseerd colorectaal kanker voldoende worden onderbouwd.

Het is belangrijk om te realiseren dat een cruciale factor in deze pilot studie de mogelijkheid was om data en resultaten van trials, zoals de MOSAIC en CAIRO trial te gebruiken, gecombineerd met de beperkte dynamiek in de dagelijkse, klinische praktijk, met andere woorden de beperkte behandelvariatie. Het combineren van databronnen bevestigt dat bij het vaststellen van de effectiviteit en kosteneffectiviteit van een medicijn in de dagelijkse, klinische praktijk alle beschikbare data gebruikt dient te worden. Deze benadering is afhankelijk van het type data en het type bewijs dat aanwezig is op moment T = 3.

Background

Policy regulation

At the request of the Minister of Health, Welfare and Sport, the Dutch Healthcare Authority (NZa) amended the existing 'expensive medicines' policy regulation as of 1st January 2006. Provisional inclusion in this policy regulation makes it obligatory for the applying party to perform outcomes research. Outcomes research is described as the collection and analysis of data from daily clinical practice that are useful to assess the degree of appropriate use and determine the degree of cost-effectiveness of expensive hospital medicines within the framework of the additional financing of hospital based medicines.[1]

Research

At the request of the *College voor zorgverzekeringen* (CVZ, Health Care Insurance Board), the institute for Medical Technology Assessment (iMTA) conducted research into the methodological aspects that are important when carrying out outcomes research. An initial report relating to a literature study has already been issued. The present study is a study of daily practice in which two pilot studies take a central position. In addition to the literature study, the results of the pilot studies will contribute valuable information for the Guidance on outcomes research. The methodological problems brought to light by the two pilot studies will be described in a separate report. The present report discusses the content of the results of the outcomes research on one of the pilot studies: oxaliplatin. This drug is available in the Netherlands for the treatment of high-risk stage II, stage III, and metastatic colorectal cancer.

Colorectal cancer

Each year about 10,000 new patients are diagnosed with colorectal carcinoma. In the Netherlands, the incidence of colorectal carcinoma among men, with 14% of the total number of tumours, takes third place after prostate (21%) and long cancer (16%), and with 13% among women, it takes second place after breast cancer (33%). The number of patients diagnosed with colorectal carcinoma is expected to rise to about 14,000 in 2015 due to a slowly increasing incidence (particularly among men), the growing population and the ageing population.[2, 3]

Colorectal carcinoma usually develops from a polyp. Such a polyp, which is a growth or thickening of the mucous membrane that lines the intestines, is usually benign, but some develop into cancer over time. Stage I and II invasive colorectal cancers confined to the wall of the colorectum comprise 40% of all cases of colorectal cancer. In stage III, occurring in 37% of the patients, the carcinoma extends to the regional lymphatic glands. In stage IV

patients, which comprise 19% of all colorectal cancer patients at diagnosis, the cancer has already spread to distant sites.

The stage of disease plays an important role in treatment options. In stage I, II and III patients, surgery is the recommended treatment option and is performed with curative intent. However, nearly half of the patients who undergo curative surgery will ultimately relapse and die of metastatic disease.[4, 5] In patients with stage III colon cancer, 6 months of adjuvant chemotherapy decreases the risk of recurrence and has become part of the standard treatment. Stage IV patients have advanced or metastatic disease which is usually not curable. Chemotherapy is part of the standard treatment of metastatic colorectal cancer, since it has clearly been shown to lengthen the progression free and overall survival.

Oxaliplatin

For a long time, treatment with intravenous 5-fluorouracil and leucovorin (5FU/LV) was the only effective chemotherapy for patients with colorectal cancer.[67, 8] However, during the past decade clinical trials have shown the efficacy of new products that are either equivalent in efficacy but less toxic or superior in efficacy to 5FU/LV. Oxaliplatin is a third-generation oncolytic, derived from platinum. In 2002 the drug was included in the list of 'expensive medicines' for metastatic colorectal cancer. Since 2005 oxaliplatin has also been eligible for additional reimbursement in stage III colon cancer after obtaining a positive advice from the CVZ on including it in the NZa policy regulation.

Objectives

The questions that are addressed in the present study are:

<u>Stage III colon cancer (section 1)</u>

1) How is oxaliplatin used in daily practice for the treatment of stage III colon cancer?
2) What are the real-world effects and costs of oxaliplatin in stage III colon cancer?
3) What is the cost-effectiveness of oxaliplatin in stage III colon cancer?

<u>Metastatic colorectal cancer (section 2)</u>

1) How is oxaliplatin used in daily practice for the first-line treatment of metastatic colorectal cancer?
2) What are the real-world effects and costs of oxaliplatin in metastatic colorectal cancer?
3) What is the cost-effectiveness of oxaliplatin as first-line treatment in metastatic colorectal cancer?

These items will be discussed in two different sections. In section 1, we describe a retrospective analysis of population-based data for patients treated with adjuvant chemotherapy following diagnosis of stage III colon cancer in 2005 and 2006. In section 2, we describe a retrospective analysis of population-based data of patients receiving chemotherapy for metastatic colorectal cancer. Here a cohort of stage IV patients diagnosed in 2003 and 2004 was selected, since oxaliplatin was already available by that time for metastatic colorectal cancer.

For this study, iMTA worked in close collaboration with the Radboud University Nijmegen Medical Centre, the core institution of the Dutch Colorectal Cancer Group (DCCG). Annex I contains a specification of this collaboration.

Section 1 Oxaliplatin in stage III colon cancer

1. Introduction

The initial treatment for about 80% of the patients with stage III colon carcinoma is a complete resection of the primary tumour. Almost half of these patients will eventually relapse.[5] As adjuvant chemotherapy has clearly been shown to lengthen disease-free and overall survival, it has become part of the standard treatment.[9] For a long time, treatment with intravenous 5-fluorouracil and leucovorin (5FU/LV), with a 3-years survival of 65% was the only available effective adjuvant chemotherapy for patients with stage III colon carcinoma.[7, 8] However, during the past decade clinical trials have shown that new products are either equivalent in efficacy but less toxic or even superior in efficacy.

Capecitabine

Capecitabine is the oral pro-drug of fluorouracil. The X-ACT trial compared treatment using oral capecitabine with the Mayo clinic 5FU/LV schedule.[10, 11] The primary endpoint of this study was non-inferiority with respect to disease-free survival. After a 7-year median follow-up, no difference in disease-free and overall survival could be demonstrated between the two treatment groups. In addition, toxicities required comparable dose reductions in both treatment groups (5FU/LV 52% versus capecitabine 57%). In comparison with 5FU/LV, the incidence of stomatitis, alopecia and neutropenia was lower and the incidence of hand-foot syndrome higher in the capecitabine group. Overall, capecitabine was better tolerated compared to 5FU/LV. Based on these results and the fact that these data are supported by comparable findings relating to metastatic colorectal carcinoma, current advice is to prescribe capecitabine as standard adjuvant therapy in situations where 5FU/LV was previously used.

Economic evaluations based on the X-ACT trial have estimated that the costs of capecitabine are about € 5,400 lower than those of 5FU/LV.[12-1415] This cost saving in comparison with 5FU/LV was particularly due to a reduction in inpatient hospital days and adverse effects.

Oxaliplatin

A systematic literature study was carried out regarding the clinical efficacy and cost-effectiveness of oxaliplatin for the adjuvant treatment of colon carcinoma. The study relates to literature published between January 2005 and February 2009 (between T=0 and T=3). Annexes II and III provide a complete review of this literature study. The most important findings are described below.

Oxaliplatin combined with 5FU/LV

The literature review revealed seven publications, 4 publications based on the MOSAIC trial and 3 based on the NSABP C-07 trial. None of the publications relating to the NSABP C-07 trial reported specifically on the sub-group of stage III patients with colon carcinoma. Dutch guidelines on oxaliplatin for the adjuvant treatment of stage III colon carcinoma are exclusively based on the MOSAIC trial. This trial is discussed here separately. [5, 16 17, 18]

The MOSAIC trial compared 5FU/LV with the combination therapy of 5FU/LV and oxaliplatin (FOLFOX). Table 1.1.1 provides a summary of the trial results after a median 6-year follow-up. Treatment with FOLFOX led to a significantly better disease-free ($p = 0.005$) and overall survival ($p = 0.046$) than 5FU/LV alone. Neurotoxicity was the most important adverse event of oxaliplatin. However, this side effect decreased in most patients within 1 year. At 18 months after treatment, about 25% of the patients still had some degree of neurological symptoms. In addition, FOLFOX was associated with more neutropenia, diarrhoea, nausea and vomiting than 5FU/LV alone. [16, 17]

Table 1.1.1 Summary MOSAIC trial, limited to stage III colon carcinoma

André T, et al. (2009). Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. J Clin Oncol 27:3109-3116

Study design	Phase III randomized controlled trial	
TNM tumour stage	stage III after complete resection of primary tumour	
Intervention/ treatment arms	5-FU/LV	5-FU/LV with oxaliplatin
Number of patients randomized	n=675	n=672
Planned cumulative dose		
Oxaliplatin	NA	1,020 mg/m2
Fluorouracil (5-FU)	12,000 mg/m2	12,000 mg/m2
Leucovorin (LV)	2,400 mg/m2	2,400 mg/m2
Primary endpoint	Disease free survival (DFS)	
DFS defined	Time to progression or death, whichever comes first	
Primary analyses cut-off	3 years from enrollment of last patiënt or 303 events (relapse or death) in test arm, whichever comes later	
Secondary endpoints	Safety, overall survival (OS), long-term adverse events	
Statistical power	90% to detect a 6% increase in DFS at 3 years	
Clinical effects		
Disease free survival	58.9%	66.4%
Hazard Ratio (95% CI)	0.78 (0.65 tot 0.93)	
Overall survival	68.7%	72.9%
Hazard Ratio (95% CI)	0.80 (0.65 tot 0.97)	
Safety	Oxaliplatin is associated with a 20% mortality reduction Oxaliplatin increases the risk of severe neutropenia and diarrhea	
Long-term adverse events	Neurotoxicity is present in >85% of the oxaliplatin patients	

NA = not applicable

With respect to disease-free and overall survival, the relative advantage of 5FU/LV with oxaliplatin in comparison with 5FU/LV alone was not age-related. Although severe neutropenia and/or thrombocytopenia were observed more often in patients of at least 70 years of age (p = 0.040), no difference could be demonstrated in patients younger than 70 years with respect to other grade ≥ 3 adverse effects.[19]

Various economic evaluations were carried out based on the MOSAIC trial.[12, 20-22] All economic evaluations revealed lower costs for 5FU/LV in comparison with FOLFOX, although to a varying degree, depending in part on perspective of the study. Compared with 5FU/LV, the life-time costs of the FOLFOX were estimated to be € 5,000 more expensive from the NHS perspective in the United Kingdom and € 16,000 more expensive from the perspective of Medicare in the United States.[20, 21]

Oxaliplatin combined with capecitabine

Within the timeframe of our study (2005-2009), no data were available regarding prospective studies demonstrating the efficacy of the combination therapy with capecitabine and oxaliplatin (CAPOX) for use in the adjuvant setting.

National guidelines

Based on the results of these randomized controlled trials (RCTs), national guidelines in the Netherlands have recommended the use of FOLFOX as the primary treatment option for stage III colon cancer since the beginning of 2005. These guidelines do not routinely support the use of adjuvant chemotherapy in stage III rectal cancer. For patients who are not eligible or who refuse treatment with oxaliplatin, adjuvant treatment with capecitabine is indicated. [23, 24] The Dutch Society of Medical Oncology (NVMO) at that time also supported the use of CAPOX as an alternative to FOLFOX, as these treatments had shown comparable efficacy in metastatic colorectal cancer. [25]

Oxaliplatin in daily practice

Economic evaluations piggy-backed on a randomized clinical trial are generally regarded as the most scientific substantiation of the cost-effectiveness of pharmacotherapeutic treatments. Data based on clinical trials may not be representative of daily practice, as clinical trials are conducted under controlled conditions.

Outcomes research collects data from daily clinical practice that are useful for determining appropriate use and cost-effectiveness of pharmacotherapeutic treatments. This section describes the results of outcomes research that investigated the appropriate use and cost-effectiveness of oxaliplatin for the treatment of stage III colon carcinoma. The economic burden of colorectal carcinoma is expected to increase in the next few years due to the increasing incidence of colon carcinoma and the increasing use and high costs of oxaliplatin. This makes it important to obtain answers to the following subquestions:

- **How is oxaliplatin used in daily practice?** (sections 2.3 and 3.3)
- **What clinical effects does the use of oxaliplatin involve?** (sections 2.4 and 3.4)
- **What costs are involved in the use of oxaliplatin?** (sections 2.5 and 3.5)
- **What is the relationship between the results of this outcomes research and the results of clinical trials?** (sections 2.6 and 3.6)
- **What is the cost-effectiveness of oxaliplatin?** (2.7 and 3.7)

2 Methods

2.1 Patient population

All patients newly diagnosed with stage III colon carcinoma (pTanyN1,2M0, ICD-O C18-C19.9) in 2005 or 2006 were eligible for this outcomes research provided that they received adjuvant chemotherapy. Firstly, patients were identified retrospectively in June 2007 via the database of the Dutch Cancer Registry. This databank registers the data of all cancer patients who were admitted to a hospital or whose disease was diagnosed by means of tissue examination. This amounts to more than 95% of all cancer patients in the Netherlands. Subsequently, using 'minimal' case record forms (CRFs), additional information was collected from the medical records of all patients identified in 19 selected hospitals. Afterwards, further selection of patients took place based on the information obtained via the 'minimal' CRFs.

Patients were excluded from the analyses if their medical records revealed that they had evidence of distant metastases, did not receive any chemotherapy, or did not start chemotherapy at the selected hospitals. Moreover, patients receiving pre-operative radiotherapy were excluded because their tumours were clinically considered to be rectal carcinoma. Three patients receiving bevacizumab (<1%) and 2 patients receiving UFT (<1%) were excluded from the analyses. Lastly, patients were excluded if they had been diagnosed with a second malignancy in the past five years - with the exception of adequately treated carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin.

A randomly selected representative sub-group was selected from the patient population as defined. From this subgroup extra detailed data was collected from patients medical records by making use of 'maximal' CRFs.

2.2 Data collection

The data collection took place via three sources.

Firstly, information was obtained via the databank of the Dutch Cancer Registry. This databank contains information about, among other things, age, gender, date of diagnosis, hospital where the diagnosis was made, tumour location, number of lymph glands

examined/found to be positive, the size and/or degree of dissemination of the tumour, stage, initial treatment data and survival.

A second data source was formed by additional 'minimal' information obtained via the 'minimal' CRFs, which could be completed based on medical records. This minimal data source contained information on co-morbidity, tumour characteristics, type of adjuvant chemotherapy, and data relating to disease-free and overall survival.

Patients could be included or excluded from the pilot study based on the information obtained from the database of the Dutch Cancer Registry and the minimal dataset. This dataset also contained sufficient information for carrying out analyses relating to:

- Baseline characteristics (section 2.3)
- The diffusion of oxaliplatin (section 2.3)
- Considerations regarding choice of treatment regimen (section 2.3)
- Clinical effects of oxaliplatin (section 2.4)

A third data source was obtained by collecting extra, more detailed data for a sub-group of patients, also based on patient files. The completion of a 'maximal' CRF provided additional data relating to exact dose schedules, adverse effects and resource use. This additional dataset facilitated extra analyses relating to:

- Dose schedules (section 2.3)
- Toxicity (section 2.3)
- Costs (section 2.5)

Between July 2008 and March 2009, all 'minimal' and 'maximal' data were collected by medical students under the supervision of the researchers. A detailed overview of the data obtained from the Dutch Cancer Registry and via the minimal and maximal CRFs can be found in Annex IV. The original versions of the minimal and maximal CRFs are also enclosed in Annexes V and VI.

2.3 Use of oxaliplatin

The use of oxaliplatin in daily practice was examined by considering five different parameters. Each of those parameters provides an indication of who received oxaliplatin or how much oxaliplatin they received.

Baseline characteristics

The baseline patient and tumour characteristics provide a pointer for the 'profile' fulfilled by a patient being treated with oxaliplatin in daily practice. Among other things, the effect of age distribution was examined in order to explain significant differences between the treatment groups. We recorded established prognostic factors related to comorbid conditions from the medical records using a slightly adapted version of the Charlson index, which classifies all serious comorbid conditions based on possible prognostic impact into eight groups (i.e. previous malignancies, chronic obstructive pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, hypertension, diabetes mellitus, digestive tract diseases and other). In the analyses we classified comorbidity as zero to one comorbid condition versus two or more comorbid conditions.[26 27]

Diffusion of oxaliplatin

The first moment that oxaliplatin was prescribed for stage III colon carcinoma was established for each hospital. In addition, the cumulative diffusion of oxaliplatin and the distribution of 5FU/LV, capecitabine and oxaliplatin were charted for the period 2005 and 2006.

Considerations in choice of treatment regimen

Possible predictors for receiving a certain treatment were analysed. Reasons for not prescribing oxaliplatin were also analysed.

Dose schedules

The planned and actual dose schedules and reasons for dose reductions were recorded per individual patient and compared between the treatment groups.

Toxicity

Toxicity was registered if it led to dose modification. Distinctions were made between haematological toxicity, gastrointestinal toxicity, neurological toxicity and toxicity as a result of the hand-foot syndrome.

2.4 Clinical efficacy of oxaliplatin

The clinical efficacy of oxaliplatin in daily practice was assessed by means of the following outcome parameters:

Disease-free survival

Disease-free survival was defined as the time to relapse or death. A relapse was determined based on diagnostic examination and, where necessary, cytology or biopsy. An increased carcinoembryonic antigen (CEA)-value as sole finding was not accepted as proof of a relapse.

Statistical analyses of clinical data

We first assessed the frequency of administration of treatment. To compare baseline characteristics, the administered regimens were grouped into “oxaliplatin-containing regimens” and “regimens without oxaliplatin”. Continuous data were expressed in terms of the mean value and categorical data as a percentage, unless otherwise denoted. The Student’s t-test and the chi-square test with the Fisher’s exact correction for frequencies less than five were used for continuous and categorical variables, respectively. To better explore the reasons for significant findings, we evaluated the effect of age distribution on the comparison of baseline characteristics between the different treatment groups. Additionally, we investigated the diffusion of new treatments as recommended by the new guidelines by the hospitals. We used the Cochran-Armitage trend test to examine the change in use of different treatment regimens over time. Reasons for not prescribing oxaliplatin were explored using descriptive statistics. A multivariate logistic regression analysis was performed to identify independent predictors of non-prescription of oxaliplatin. Survival curves were visualised according to the Kaplan-Meier methods. A multivariate Cox regression was carried out on all expected prognostic factors in order to correct for differences in baseline characteristics. Approximately 100 patients who received treatment with oxaliplatin and 100 patients who received treatment without oxaliplatin were selected for the population of representative patients. This selection took place

at random, stratified for hospital and oxaliplatin use. This number is based on practicability in terms of time and finance and on experience with previous iMTA studies. An evaluation of dose schedules and modifications per treatment regimen was performed in this selected subset of patients. For this evaluation, the tests for continuous and categorical variables mentioned above were used. Significant variables are reported with their respective p-value. In all analyses, statistical significance was assumed if the two-tailed probability value was <0.05. The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA, 1999).

2.5 Costs of oxaliplatin

Limitations in time and information meant that it was impossible to collect retrospective data on all types of societal costs. We therefore conducted the cost analysis using the hospital perspective (i.e., a health care sector perspective limited to hospital activities). Use of this perspective meant that some cost categories like productivity costs and costs associated to informal care were not taken into account. However, the inclusion of productivity costs is unlikely to have any major impact on the results, since most of the patients in this study were near or beyond retirement age. While inclusion of costs of informal care would increase total costs, there was no reason to expect any *difference* in costs of informal care between treatments. As a consequence, the inclusion of these costs would therefore have no impact on the difference in total costs. Given these arguments, we believe that the exclusion of those cost components from the analyses had no important impact on the estimate of the real-world cost-effectiveness of oxaliplatin.

Total costs for individual patients were determined by the identification of resource use and unit costs of the following cost components: inpatient hospital days, intensive care days, outpatient visits, consultations by telephone, daycare treatments, emergency room visits, radiotherapy, surgical procedures, laboratory services, medical imaging services, chemotherapy and concomitant medications.

Resource use was divided into two time periods. Period 1 began on day 1 of the first administration of adjuvant chemotherapy. To capture resource use resulting from treatment related toxicity, period 1 ended one month after the last administration of

chemotherapy. Period 2 started one month after the last administration of chemotherapy and lasted until disease progression (or end of follow up).

Table 1.2.1 presents the unit costs of inpatient hospital days, intensive care days, outpatient visits, consultations by telephone, daycare treatments and emergency room visits. The unit cost calculations were based on detailed microcosting studies reflecting full hospital costs, including overhead costs.[28, 29] We conducted this microcosting study to compute oncological specific unit prices since they are known to be slightly higher compared to the average prices in the Dutch Costing Manual 2004. Some unit costs were weighted for their origin: 67% of the unit costs were based on data from the general hospitals and 33% on those from university hospitals. These shares reflect the distribution of patients among hospitals in Dutch daily practice.

Table 1.2.1 Unit costs (Euro 2009)

Oncological inpatient hospital day *	**€ 490**
general hospital	€ 408
university hospital	€ 657
Intensive care day	**€ 2,080**
Oncological outpatient visit *	**€ 98**
general hospital	€ 84
university hospital	€ 125
Consultation by telephone	**€ 13**
Oncological day-care treatment *	**€ 167**
general hospital	€ 140
university hospital	€ 222
Emergency room visit	**€ 174**

* weighting factor of 67:33 for general and university hospitals

The resource use of surgical procedures, laboratory services and medical imaging services was valued using the fees as issued by the NZa.[30] Unit costs of chemotherapy are shown in table 1.2.2. Unit costs of chemotherapy were acquired from the Committee Pharmacotherapeutic Aid.[23] Unit costs of concomitant medications were also acquired from the Committee Pharmacotherapeutic Aid; those costs were based on costs per unit, for example grams or milligrams.

Table 1.2.2 Unit costs (Euro 2009)

5-Fluorouracil (mg)	€ 0.01
Leucoforin (mg)	€ 0.28
Capecitabine (mg)	€ 0.01
Oxaliplatin (mg)	€ 4.35
Uracil/tegafur (mg)	€ 0.05

mg = milligram

To determine the uncertainty of the obtained cost estimates, one-way sensitivity analyses were carried out by varying the unit cost values of inpatient hospital day, outpatient visit and daycare treatment unit costs between 50% and 150%. Unit costs other than those of hospital days were considered to be fairly stable or of less influence and were therefore not subjected to sensitivity analyses.

Statistical analysis of cost data

Statistical analyses were conducted with the statistical software programmes SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). In addition to descriptive statistics, differences between the four treatment groups were assessed by means of the one-way analysis of variance (ANOVA) test for variables showing a normal distribution, the Kruskal-Wallis test for variables not normally distributed and the Pearson Chi-square test for variable fractions. To adjust for multiple testing, one way analyses of variance with post hoc testing (type Bonferroni) were additionally performed. In all cases $p < 0.05$ was taken as statistically significant. All costs were based on Euro 2009 cost data. Where necessary, costs were adjusted to 2009 using the general price index from Statistics Netherlands.[31]

2.6 Daily practice versus clinical trials

We examined the similarities and differences between the results of our outcomes research and the results of the MOSAIC trial by comparing the baseline characteristics of the two populations, how patients were treated, and the effects and costs of oxaliplatin. This was achieved by comparing results in the following categories: baseline characteristics, dose schedules, clinical effects of oxaliplatin, and costs of oxaliplatin.

2.7 Cost-effectiveness of oxaliplatin

A Markov model was developed in order to assess the cost-effectiveness of oxaliplatin plus standard adjuvant treatment versus standard adjuvant treatment alone in the treatment of stage III colon cancer. The cost-effectiveness estimate is based on two main sources of evidence:

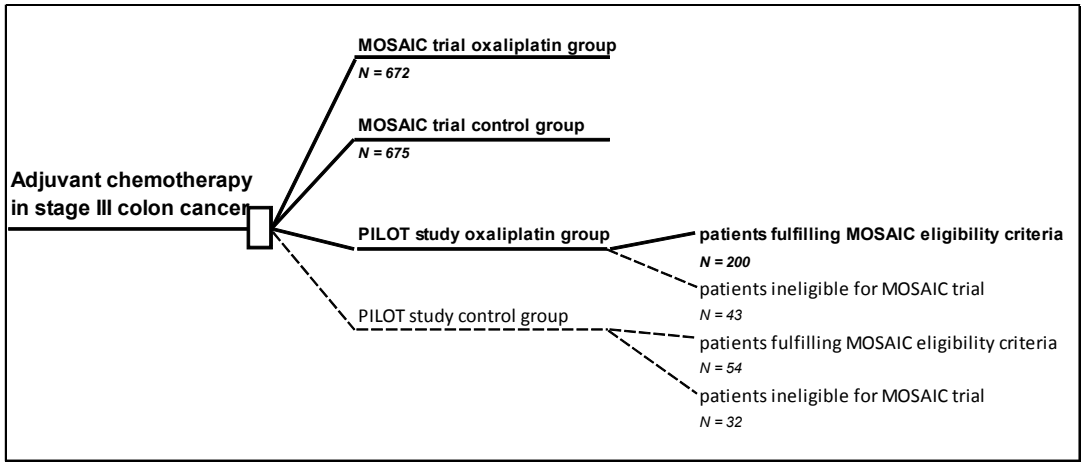
1. Results from the outcomes research investigating costs and effects of the use of oxaliplatin in daily clinical Dutch practice (sections 3.1 - 3.6)
2. Results from the MOSAIC trial[16, 17]

Model overview

Target population

The target population in the model is based on the populations from both the PILOT and the MOSAIC study. Figure 1.2.1 shows the possible populations to be used in the cost-effectiveness model. In order to make proper comparisons, demographic and baseline clinical characteristics need to be similar between patients treated with oxaliplatin and those treated without oxaliplatin. The oxaliplatin arm and control arm of the MOSAIC study are comparable since this trial was randomised. As shown in section 3.6, the oxaliplatin patients in the PILOT study who fulfilled the MOSAIC eligibility criteria (82%), were similar to the MOSAIC patient population. However, eligible control patients in the PILOT study were not comparable with the eligible oxaliplatin patients. Even correction for differences in baseline characteristics between oxaliplatin patients and control patients in the pilot study did not result in comparable patient groups (see section 3.4). Furthermore, ineligible patients were not comparable with eligible patients regarding their baseline prognostic factors.

Figure 1.2.1 Overview of target populations



Because of the incomparability of the control group and the ineligible patients of the pilot study, we decided to use only the comparable populations (MOSAIC population and PILOT eligibles) in the base case analyses. The possible impact of the remaining patient groups in the PILOT study were explored via scenario analyses.

The patient population in the model was based on:

1. MOSAIC trial, stage III patients
2. PILOT study, eligible patients receiving oxaliplatin

Different treatment arms in the model were:

1. MOSAIC study, control arm (n = 675)
2. MOSAIC study, oxaliplatin arm (n = 672)
3. PILOT study, oxaliplatin arm (n = 200)
4. Oxaliplatin arm, PILOT and MOSAIC studies combined (n = 872)

All patients in the model were diagnosed with stage III colon cancer and received adjuvant chemotherapy following radical surgery of the primary tumour. None of the patients participated in both the PILOT and MOSAIC studies, which enabled us to sum the PILOT and MOSAIC oxaliplatin populations (4^{th} arm).

Regimens without oxaliplatin given in control arm

- 5FU/LV
- Capecitabine

Regimens with oxaliplatin given in oxaliplatin arm

- 5FU/LV + oxaliplatin
- Capecitabine + oxaliplatin

In both arms the regimens were given for 6 months or until serious adverse events, relapse of disease or death occurred. After 6 months, the patients were followed until relapse of disease, death or censoring.

Endpoints

The endpoints used in the model were:

- incremental costs per life-year gained
- incremental costs per quality-adjusted life-year (QALY) gained

Disease-free survival estimates were directly derived from the MOSAIC trial (both oxaliplatin and control arms) and PILOT study (oxaliplatin treatment in eligibles). Overall survival estimates were derived from both the MOSAIC study and published literature. The utility (quality of life) component was derived from published literature.

Direct costs such as drug, drug administration, adverse events (AE), and follow-up costs were included. All cost data (both control and oxaliplatin arms) were taken from the PILOT study.

The cost-effectiveness analysis was conducted using TreeAge Pro Suite 2009 to compare the clinical and economic benefits of the treatment versus alternative treatments.

Model structure

A Markov model was developed to simulate the transition of patients receiving adjuvant treatment for stage III colon cancer through clinical states that are typically observed in a clinical setting. Each state is mutually exclusive, meaning that a patient can only be in one state at one time.

Figure 1.2.2 Conceptual model stage III colon cancer

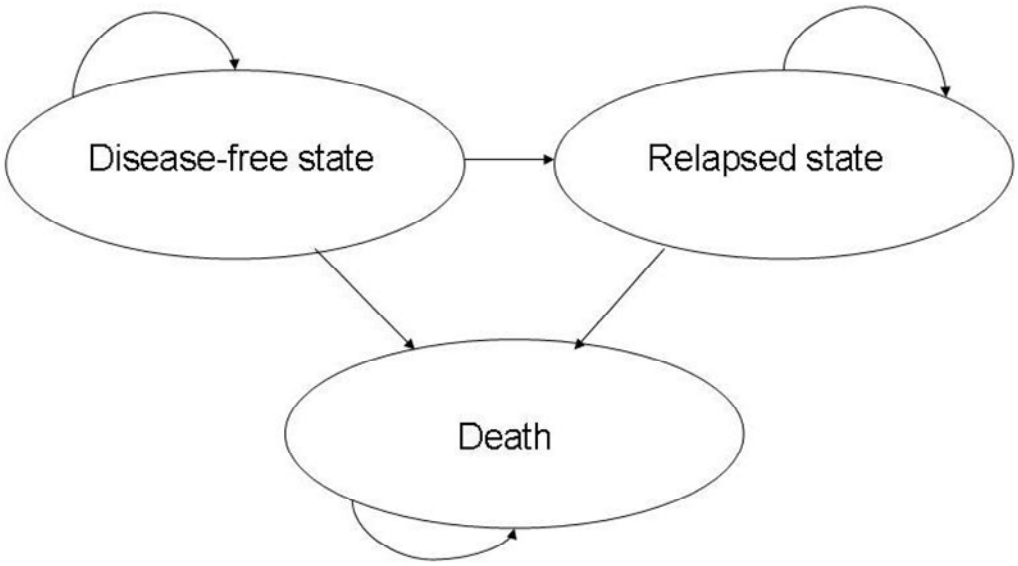
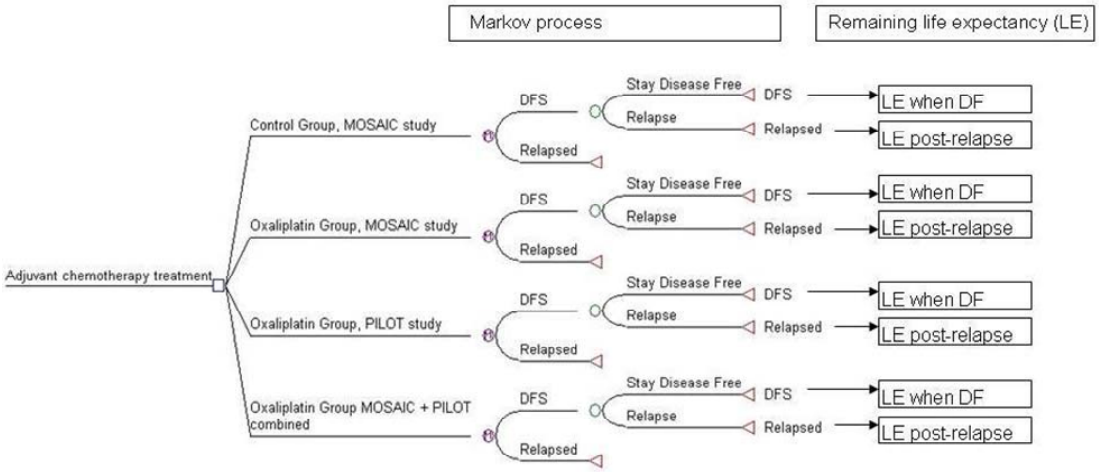


Figure 1.2.2 shows the conceptual model used in the cost-effectiveness model. The clinical states incorporated in the model were: (i) disease-free health state (DFS), (ii) relapsed health state and (iii) death. A similar model was used by Pandor et al., 2006.[12] In their analysis, a comparable cost-effectiveness analysis was used based on the MOSAIC trial. In our present cost-effectiveness analysis, we used a slightly simplified version of this conceptual model as is shown in Figure 1.2.3.

Figure 1.2.3 Model used in this cost-effectiveness analysis



Model overview

The Markov model shown in Figure 1.2.3 calculates the incremental costs per disease-free life-year gained over a 5-year time horizon. After a 5-year period, the Markov process halts. The health state of death was not included in this model, since the overall survival of patients receiving adjuvant treatment for stage III colon cancer is limited. Instead, we included life expectancy in the model and we assumed that the life expectancy after a relapse was not associated with the type of treatment. We also assumed that the average life expectancy of patients who have no relapse after 5 years was equal for all treatment alternatives. The estimation of the incremental costs per life-year and QALY are deducted from the average life-expectancy of patients who are disease-free and patients who relapsed in the modelled time period.

Model features

- Patients with stage III colon cancer receiving control treatment are treated with either 5FU/LV or capecitabine. Patients who receive regimens that include oxaliplatin receive either oxaliplatin combined with 5FU/LV (FOLFOX) or oxaliplatin combined with capecitabine (CAPOX).
- Patients can be in only one of the two states (DFS or relapse) at any point in time.
- All patients start in the DFS state.
- Patients who are disease-free in the current cycle can remain disease-free in the next cycle (stay in DFS state) or transition to the relapse state, which is an absorbing state (see Figure 1.2.3).
- The cycle length is 6 months.
- The Markov process stops after 10 cycles, which corresponds with a 5-year time horizon.
- It is assumed that after 5 years of follow-up, the probability of relapse is negligible and equal for all treatment alternatives.
- Total direct medical costs of adjuvant treatment, costs of follow-up, and costs of relapse are calculated for each therapy.
- The average life-expectancy of disease-free patients is assumed to be equal for all treatment alternatives beyond 5 years of follow-up
- The average life-expectancy of relapsed patients is assumed to be equal for all treatment alternatives
- Utility estimates from published literature are attributed to the different health states.

- The calculated incremental costs per life-year and QALY gained reflect a lifetime time horizon.
- Advice and feedback from a clinical expert were frequently sought during the development of the model.

Parameter estimates – clinical inputs

Probability of staying disease-free

The probability of staying disease-free at 6-month interval until the last time points available was obtained from the MOSAIC trial (oxaliplatin and control arms) and the PILOT study (eligible oxaliplatin group). Data from 672 patients in the oxaliplatin arm and 675 patients in the control arm obtained from the MOSAIC trial were used in the model.[17] Furthermore, use was made of data from 200 eligible oxaliplatin patients obtained from the PILOT study.

The transition probabilities related to relapse are time-related variables in which transitions take place every six months. In the Markov model, patients in the DFS state may either stay in that phase [Prob(stay DFS)] or relapse [1- Prob(stay DFS)]. These probabilities were obtained from Kaplan-Meier curves obtained from both the MOSAIC trial and the PILOT study (Annex IX).

Table 1.2.3 shows the cumulative probabilities that were derived directly from the Kaplan-Meier curves. However, these probabilities are cumulative probabilities. In order to use these in the Markov Model it was necessary to convert the cumulative probabilities into transition probabilities.

Table 1.2.3 Oxaliplatin PILOT versus Oxaliplatin MOSAIC versus Control MOSAIC cumulative probabilities of staying disease-free

Time since start adjuvant treatment (months)	Cumulative probability of staying disease free (DFS)		
	PILOT Study	MOSAIC Trial	
	Oxaliplatin (n = 200)	Oxaliplatin (n = 672)	Control (n = 675)
0	1.000	1.000	1.000
6	0.965	0.970	0.955
12	0.889	0.900	0.880
18	0.837	0.825	0.785
24	0.779	0.795	0.725
30	0.743	0.755	0.685
36	*0.718**	0.730	0.665
42	*0.698**	0.710	0.645
48	*0.694**	0.705	0.630
54	*0.684**	0.695	0.610
60	*0.653**	0.664	0.589

**Follow-up time limited in pilot study. From 30 up to 60 months the hazard of relapsing was assumed to be equal to the hazard of relapsing in the oxaliplatin arm of the MOSAIC trial.*

Prob(stay DFS)

The cumulative disease-free survival data were converted to transition probabilities using the following formula:

$$p_t = \frac{P_t}{P_{t-1}}$$

Where Pt and Pt-1 denote the cumulative probability of surviving at the end of time t and t-1, respectively; pt denotes the transition probability for time t. For example, the MOSAIC oxaliplatin transitional prob(stay DFS) at 24 months is 0.795/0.825 (=0.9636, see table 1.2.3).

Follow-up time is limited in the PILOT study. In order to obtain transition probabilities for DFS up to 5 years, estimates from 30 up to 60 months were derived from the MOSAIC oxaliplatin arm. The hazard of relapsing in the PILOT oxaliplatin group was assumed to be equal to the hazard of relapsing in the oxaliplatin group of the MOSAIC trial (gray shaded area in table 1.2.4).

Table 1.2.4 Transition probabilities used in the Markov Model

Time	Initial state	Ending state	Transitional probabilities		
			PILOT Study	MOSAIC Trial	
			Oxaliplatin	Oxaliplatin	Control
6 months	DFS	DFS	0.9650	0.9700	0.9550
		Relapse	0.0350	0.0300	0.0450
12 months	DFS	DFS	0.9212	0.9278	0.9215
		Relapse	0.0788	0.0722	0.0785
18 months	DFS	DFS	0.9416	0.9167	0.8920
		Relapse	0.0584	0.0833	0.1080
24 months	DFS	DFS	0.9301	0.9636	0.9236
		Relapse	0.0699	0.0364	0.0764
30 months	DFS	DFS	0.9539	0.9497	0.9448
		Relapse	0.0461	0.0503	0.0552
36 months	DFS	DFS	0.9669	0.9669	0.9708
		Relapse	0.0331	0.0331	0.0292
42 months	DFS	DFS	0.9726	0.9726	0.9699
		Relapse	0.0274	0.0274	0.0301
48 months	DFS	DFS	0.9930	0.9930	0.9767
		Relapse	0.0070	0.0070	0.0233
54 months	DFS	DFS	0.9858	0.9858	0.9683
		Relapse	0.0142	0.0142	0.0317
60 months	DFS	DFS	0.9554	0.9554	0.9656
		Relapse	0.0446	0.0446	0.0344

* Gray area reflects projected data. Transitional probabilities equal to MOSAIC oxaliplatin arm transitional probabilities

Transition probabilities for oxaliplatin arm, PILOT and MOSAIC studies combined

None of the patients participated in both the PILOT and MOSAIC studies. The similar baseline characteristics and similar probability of relapsing in both the PILOT and MOSAIC oxaliplatin populations enabled us to combine the two populations in order to create a larger sample size. Prob(stay DFS) for the combined oxaliplatin arm were directly derived from the separate transition probabilities of the oxaliplatin PILOT group and the oxaliplatin MOSAIC group. The separate probabilities were weighted by the number of patients at risk at each time point.

For example, the MOSAIC oxaliplatin transition prob(stay DFS) at 24 months is 0.9636 (see table 1.2.4). The PILOT oxaliplatin transition prob(stay DFS) at 24 months is 0.9301. The numbers of patients at risk at 24 months are 521 for the MOSAIC study and 111 for the PILOT study (see table 1.2.5). Consequently, the combined transition probability at 24 months = ((0.9636*521) + (0.9301*111))/ (521+111). Table 1.2.5 shows the number of patients at risk at each time point.

Table 1.2.5 Number of patients at risk in DFS model

	PILOT study	MOSAIC trial	
Months	oxaliplatin	oxaliplatin	control
0	200	672	675
6	192	642	633
12	174	595	573
18	155	543	511
24	111	521	472
30	72	493	445
36	35	475	429
42	7	462	411
48	1	453	395
54	0	439	377
60	0	347	283

Clinical inputs regarding patients' prognosis after 5 years

After 10 cycles, i.e., 5 years, the Markov process stopped. We added the patients' average life-expectancy (after the 5-year period) in both the DFS and the relapse health states in order to calculate the life-years and QALYs over a lifetime horizon.

Life-expectancy for disease-free patients

We assumed that after 5 years of follow-up the probability of relapse is negligible and equal for all treatment alternatives. Furthermore, ages were similar between arms. As a result, we assumed the life-expectancy of disease-free patients to be equal for all treatment alternatives. At the start of the model period (beginning of adjuvant chemotherapy, first cycle), the average age is 61 years across all patient populations. In 2000, the life-expectancy of 61-year olds was 18.0 years for men and 22.2 years for women.[31] In accordance to the sex distributions shown in table 1.3.12, the

average life-expectancy of the total target population is 19.8 years. After 5 years of follow-up the remaining life-expectancy of disease-free patients is estimated at 14.8 years. This estimation was used as an input in our model

Life expectancy for patients post-relapse

We assumed the average life expectancy of relapsed patients to be equal for all treatment alternatives. This assumption was based on the comparison of the disease-free and overall survival curves of the MOSAIC study. This study showed a similar difference in effect between the oxaliplatin and control arms in both curves. The remaining average life expectancy of patients after a relapse was assumed to be 1.7 years. This was derived from the study of Tol et al., 2009, who compared two first-line chemotherapy treatments for advanced colorectal cancer in Dutch patients. The overall survival of the two treatment groups did not differ and was estimated to be an average of 20 months.[32] However, one could argue that patients eligible to participate in a clinical trial would be expected to be healthier than patients in daily practice. Therefore, we performed a supplemental analysis to examine the impact of this assumption. In this worst-case scenario, we set the life expectancy after a relapse to zero in order to see how much this affected the ICER. However we expected that this would not influence our conclusions that much, since a reduction in the life expectancy would have an impact on both arms and because most patients do not experience a relapse.

Parameter estimates – quality-adjusted survival benefits

In order to derive QALY estimates for each treatment, the survival benefits seen within the studies need to be weighted by a patient's quality of life over that period. A method to derive QALY estimates is to assign health utilities to the various health states. However, quality of life (QoL) data were not routinely collected in the PILOT study and MOSAIC trial. Therefore, another strategy had to be used to estimate the potential QALY gain from using oxaliplatin. In the report published by Pandor et.al., 2006, a literature search relating to QoL in patients with colon cancer was carried out to determine appropriate utilities for the following health states:

- Utility whilst on adjuvant chemotherapy (with no serious side effects)
- Utility whilst on adjuvant chemotherapy (with serious side effects)
- Utility whilst in remission (post-adjuvant treatment)
- Utility whilst on palliative chemotherapy

Table 1.2.6 shows the utility parameters used in the cost-effectiveness model of Pandor et al.[12, 33, 34]

Table 1.2.6 Utility parameters used in the Markov model

Health state	Utility	Standard error	Reference
On adjuvant chemotherapy without significant side-effects)	0.70	0.036	Ness et al., 1999
On adjuvant chemotherapy with significant side-effects)	0.63	0.036	Ness et al., 1999
In remission	0.92	0.050	Ramsey et al., 2000
On palliative chemotherapy	0.24	0.041	Ness et al., 1999

The frequencies of significant side effects during the MOSAIC study have not been reported in the published literature. In the PILOT study significant side effects were defined as: side effects requiring dose modification. Table 1.3.4 shows the percentage of patients requiring dose modifications. A weighted average for each treatment group (control versus oxaliplatin) was used in the DFS Markov model as is shown in table 1.2.7.

Table 1.2.7 Percentages of significant side effects in PILOT study

	Treatment without oxaliplatin		Treatment with oxaliplatin	
	5FU/LV	Capecitabine	FOLFOX	CAPOX
	n = 17	n = 93	n = 136	n = 145
% of patients requiring dose modifications	53%	57%	59%	70%
Weigthed average %	56%		65%	

For example, 65% of the patients in the oxaliplatin groups experienced significant side effects. As a consequence, 65% of the patients had a health utility value of 0.63 assigned to the first cycle. 35% remained without significant side effects, so 35% had a utility value of 0.70 during the first cycle (divided by 0.5 since the first cycle reflects only 6 months). In subsequent cycles, the yearly utility value was 0.92 as long as the patient was disease-free. Patients experiencing relapse were considered to be on palliative therapy (utility value of 0.24) for the remainder of their life.

Parameter estimates – cost analyses

All costs incorporated in the Markov model were based on the PILOT studies. Three costing periods can be distinguished. In the first period (period 1) patients are treated with adjuvant chemotherapy (see table 1.3.8). The second period (period 2) reflects costs of follow-up (see table 1.3.9). Patients are disease-free during this period. Period 3 starts when patients experience a relapse and reflects the costs post-relapse.

Period 1. Treatment costs

Period 1 lasts for 6 months and its costs are encountered during the first cycle of the Markov model. Table 1.2.8 contains an overview of the total treatment costs per treatment group (control versus oxaliplatin). The weighted means were used in the model.

Table 1.2.8 Total treatment costs period 1 (Euro 2009)

Costs per treatment regimen		Mean costs	SD costs
5FU/LV (1)	15%	5,802	2,895
Capecitabine (2)	85%	4,944	3,238
FOLFOX (3)	48%	25,839	11,239
CAPOX (4)	52%	13,888	5,582

Costs per treatment group	Weighted Mean	Pooled SD
Control group (1+2)	5,073	2,790
Oxaliplatin group (3+4)	19,624	6,128

Period 2. Follow-up costs

The follow-up period lasts as long as patients are in remission, for a maximum duration of 5 years. Since the follow-up time of the pilot study was limited to approximately 2 years, the total follow-up costs shown in table 1.3.9 are censored and only reflect costs made during the first two years of follow-up. Table 1.2.9 contains an overview of the total follow-up costs per treatment group (control versus oxaliplatin). The weighted mean costs of the treatment groups were similar (€ 4,132 versus € 4,145). These total costs of follow-up reflect costs of monitoring (actual follow-up costs), costs of surgeries (mainly related to closure of ileostomy) and other

costs unrelated to colon cancer. Because the costs of follow-up were found to be independent of adjuvant treatment, a 6-monthly cost of € 1,140 was applied over the first two years of follow-up in both treatment arms of the DFS Markov model. For the remainder of the follow-up period a 6-monthly cost of € 257 was assumed. This was based on expected resource use according to current Dutch guidelines: monitoring visits and laboratory testing each 6 months, yearly assessments of thorax and liver, and 1 colonoscopy.[34]

Table 1.2.9 Total costs of follow-up period 2 (Euro 2009)

Costs of follow-up per treatment regimen		Mean follow duration	Mean costs	SD costs
5FU/LV (1)	15%	25.0	3,312	3,637
Capecitabine (2)	85%	22.1	4,276	7,598
FOLFOX (3)	48%	22.7	5,034	7,071
CAPOX (4)	52%	19.4	3,324	4,013

Costs per treatment group	Weighted Mean	Pooled SD
Control group (1+2)	4,132	
Oxaliplatin group (3+4)	4,145	
Costs per 6 months, first 2 years of follow-up	1,140	1,428
Costs per 6 months, remainder of follow-up	257	

Period 3. Post-relapse costs

The costs of period 3 reflect the cost of metastatic disease until death. These costs were not measured for the stage III colon cancer pilot. As a proxy for the total costs of period three, the treatment costs of the oxaliplatin arm (period 1 € 19,624, table 1.2.8) were used. We assumed the costs of period 3 three to be equal in both treatment arms (with and without oxaliplatin). Total costs per treatment arm are shown both with and without the costs of period 3.

Time horizon and discounting

The time horizon of the DFS Markov model was limited to 5 years regarding the disease-free survival estimate. It was assumed that the probability of relapse after 5 years of follow-up is negligible and equal in the whole target population. This assumption has often been used in the past.[9] Implementation of remaining life-expectancies for both disease-free and relapsed patient groups into the model made it possible to model costs and benefits over a lifetime horizon.

Cost and benefits incurred after the first year in the model were discounted at 4% and 1.5% per annum respectively, consistent with current Dutch guidelines.

Half-cycle correction

The half-cycle correction technique was applied to more accurately reflect the continuous nature of state transitions.

Model assumptions

Certain assumptions were made to simplify the Markov model, yet to best reflect the clinical practice. The clinical assumptions critical to the modelling approach are listed below:

A1. Disease-free survival data of the PILOT oxaliplatin population beyond the PILOT study follow-up period were derived from the probabilities of the MOSAIC oxaliplatin patients. The hazard of relapsing was assumed to be equal to the hazard of relapsing in the oxaliplatin arm of the MOSAIC trial.

A2. It was assumed that all adverse events that resulted in dose modifications were significant and had an impact on the patient's quality of life.

A3. Deaths due to adverse events or background mortality were assumed not to influence the results during the first 5 years.

A4. After 5 years of follow-up the probability of relapse is negligible and equal in the whole target population.

A5. The average life expectancy of patients after a relapse is equal for all treatment alternatives.

A6. The average life expectancy of patients who have no relapse after 5 years is equal for all treatment alternatives.

Base case analysis

Incremental cost-effectiveness analyses were conducted. Total costs (with and without the post-relapse costs of period 3) were estimated for all treatment groups. Overall survival and disease-free survival were calculated in each cycle based on the number of patients in each health state (i.e., the total – disease-free – life-years

accumulated by the cohort in that cycle). Utility values were applied to each life-year in each cycle and were summed to determine the total quality-adjusted life-years. The incremental costs, incremental health gain, and incremental cost-effectiveness ratio (ICER, calculated by dividing the incremental costs by the incremental health gain) were then calculated.

The base case results incorporated the following endpoints:

Costs per life-years (LY) gained

- MOSAIC oxaliplatin versus MOSAIC control treatment
- PILOT oxaliplatin versus MOSAIC control treatment
- MOSAIC + PILOT oxaliplatin combined versus MOSAIC control treatment

Costs per quality-adjusted life-years (QALY) gained

- MOSAIC oxaliplatin versus MOSAIC control treatment
- PILOT oxaliplatin versus MOSAIC control treatment
- MOSAIC + PILOT oxaliplatin combined versus MOSAIC control treatment.

Discounting

In order to see the effect of discounting, the base case results are first shown without discounting, followed by the results with discounting.

Sensitivity analysis

Probabilistic sensitivity analysis was conducted. This approach involves specifying distributions for the model's input parameters that quantify the uncertainty about their values and employing Monte Carlo simulation to select values randomly from those distributions. In this way, probabilistic models allow the effects of joint uncertainty across all of the model's input parameters to be included in a single analysis.

Probability Distributions

Table 1.2.10 contains an overview of all distributions used in the DFS Markov model.

Transition probability parameters

The transition probabilities in the model reflecting Prop(stay DFS) were based on Kaplan-Meier curves (from the PILOT and MOSAIC studies, Annex IX). They express the observed proportions of the event of interest. The beta distribution is recommended and commonly used to describe uncertainty around proportions (e.g., transition probabilities).[35] The beta distribution incorporates the number of observations (or patients) that were actually studied. The initial total study population of patients from the MOSAIC study consisted of 675 (control arm) + 672 (oxaliplatin arm) = 1347 patients. The initial total study population of eligible oxaliplatin patients in the PILOT study consisted of 200 patients. Table 1.2.5 shows the number of patients at risk of relapse at each time point. With known probabilities and population numbers, the inputs for beta distribution, α and β, could be estimated.

Cost parameters

All costs in period 1 followed a normal distribution. Normal distributions were therefore used to reflect the variation in costs in periods 1 and 3. Table 1.2.8 and shows the mean values and standard deviations used in the normal distributions. Due to the skewed cost of period 2 (first 2 years), a gamma distribution was used to accurately reflect the variation.

Utility values

Normal distributions were used to reflect the variation in the utility values. Table 1.2.6 shows the mean values and standard deviations that were used in the normal distributions.

Table 1.2.10 Probability distributions of parameters included in sensitivity analyses

Transitional probability parameters			
	Distribution	alpha	beta
Prob(stay DFS) Control treatment MOSAIC	Beta	Derived from table 3 and 5	
Prob(stay DFS) Oxaliplatin treatment MOSAIC	Beta	Derived from table 3 and 5	
Prob(stay DFS) Oxaliplatin treatment PILOT	Beta	Derived from table 3 and 5	
Prob(stay DFS) Oxaliplatin treatment combined	Beta	Derived from table 3 and 5	
cost parameters			
	Distribution	mean	SD
Total costs period 1 Control group	Normal	5,073	2,790
Total costs period 1 Oxaliplatin group	Normal	19,624	6,128
Total costs period 3	Normal	19,624	6,128
		alpha	labda
Total costs period 2, first 2 years	Gamma	0.6369	0.0006
Utility values			
	Distribution	mean	SD
Utility of being on Oxaliplatin treatment	normal	0.65	0.036
Utility of being on Control treatment	normal	0.66	0.036
Utility of being disease free	normal	0.92	0.050
Utility of being relaped	normal	0.24	0.041

Monte Carlo simulation

Monte Carlo simulations were performed to estimate the costs per QALY gained.

Costs per QALY gained

- MOSAIC oxaliplatin versus MOSAIC control treatment
- PILOT oxaliplatin versus MOSAIC control treatment
- MOSAIC + PILOT oxaliplatin combined versus MOSAIC control treatment

Parameters were randomly selected from all distributions. This procedure was repeated 10,000 times. These 10,000 iterations generated 10,000 estimates of costs and DFS/OS/QALY for each treatment. By comparing the estimates for the two treatments, scatter plots on a cost-effectiveness plane were created to explore the degree of uncertainty regarding the differences in costs and health. In addition, a cost-effectiveness acceptability curve (CEAC) could be created to quantify the probability of cost-effectiveness of oxaliplatin vs. alternative treatment over a range of willingness-to-pay thresholds.

Scenario analyses

In order to gain a complete view of the cost-effectiveness in the Dutch population, we modelled two scenarios.

Scenario 1: FOLFOX versus CAPOX

In this scenario the same values for almost all of the model parameters were used as in the base case. The only exception relates to the costs of the oxaliplatin treatment, which were entirely based on the costs of FOLFOX and CAPOX separately rather than being integrated in a weighted mean costs.

Scenario 2: Ineligible patients integrated

In the base case analyses, ineligible patients (i.e., patients ineligible for oxaliplatin) (Figure 1.2.1) were ignored because the PILOT population was not comparable to the MOSAIC populations. However, 18% of the PILOT patients receiving oxaliplatin were ineligible and it remains questionable whether this population has the same benefit from the oxaliplatin treatment as the eligible patients. Scenario 2 examined ineligible patients in order to investigate the possible impact of their inclusion on the incremental costs, effectiveness and ICER.

Cumulative probabilities, transition probabilities and number of patients at risk were derived from the disease-free survival KM curve of ineligible PILOT patients. When comparing the 6-monthly probabilities of relapse of the first 30 months of follow-up, we observed the hazard of relapse to be on average 2.5 times larger in the ineligible oxaliplatin patient group (PILOT study) than in the eligible oxaliplatin patient groups (both PILOT and MOSAIC studies). The extrapolated transition probabilities from 30 up to 60 months were taken from the MOSAIC oxaliplatin arm, multiplied by 2.5, assuming a constant hazard rate of relapse. Next, an ‘ineligible’ control arm had to be simulated. This was performed in two ways.

1. Assuming an equal HR of effect (control vs oxaliplatin) as seen in eligible patients (full treatment effect)

The 6-monthly hazard of relapse as found in the eligible control population was multiplied by 2.5 to reflect a simulated ineligible control population.

2. Assuming no treatment effect of oxaliplatin

The 6-monthly hazard of relapse was set equal to the hazard of relapse in the ineligible oxaliplatin population.

Because there were only 43 ineligible patients in the PILOT study, the number of patients at risk in the simulated populations was also adapted to 43, in order to accurately reflect the degree of uncertainty.

Tables 1.2.11, 1.2.12 and 1.2.13 show the cumulative probabilities of staying disease-free, transitional probabilities and number of patients at risk for the ineligible oxaliplatin PILOT population and the two simulated ineligible control populations ('full' effect and 'no' effect).

Table 1.2.11 Cumulative probabilities of staying disease-free

	Cumulative probability of staying disease free (DFS)		
Time since start adjuvant treatment (months)	PILOT Study Oxaliplatin ineligibles	Simulated control groups Control ineligibles Full effect	Control ineligibles No effect
0	1.000	1.000	1.000
6	0.954	0.888	0.954
12	0.744	0.713	0.744
18	0.624	0.521	0.624
24	0.567	0.421	0.567
30	0.473	0.363	0.473
36	0.433	0.337	0.433
42	0.404	0.311	0.404
48	0.397	0.293	0.397
54	0.383	0.270	0.383
60	0.340	0.247	0.340

Table 1.2.12 Transition probabilities used in the Markov Model

Time	Initial state	Ending state	Transitional probabilities		
			PILOT Study Oxaliplatin ineligibles	Simulated control groups control ineligibles	
				Full effect	No effect
6 months	DFS	DFS	0.954	0.888	0.954
		Relapse	0.047	0.113	0.047
12 months	DFS	DFS	0.780	0.804	0.780
		Relapse	0.220	0.196	0.220
18 months	DFS	DFS	0.839	0.730	0.839
		Relapse	0.161	0.270	0.161
24 months	DFS	DFS	0.909	0.809	0.909
		Relapse	0.091	0.191	0.091
30 months	DFS	DFS	0.833	0.862	0.833
		Relapse	0.167	0.138	0.167
36 months	DFS	DFS	0.917	0.927	0.917
		Relapse	0.083	0.073	0.083
42 months	DFS	DFS	0.932	0.925	0.932
		Relapse	0.068	0.075	0.068
48 months	DFS	DFS	0.982	0.942	0.982
		Relapse	0.018	0.058	0.018
54 months	DFS	DFS	0.965	0.921	0.965
		Relapse	0.035	0.079	0.035
60 months	DFS	DFS	0.888	0.914	0.888
		Relapse	0.112	0.086	0.112

Table 1.2.13 Number of patients at risk

Patients at risk DFS

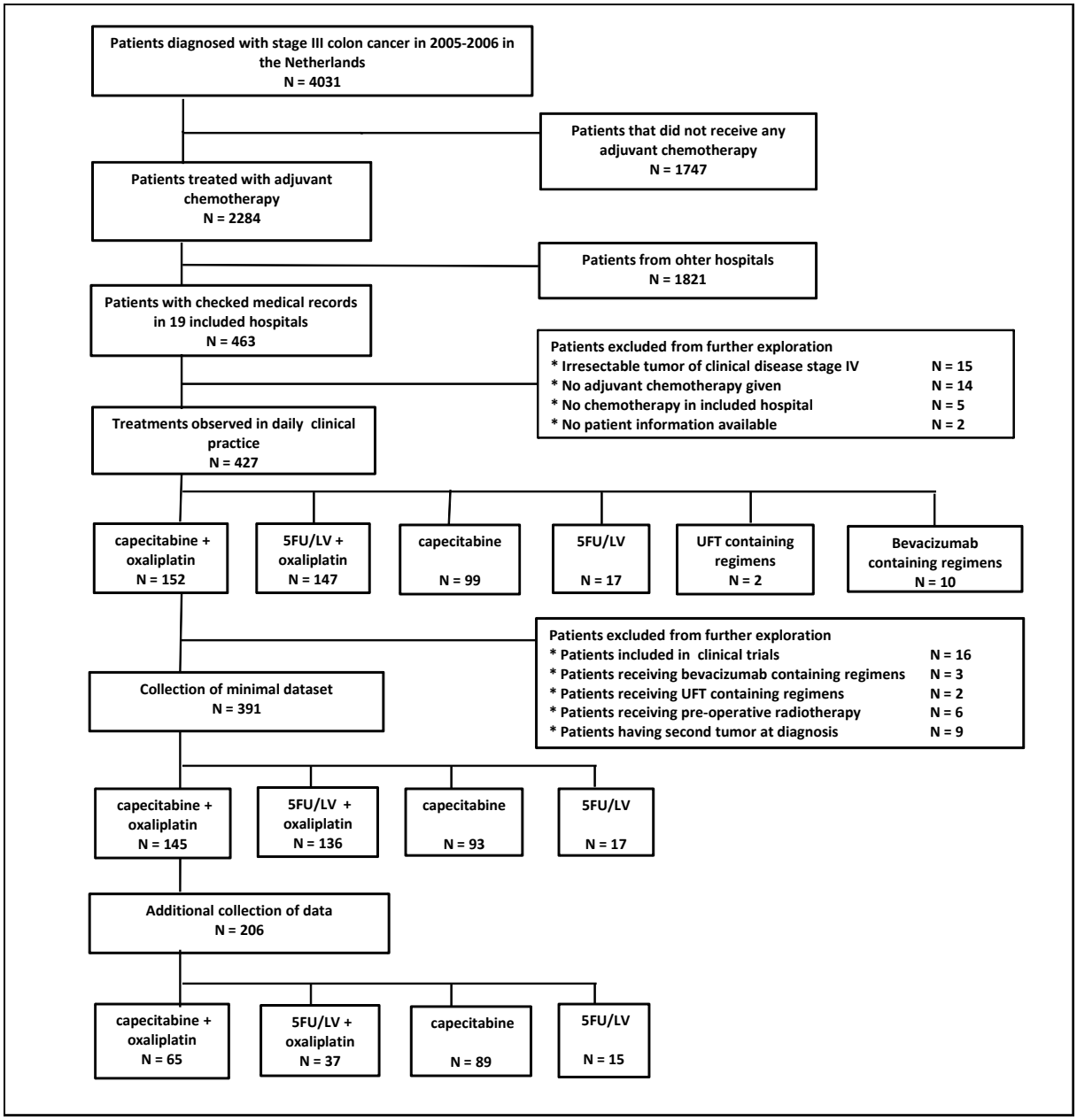
Months	PILOT study oxaliplatin ineligibles	Simulated control groups control ineligibles	
		Full effect	No effect
0	43	43	43
6	41	38	41
12	31	30	31
18	23	19	23
24	18	12	18
30	11	6	11
36	2	2	2
42	1	0	1
48	0	0	0
54	0	0	0
60	0	0	0

3 Results

3.1 Patient population

A patient flowchart is shown in Figure 1.3.1. Between January 2005 and December 2006, 4031 patients were diagnosed with stage III colon cancer, of whom 2284 (57%) were treated with adjuvant chemotherapy. A total of 463 patients were treated at one of the 19 hospitals included in our study, of which 427 met our initial inclusion criteria. As to the administered chemotherapy regimens, the four most common regimens were: 5FU/LV (N = 17), capecitabine (N = 99), FOLFOX (N = 147), and CAPOX (N = 152). A total of 391 patients were included based on the minimal CRF. Subsequently 206 patients were selected for more extensive data collection from the medical records. This selection occurred at random but was stratified by hospital and oxaliplatin use with the aim of balancing the number of patients that received oxaliplatin with that of those who did not.

Figure 1.3.1 Patient distribution



3.2 Data collection

Data collection took place via the database of the Dutch Cancer Registry and via patient files from 19 hospitals; 'minimal' data were collected for 391 included patients, which were supplemented with 'maximal' data for 206 patients.

Cancer registry

In October 2007 an application for data was submitted to the Dutch Cancer Registry with the aim of obtaining the data available on all patients diagnosed with stage III colon carcinoma in 2005 and 2006. Although the application was honoured in December 2007, the data were not

released until July 2008. This was partly due to the merger of the regional databases into 1 national database. Furthermore, the permission of the doctors treating the patients was necessary before insight could be granted into privacy-sensitive data.

Hospitals

Close collaboration with the DCCG in Nijmegen made it possible to make use of their relationships with oncologists in more than 80 hospitals in the Netherlands. As a result, permission was granted immediately for the collection of data from 40 hospitals. For logistical and pragmatic reasons, 19 hospitals were selected that would reflect the variety of clinical practice. Annex X provides an overview of the hospitals that participated. Participating centres included both academic and general hospitals, and thereby reflect the diversity of clinical practice in the Netherlands.

Additional data collection: minimum CRF

At each hospital, 'minimal' data were collected for all patients (identified via the Dutch Cancer Registry). As the minimal CRF data collection was limited to the information that could often be retrieved from a single patient letter, data on a maximum of 25 patients could be processed per day.

Additional data collection: maximum CRF

Per hospital, 'maximal' data were collected for a sub-group of patients. As maximal CRF data collection was extensive and required a detailed exploration of patient files, on average no more than 6 patients could be processed per day.

3.3 Use of oxaliplatin

Baseline characteristics

The baseline patient characteristics of the total population fulfilling the eligibility criteria (N = 391), as well as those of the four treatment groups, are summarised in Table 1.3.1. Patients receiving oxaliplatin were significantly younger ($p < 0.0001$) and had fewer comorbidities ($p = 0.0011$) than patients who did not receive oxaliplatin. Furthermore, patients receiving oxaliplatin more often had well-differentiated tumour histology ($p = 0.0073$), and higher serum carcinoembryonic antigen (CEA) levels ($p = 0.0282$). Additional stratification by age (older versus younger than 70 years of age) revealed that differences in tumour differentiation and CEA levels between those patients receiving oxaliplatin and those patients not receiving

oxaliplatin could be explained by the different age distribution in the two groups. Patients receiving FOLFOX were comparable to patients receiving CAPOX.

Table 1.3.1 Baseline Characteristics of Patients receiving chemotherapy in Dutch practice

		Regimens without oxaliplatin		Oxaliplatin containing regimens		
Baseline Characteristics	Total population N = 391	5FUL/LV N = 17	Capecitabine N = 93	5FU/LV + Oxaliplatin N = 136	Capecitabine + Oxaliplatin N = 145	P-values
Age - yr						
Median	64	71	73	61	62	< 0.0001
Range	22-85	41-80	46-85	30-78	22-82	
Age group - no. (%)						
< 70	279 (71.4)	7 (41.2)	31 (33.3)	118 (86.8)	123 (84.8)	< 0.0001
≥ 70	112 (28.6)	10 (58.8)	62 (66.7)	18 (13.2)	22 (15.2)	
No. of comorbid conditions - no. (%)						
0 - 1	332 (84.9)	12 (70.6)	71 (76.3)	115 (84.6)	134 (92.4)	0.0011
2^{+}	59 (15.1)	5 (29.4)	22 (23.7)	21 (15.4)	11 (7.6)	
Sex - no. (%)						
male	209 (53.5)	9 (52.9)	47 (50.5)	72 (52.9)	81 (55.9)	0.5281
female	182 (46.5)	8 (47.1)	46 (49.5)	64 (47.1)	64 (44.1)	
Depth of invasion - no. (%)						
T2 -T3	336 (86.2)	15 (88.2)	82 (89.1)	116 (85.3)	123 (84.8)	0.3130
T4	54 (13.8)	2 (11.8)	10 (10.9)	20 (14.7)	22 (15.2)	
Unknown	1					
No of nodes involved - no (%)						
N1	242 (61.9)	11 (64.7)	62 (66.7)	84 (61.8)	85 (58.6)	0.2553
N2	149 (38.1)	6 (35.3)	31 (33.3)	52 (38.2)	60 (41.4)	
Histologic appearance - no (%)						
Well differentiated	322 (86.3)	11 (64.7)	75 (81.5)	111 (86.7)	125 (91.9)	0.0073
poorly differentiated	51 (13.7)	6 (35.3)	17 (18.5)	17 (13.3)	11 (8.1)	
Unknown	18		1	8	9	
CEA level - no.						
< 5 ng/ml (ULN)	278 (84.5)	10 (83.3)	69 (93.2)	94 (83.2)	105 (80.8)	0.0282
≥ 5 ng/ml (ULN)	51 (15.5)	2 (16.7)	5 (6.8)	19 (16.8)	25 (19.2)	
Unknown	62	5	19	23	15	

CEA = carcinoembryonic antigen
ULN = upper limit of normal

Diffusion of oxaliplatin

After the inclusion of oxaliplatin for the adjuvant treatment of colon cancer in the National Guidelines, we observed a quick diffusion rate of oxaliplatin in the hospitals. Of the 19 hospitals included in our survey, 8 were already using oxaliplatin in the first quarter of 2005, followed by a total of 16 hospitals that started to use oxaliplatin during the second quarter of 2005. In January 2006, oxaliplatin was standard therapy in all 19 hospitals (Figure 1.3.2). However, even after their implementation, a substantial proportion of the patients did not receive oxaliplatin-based regimens. The percentage of patients not receiving oxaliplatin was 28% and this percentage did not change over time (P trend = 0.5). In contrast, the use of different regimens changed between January 2005 and December 2006 (Figure 1.3.3). The former standard therapy 5-FU/LV was prescribed to only 4% of the patients and was replaced by the FOLFOX or CAPOX regimens. Between January 2005 and December 2006,

a trend towards a shift from the use of FOLFOX to CAPOX was observed (test for trend, $p < 0.05$). In the second quarter of 2005, 82% of the patients receiving oxaliplatin were treated with FOLFOX versus 18% with CAPOX. During the course of 2005-2006, FOLFOX was gradually replaced by CAPOX, resulting in only 27% being treated with FOLFOX versus 73% with CAPOX at the beginning of 2007. Between the second quartile of 2005 and the beginning of 2007, the proportion of patients who received CAPOX increased from 19% to 73%.

Figure 1.3.2 Cumulative Diffusion of oxaliplatin in 19 hospitals

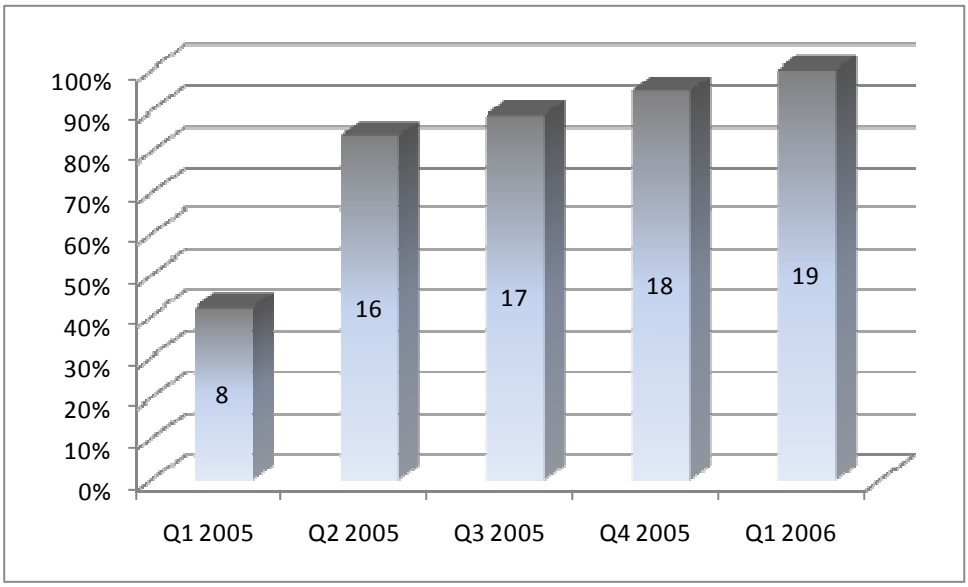
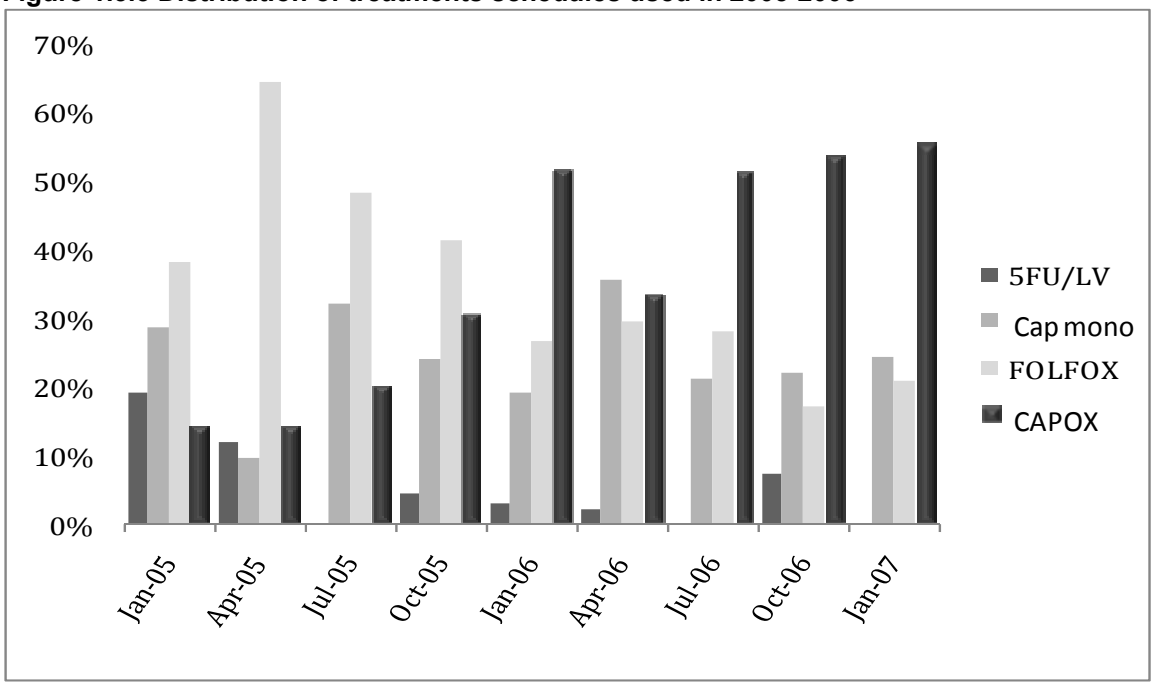


Figure 1.3.3 Distribution of treatments schedules used in 2005-2006



Considerations in choice of treatment regimen

We next explored reasons for non-prescription of oxaliplatin in all patients who did not receive this drug (N = 111). This is shown in table 1.3.2 The reasons for non-prescription were: advanced age (21%), comorbidity or poor health status (10%), specific contra-indications for oxaliplatin (2%), patient refusal (18%), not in line with hospital policy (23%), combination of these factors (7%), and unknown (23%). To assess independent predictors of non-prescription of oxaliplatin, we performed a multivariate logistic regression on baseline characteristics and included the variables age, presence of comorbid conditions, gender, depth of invasion of primary tumour (T-stage), lymph node involvement (N-stage), differentiation and serum CEA level. The multivariate analysis identified only age and comorbidity as being independent predictors of non-prescription of oxaliplatin (OR [95 CI] of 0.765 [0.708-0,826] and 0.426 [0.169-1.075], respectively).

Table 1.3.2 Reasons for not prescribing oxaliplatin (N = 111)

Reasons	No of patients (%)
Advanced age	23 (21)
Comorbidity or poor health state	11 (10)
Specific contra-indication for oxaliplatin	2 (2)
Patient declined treatment	21 (19)
Prescription of oxaliplatin is no hospital policy	20 (18)
Combination of reasons	8 (7)
Unknown	25 (23)

Dose schedules

The most frequently used treatment regimens in the Netherlands during the study period are presented in Table 1.3.3. In total, 37% of patients received CAPOX, 35% received FOLFOX-4, 24% received capecitabine monotherapy, and 4% received different 5-FU/LV regimens. The use of these regimens in clinical practice is presented in Table 1.3.4. With six months of chemotherapy being accepted as the standard duration of adjuvant treatment, and duration of the treatment cycle of 2 weeks for FOLFOX and 3 weeks for CAPOX and capecitabine monotherapy, the number of planned cycles is 12 and 8, respectively. The median number of cycles received equals the planned number of cycles in FOLFOX and capecitabine monotherapy, indicating that at least 50% of the patients were able to complete the number of cycles according to protocol. The median number of oxaliplatin cycles for patients receiving the CAPOX regimen was 7. The planned dose for each regimen is equal to the dosing recommendations as advised by the national guidelines. The mean dosages in milligrams per square metre per week across all cycles administered were slightly lower than the planned dosage. However, regarding mean dose over all planned cycles, we found that the mean dose of oxaliplatin in CAPOX was significantly lower than that in FOLFOX, with 30 $mg/m^2/wk$ versus 36 $mg/m^2/wk$, respectively ($p = 0.00213$). Furthermore, 70% of patients receiving CAPOX required dose modification and 71% of the total planned dose were administered versus 59% and 84%, respectively, in patients receiving FOLFOX ($p = 0.2661$ and $p = 0.0896$, respectively), suggesting that oxaliplatin may be less well tolerated when administered in the CAPOX regimen.

Table 1.3.3 Dose schedules observed in Dutch clinical practice

Regimen	% of patients receiving regimen	Dose-Schedule				Duration of treatment cycle (weeks)
		Oxaliplatin	Capecitabine	Fluorouracil	leucovorin	
CAPOX	37%	130 mg/m^2 day 1	1000 mg/m2 bid days 1-14 (ie, 28 doses)	–	–	3 wk
FOLFOX-4	35%	85 mg/m^2 day 1	–	400 mg/m^2/d bolus days 1,2; 600 mg/ m2/d CI days 1,2	200 mg/m^2/d bolus days 1,2	2 wk
Capecitabine	24%	–	1250 mg/m2 bid days 1-14 (ie, 28 doses)	–	–	3 wk
Aio/Ardalan	2%	–	–	2600 mg/m^2 CI	500 mg/m^2	1 wk
Mayo	1%	–	–	370 mg/m^2/d bolus days 1-5	20 mg/m^2/d bolus days 1-5	4 wk
Other 5FU/LV	1%	–	–	*not reported*	*not reported*	*not reported*

Abbreviations: CI, continuous infusion for 24 hours;

Table 1.3.4 Planned and actually delivered dose in clinical practice

	Regimens without oxaliplatin		**Oxaliplatin containing regimens**			
			FOLFOX		**CAPOX**	
	5FUL/LV All regimens	**Capecitabine**	**5FU/LV**	**Oxaliplatin**	**Capecitabine**	**Oxaliplatin**
		(1)	**(2)**		**(3)**	
	N = 15	**N = 89**	**N = 37**		**N = 65**	
Median nr of cycles received (planned nr of cycles)	**	8 (8)	12 (12)	12 (12)	8 (8)	7 (8)
Dose according to schedules in mg/m^2/wk	**	11666	1000 / 200	43	9333	43
Mean dose over all cycles given in mg/m^2/wk	**	9659	890 / 178	42	8049	42
Mean dose over all planned cycles in mg/m^2/wk	**	8250	800 / 160	36[*1]	7052	30[*1]
% of patients requiring modification (for dose reduction or interrupation)	53%	57%	54%	59%[*2]	50%	70%[*2]
% of planned dose given	72%	83%	84%	84%[*3]	79%	71%[*3]

** Not reported because of diversity of dose schedules and low patient numbers

[*1] p - value = 0.0213, [*2] p - value = 0.2661, [*3] p - value = 0.0896, Oxaliplatin in FOLFOX versus CAPOX

Toxicity

Haematological toxicity and neurotoxicity are the most frequent reasons for dose adjustment and/or interrupting treatment with oxaliplatin (Table 1.3.5). The hand-foot syndrome is a toxicity that occurs only in schedules involving capecitabine. The hand-foot syndrome also usually plays a role when “combination” is quoted as the reason for a dose adjustment and/or interruption of a schedule with capecitabine. Treatment with CAPOX seems to result more often into toxicities necessitating a dose adjustment and/or interruption than FOLFOX

(respectively 56% versus 35% for dose adjustments, P = 0.059; 42% versus 24% for interruption, P =0.072).

Table 1.3.5 Toxicities

	5FU/LV	Capecitabine	FOLFOX		CAPOX	
			5FU/LV	oxaliplatin	capecitabine	oxaliplatin
Adverse events	(N =15)	(N=89)	(N=37)		(N=65)	
Requiring dose reduction - nr (%)						
Hematological toxicity	0 (0)	2 (2)	3 (8)	3 (8)	7 (11)	8 (13)
Gastrointestinal toxicity	0 (0)	8 (9)	2 (5)	0 (0)	4 (6)	4 (6)
Neurological toxicity	0 (0)	2 (2)	2 (5)	3 (8)	3 (5)	9 (14)
Hand-Foot syndrome	0 (0)	8 (9)	0 (0)	0 (0)	2 (3)	3 (5)
Combination	0 (0)	3 (3)	2 (5)	1 (3)	3 (5)	6 (10)
Other	1 (7)	8 (9)	2 (5)	3 (8)	4 (6)	5 (8)
Unknown	0 (0)	5 (6)	2 (5)	3 (8)	0 (0)	0 (0)
Any	*1 (7)*	*36 (40)*	*13 (35)*	*13 (35)**	*23 (36)*	*35 (54)**
						1
Requiring interrupation - nr (%)						
Hematological toxicity	0 (0)	0 (0)	1 (3)	1 (3)	4 (6)	6 (9)
Gastrointestinal toxicity	1 (7)	1 (1)	0 (0)	0 (0)	2 (3)	3 (5)
Neurological toxicity	0 (0)	0 (0)	0 (0)	1 (3)	3 (5)	7 (11)
Hand-Foot syndrome	0 (0)	3 (3)	0 (0)	1 (3)	1 (2)	2 (3)
combination	0 (0)	4 (4)	4 (11)	3 (8)	3 (5)	5 (8)
Other	2 (0)	6 (7)	1 (3)	3 (8)	1 (2)	4 (6)
Unknown	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Any	*3 (20,0)*	*15 (17)*	*6 (16)*	*9 (24)***	*14 (22)*	*27 (42)***
requiring hospitalisation						
Any	*1 (7)*	*6 (7)*	*2 (5)*		*4 (6)*	

* chi-square p-value = 0.059

** chi-square p-value = 0.072

3.4 Clinical efficacy of oxaliplatin

Disease-free survival

We found that patients who did not receive oxaliplatin were significantly older and had more comorbidities than patients who did receive oxaliplatin. We also found a quick diffusion of oxaliplatin and clear reasons why patients did not receive oxaliplatin. From this we can conclude that patients who did and did not receive oxaliplatin are not comparable in terms of their prognosis. Therefore, a direct comparison of the disease-free survivals of the two patient groups would not be valid. For this reason, we present the DFS survival curves of the two treatment groups separately. The median duration of the follow-up exceeds 2 years for

all treatment groups (table 1.3.6). The chance of remaining disease-free varies amongst all treatment groups from 72% to 88%, but this variation is not statistically significant.

Table 1.3.6 Follow-up and disease free survival (DFS), unadjusted

	5FU/LV	Capecitabine	FOLFOX	CAPOX
	(N =17)	(N=93)	(N=136)	(N = 145)
Follow-up - mo				
median	29.6	27.4	26.7	23.2
Range	5.2 - 44.1	2.1 - 47.6	2.1 - 46.6	0.95 - 50.9
Probability of DFS				
at 2 year - % (95% CI)	88.2 (72.9 - 103.5)	80.8 (72.5 - 89.0)	72.0 (64.3 - 79.7)	72.8 (65.1 - 80.5)
Event - no. (%)				
Relapse	2 (11.7)	17 (18.2)	37 (27.2)	36 (24.8)
Death without relapse	0	4 (4)	1 (0.7)	1 (0.7)

Figure 1.3.4 shows the Kaplan Meier curve of the disease-free survival of patients treated without oxaliplatin (5FU/LV or capecitabine monotherapy). Figure 1.3.5 shows the Kaplan Meier curve of the disease-free survival of patients treated with oxaliplatin (FOLFOX of CAPOX).

Figure 1.3.4 Kaplan Meier disease-free survival curve of patients treated without oxaliplatin

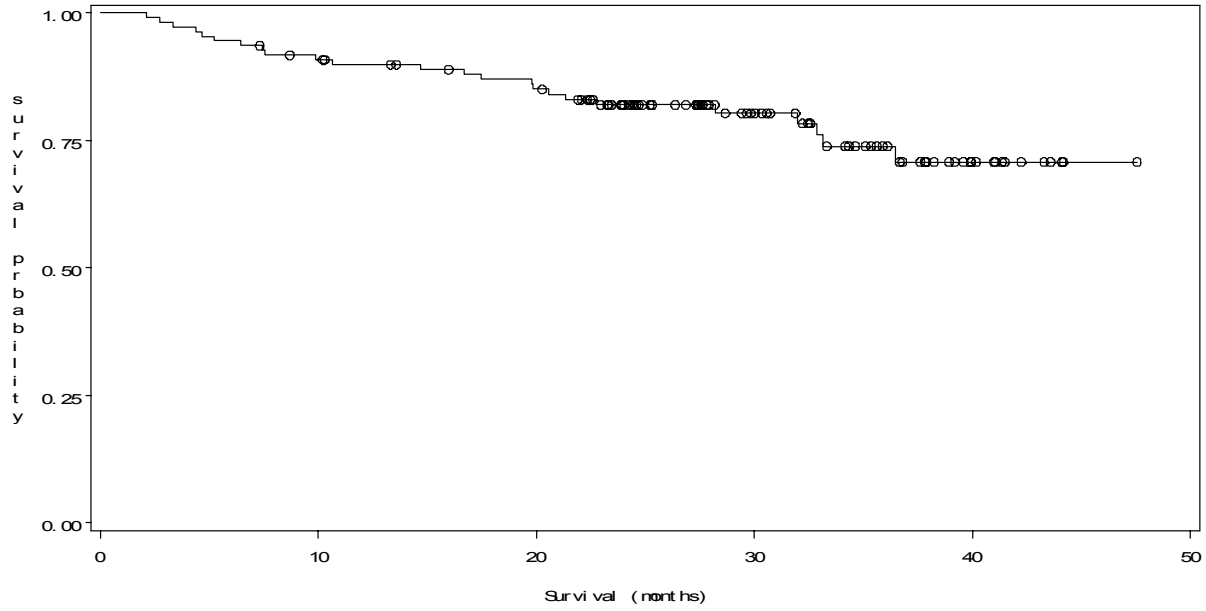
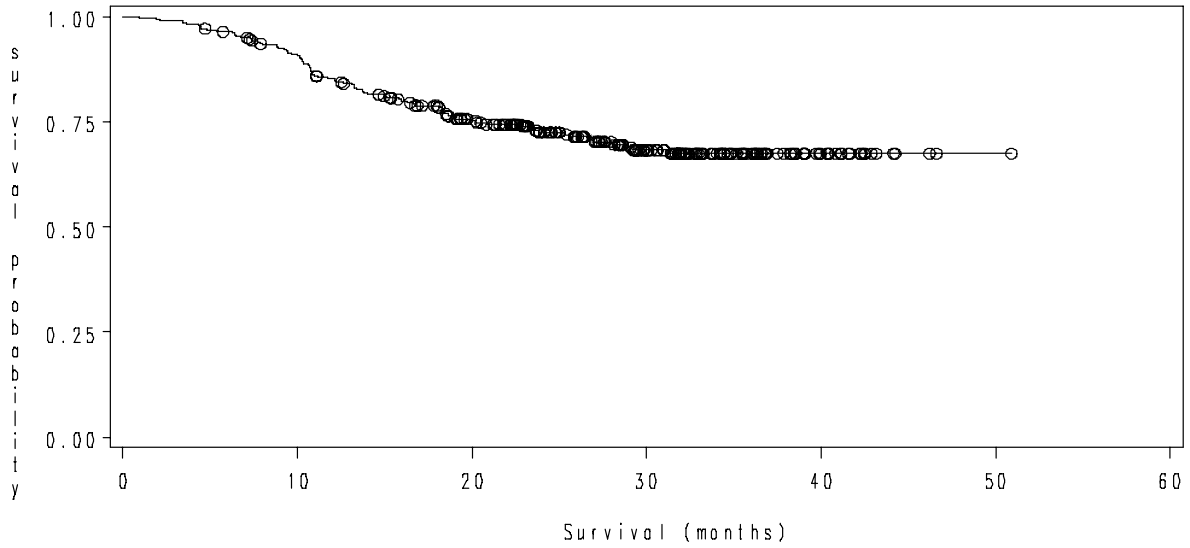


Figure 1.3.5 Kaplan Meier disease-free survival curve of patients treated with oxaliplatin



Multivariate analysis

Although we realised beforehand that an adequate adjustment for the baseline prognostic differences of the treatment groups would not be feasible, making it therefore by definition impossible to obtain an internally valid estimate of the treatment effect of oxaliplatin, we nevertheless performed a multivariate Cox regression analysis to identify prognostic factors and illustrate the problem of precision. Table 1.3.7 shows the results of the multivariate Cox regression, which included correction for differences in baseline characteristics. Disease-free survival was significantly shorter for patients younger than 70 years, patients with abnormal CEA values, patients with a T2-T3, and patients with N2-staging of the tumour. There was no significant association between survival and treatment with capecitabine or treatment with 5FU/LV (HR[CI] = 0.998 [0.631-1.578]).

Table 1.3.7 Multivariate analysis of factors associated with disease free survival

		95% CI		
Variables	**Hazard Ratio**	**Lower Limit**	**Upper Limit**	***P***
Treated with capecitabine	0.998	0.631	1.578	0.9921
Age younger than 70 years	2.006	1.085	3.706	0.0263
Elevated CEA levels	2.706	1.677	4.367	<.0001
Dept of invasion, T2-T3	1.946	1.130	3.351	0.0164
Spread to lymph nodes, N2	2.135	1.341	3.400	0.0014
Several comorbidities	1.464	0.808	2.651	0.2084
poorly differentiated tumour	1.234	0.648	2.350	0.5215

Model characteristics: lilelihood ratio, χ^2 (7) = 50.2181; probability > χ2 = <0.0001; -2 log likelihood = 815.128
Risk ratios adjusted for all covariates; Total N = 314, number of events 79, 74.8% censored

3.5 Costs of oxaliplatin

The mean costs per patient were determined for four treatment groups:

- 5FU/LV (n=15)
- Capecitabine (n=89)
- FOLFOX (n=37)
- CAPOX (n=65)

Period 1: from the first administration of chemotherapy until one month after the last administration of chemotherapy

The mean follow up durations for period 1 for the four treatment groups were as follows:

- 5.8 ± 2.3 months for patients receiving 5FU/LV (range: 5.2 to 44.2 months)
- 6.0 ± 1.3 months for patients receiving capecitabine (range: 1.0 to 47.6 months)
- 5.9 ± 1.0 months for patients receiving FOLFOX (range: 7.3 to 46.6 months)
- 6.4 ± 1.4 months for patients receiving CAPOX (range: 3.6 to 44.2 months)

Table 1.3.8 presents the total mean treatment costs per patient in period 1 for the four treatment groups. Mean costs per patient amounted to € 5,802 for 5FU/LV, € 4,944 for capecitabine, € 25,839 for FOLFOX and € 13,888 for CAPOX (Kruskal Wallis test: $p < 0.001$). Mean costs for FOLFOX and CAPOX were significantly different ($p < 0.001$), while mean costs for 5FU/LV and capecitabine were not significantly different ($p = 0.060$). A substantial cost variation was found in the total costs obtained for individual patients within treatment groups as well as in each individual cost component. Inpatient hospital days, daycare treatments, outpatient visits and chemotherapy (leucovorin, capecitabine and oxaliplatin) were the most important cost drivers.

Table 1.3.8 Total mean treatment costs per patient ~ period 1 (Euro 2009)

	5-FU/LV n=15	Capecitabine n=89	FOLFOX n=37	CAPOX n=65
Inpatient hospital days	1,013	886	10,250	2,359
Intensive care unit days	0	23	0	0
Outpatient visits	1,065	830	985	783
Consultations by telephone	10	18	13	25
Day-care treatments	1,692	152	1,174	938
Emergency room visits	371	100	24	67
Radiotherapy	0	0	0	26
Intravenous access	0	0	150	7
Colonoscopy	119	65	60	112
Other surgical procedures	180	0	32	57
Laboratory	535	290	422	398
X ray	21	23	38	26
CT scan	16	45	70	63
PET scan	94	48	0	23
Ultrasound	17	35	26	53
Other radiological procedures	0	13	9	16
Other procedures	51	5	12	11
5-Fluorouracil (bolus)	5	0	101	3
5-Fluorouracil (infusion)	94	2	143	4
Leucovorin	376	19	2,075	84
Capecitabine	0	2,184	103	1,989
Oxaliplatin	0	88	8,351	6,486
Uracil/tegafur	0	9	0	26
Concomitant medication	142	108	1,800	330
Total costs	5,802	4,944	25,839	13,888
Median	6,235	4,173	27,182	13,814
Minimum	1,070	316	2,611	1,708
Maximum	12,127	19,231	60,149	33,567

CT = Computed Tomography
PET = Positron Emission Tomography

Inpatient stay costs were € 1,013 in 5FU/LV, € 909 in capecitabine, € 10,250 in FOLFOX and € 2,359 in CAPOX. Of the inpatient admissions, 3% were to a ward other than an oncology ward, such as a surgery or pulmonary ward. Inpatient hospital days were especially important in the FOLFOX group, as the administration of 5FU/LV involved a 48-hour continuous infusion in this schedule and frequent admissions. Patients treated with FOLFOX were admitted for an average of 20.3 (SD 16.9) inpatient days, compared to 2.1 (SD 4.7), 4,1 (SD 20.2) and 4.3 (SD 9.4) days in the other three treatment groups (ANOVA test: $p < 0.001$). It should be noted that these admissions regarding the administration of FOLFOX might not have been necessary since we found hospitals where the 48-hour infusion was given via day-care treatment or outpatient visits only. Only one patient was admitted to the intensive care unit. This patient was treated with capecitabine and developed sepsis during her admission following dehydration from diarrhoea.

There was a significant difference in costs of day-care treatment between the four treatments (Kruskal Wallis test: $p < 0.001$). Daycare treatments were of minor importance in the capecitabine treatment group (€ 152; SD 374), because capecitabine is administered orally during outpatient visits. Costs for day-care treatments were much higher in the other three treatment groups (€ 1,692 for 5FU/LV, € 1,174 for FOLFOX and € 938 for CAPOX). There was also a significant difference in costs of day-care treatment between these three treatments (Kruskal Wallis test: $p = 0.027$). A substantial variation was found in number of day-care treatments per individual patient (range: 0-46).

The number of outpatient visits was of the same magnitude in the four treatment groups (ANOVA test: $p = 0.239$). The proportion of outpatient visits in total treatment costs was responsible for 18% in 5FU/LV, 17% in capecitabine, 4% in FOLFOX and 6% CAPOX.

Period 2: from one month after the last administration of chemotherapy until progression or end of follow up

The mean follow up durations in period 2 were as follows:

- 25.0 ± 8.7 months for patients receiving 5FU/LV (n=15)
- 22.1 ± 9.6 for patients receiving capecitabine (n=89)
- 22.7 ± 12.4 months for patients receiving FOLFOX (n=37)
- 19.4 ± 8.8 months for patients receiving CAPOX (n=65)

Table 1.3.9 presents the total mean treatment costs per patient in period 2 for the four treatment groups (n=206). Mean costs per patient amounted to € 3,312 for 5FU/LV, € 4,276 for capecitabine, € 5,034 for FOLFOX and € 3,324 for CAPOX (Kruskal Wallis test: $p = 0.517$). Mean costs for patients whose resource use was collected until progression were not significantly different from patients whose resource use was collected until the end of follow up ($p_{5FU/LV} = 0.167$; $p_{capecitabine} = 0.691$; $p_{FOLFOX} = 0.743$; $p_{CAPOX} = 0.072$).

Table 1.3.9 Total mean treatment costs per patient ~ period 2 (Euro 2009)

	5-FU/LV n=15	Capecitabine n=89	FOLFOX n=37	CAPOX n=65
Inpatient hospital days	1,143	1,316	2,159	882
Intensive care unit days	0	491	0	0
Outpatient visits	908	678	842	669
Consultations by telephone	7	7	8	8
Day-care treatments	56	68	42	58
Emergency room visits	23	77	39	15
Radiotherapy	0	0	0	26
Intravenous access	0	0	0	0
Colonoscopy	386	436	651	481
Other surgical procedures	0	222	477	355
Laboratory	287	363	288	277
X ray	97	76	78	64
CT scan	110	161	293	133
PET scan	94	128	0	134
Ultrasound	201	161	121	180
Other radiological procedures	0	83	27	35
Other procedures	0	10	10	7
Total costs	3,312	4,276	5,034	3,324
Median	1,813	2,156	2,235	1,976
Minimum	0	0	232	0
Maximum	10,084	62,737	38,645	20,018

CT = Computed Tomography
PET = Positron Emission Tomography

Inpatient hospital days, outpatient visits and colonoscopies were the most important cost drivers. Patients receiving FOLFOX received more computed tomography scans (ANOVA test: p = 0.002) than patients in the other three groups. Only costs related to 'other surgical site' also reached statistical significance (Kruskal Wallis test: p = 0.040).

Correction for baseline patient characteristics

The total treatment costs per patient for periods 1 and 2 jointly amounted to € 9,114 for 5FU/LV, € 9,220 for capecitabine, € 30,873 for 5FU/LV with oxaliplatin and € 17,211 for capecitabine with oxaliplatin. A multivariate linear regression on the logarithm of the total costs, involving the independent variables age, comorbidity, T-staging, N-staging, differentiation, CEA-values and the 4 treatment groups, revealed only a young age (and obviously treatment with oxaliplatin) as a possible predictor of higher costs ($p \approx 0,1$). Table 1.3.10 reflects the total costs over periods 1 and 2, stratified for age (younger than 70 years versus older than 70 years). There were no significant differences in costs between the treatment groups when the study population was stratified according to age group. This suggests that the costs incurred bear no relation to baseline characteristics.

Tabel 1.3.10 Total costs period 1+2 stratified according to age group (Euro 2009)

	No oxaliplatin		Oxaliplatin	
	5-FU/LV	Capecitabine	5-FU/LV	Capecitabine
Total population	*(n = 15)*	*(n = 89)*	*(n = 37)*	*(n = 65)*
mean total costs	**9,114**	**9,220**	**30,873**	**17,211**
Population younger than 70	*(n = 4)*	*(n = 13)*	*(n = 24)*	*(n = 44)*
mean total costs	**7,903**	**9,447**	**32,019**	**17,387**
standard deviation	768	6,024	14,918	7,232
Populatie older than 70	*(n = 11)*	*(n = 76)*	*(n = 13)*	*(n = 21)*
mean total costs	**9,554**	**9,182**	**28,756**	**16,844**
standard deviation	7,903	8,776	13,347	7,716
p-value*	*0.7940*	*0.6256*	*0.4451*	*0.8663*

* Kruskal-Wallis Test

Sensitivity analyses

Varying the unit costs of inpatient hospital days, day-care treatments and outpatient visits between 50% and 150% appeared to have a rather modest influence on the total mean costs of period one and two with the greatest influence when varying the unit price for inpatient hospital days. For patients treated with oxaliplatin, total mean costs of period one and two varied from € 19,948 to € 27,590 when inpatient hospital day unit costs were varied, from € 23,218 to € 24,320 when day-care treatment unit costs were varied and from € 22,953 to € 24,585 when outpatient visit unit costs were varied.

For patients in the control group, total mean costs of period one and two varied from € 8,107 to € 10,302 when inpatient hospital day unit costs were varied, from € 8,979 to € 9,429 when day-care treatment unit costs were varied and from € 8,415 to € 9,993 when outpatient visit unit costs were varied.

3.6 Daily practice versus clinical trials

Clinical effects: comparison with the MOSAIC trial

Table 1.3.11 provides an overview of the inclusion criteria of our study compared with those of the MOSAIC trial. In total 82% of the pilot patients who received oxaliplatin and 63% of the pilot patients who did not receive oxaliplatin fulfilled the inclusion criteria of the MOSAIC trial. Table 1.3.12 provides an overview of the baseline characteristics of the different groups. The CEA-value, an important negative prognostic factor, had to be lower than 10 ng/ml in order for a patient to fulfil the inclusion criteria. With respect to the patients who did not fulfil the MOSAIC inclusion criteria, 39.5% of the patients who received oxaliplatin had a raised CEA-value versus 9.4% in the group who did not receive oxaliplatin. Both ineligible and eligible pilot patients not receiving oxaliplatin were therefore not comparable to the MOSAIC control group. Therefore only pilot oxaliplatin patients were subject for further comparisons between the two studies.

The FOLFOX schedules of the two studies are compared in table 1.3.13. There are no differences between the studies with respect to the planned doses. The percentage of patients that received the planned number of oxaliplatin cycles is lower in the Pilot Study than in the MOSAIC trial (respectively 62% versus 75%). On the other hand, the average dose of oxaliplatin over the cycles received was higher in the Pilot study (42 mg/m2/week versus 36 mg/m2/week in the MOSAIC trial). As a result, no substantial differences were seen between the percentages of the planned total doses that were actually given (84% and 81% for the Pilot and the MOSAIC study respectively).

Table 1.3.11 Comparison eligibility criteria Pilot and MOSAIC studies

PILOT Study
> Histologically proven stage III coloncancer + clinical disease stage III
> Coloncancer as defined by ICD-O-03 code C18 and C19 and described and treated as coloncancer by physician
> Complete resection of the tumor required
> Adjuvant treatment needs to start in included hospital
> Not included in RCT
> Absence of prior chemotherapy, immunotherapy or radiotherapy
> Absence of treatment with Bevacizumab
> Absence of 2nd tumor diagnosis < 5 years ago
MOSAIC trial
> Histologically proven stage II or III coloncancer
> Coloncancer defined by presence of the inferior pole of the tumor above the peritoneal reflection, that is at least 15 cm from the anal margin (C18)
> Complete resection of the tumor required
> Treatment had to be started within seven weeks after surgery
> Age of 18 to 75 years
> karnofsky performance score of at least 60
> Carcinoembryonic antigen level of less than 10 ng/ml
> Absence of prior chemotherapy, immunotherapy or radiotherapy
> Adequate blood counts and liver and kidney function
> Written informed consent

Table 1.3.12 Baseline Characteristics of eligible versus ineligible patients

	Ineligible pilot patients		Eligible pilot patients		MOSAIC patients
	no oxaliplatin	oxaliplatin	no oxaliplatin	oxaliplatin	all
Baseline Characteristics	**N = 32**	**N = 43**	**N = 54**	**N = 200**	**N = 1347**
Age - yr					
Median	77	62	70.5	61	61
Range	59 - 85	32 - 82	55 - 75	22-75	19-75
Age group - no. (%)					
< 70	5 (15.6)	37 (86.1)	26 (48.2)	170 (85.0)	(86)
≥ 70	27 (84.4)	6 (13.9)	28 (51.8)	30 (15.0)	(14)
No. of comorbid conditions - no. (%)					
0 - 1	24 (75.0)	30 (69.8)	39 (72.2)	186 (93.0)	
2+	8 (25.0)	13 (30.2)	15 (27.8)	14 (7.0)	
Sex - no. (%)					
male	15 (46.9)	22 (51.2)	29 (53.7)	107 (53.5)	(56.1)
female	17 (53.1)	21 (48.8)	25 (46.3)	93 (46.5)	(43.9)
Depth of invasion - no. (%)					
T2 -T3	27 (84.4)	32 (74.4)	49 (92.5)	174 (87.0)	(80.5)
T4	5 (15.6)	11 (25.6)	4 (7.5)	26 (13.0)	(19)
Unknown			1		(0.5)
No of nodes involved - no (%)					
N1	19 (59.4)	26 (60.5)	36 (66.7)	123 (61.5)	(76.2)
N2	13 (40.9)	17 (39.5)	18 (33.3)	77 (38.5)	(23.8)
Histologic appearance - no (%)					
Well differentiated	25 (78.1)	34 (85.0)	41 (77.4)	176 (92.6)	(83.2)
poorly differentiated	7 (21.9)	6 (15.0)	12 (22.6)	14 (7.4)	(12.6)
Unknown				10	
CEA level - no.					
< 5 ng/ml (ULN)	29 (90.6)	26 (60.5)	50 (92.6)	173 (86.5)	
≥ 5 ng/ml (ULN)	3 (9.4)	17 (39.5)	4 (7.4)	27(13.5)	
< 10 ng/ml			54 (100)	200 (100)	(100)

CEA = carcinoembryonic antigen

ULN = upper limit of normal

Table 1.3.13 Treatment Characteristics Pilot and MOSAIC studies compared

	PILOT study		MOSAIC Trial	
	FOLFOX		FOLFOX	
	5FU/LV	Oxaliplatin	5FU/LV	Oxaliplatin
	N = 37		N = 672	
Median nr of cycles received (planned nr of cycles)	12 (12)	12 (12)	12 (12)	12 (12)
Dose according to schedules in mg/m^2/wk	1000 / 200	43	1000/200	43
Mean dose over all cycles given in mg/m^2/wk	890 / 178	42	*not reported*	36
Mean dose over all planned cycles in mg/m^2/wk	800 / 160	36	*not reported*	34
% of patients receiving planned nr of cycles	68%	62%	*not reported*	75%
% of planned dose given	84%	84%	84%	81%

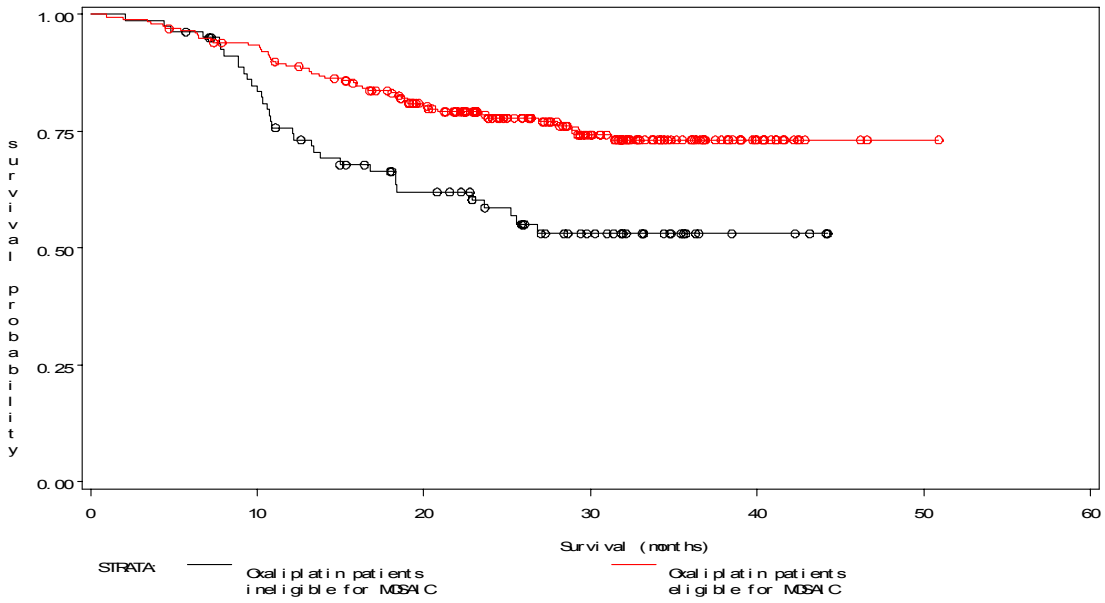
Table 1.3.14 provides an overview of the chance of disease-free survival at 24 months. After 24 months 79% of the patients who received oxaliplatin in the MOSAIC trial were disease-free. Table 1.3.6 already showed that the disease-free survival of patients who received oxaliplatin in the pilot study amounted to 72% at 24 months. After applying the inclusion criteria of the MOSAIC study to the pilot patients (treated with oxaliplatin), it appears that the selected group had a disease-free survival of 78.4% at 24 months.

What is noticeable with respect to the pilot patients treated without oxaliplatin, is that the difference in disease-free survival at 24 months is very small (83.7% for patients who did not fulfil the MOSAIC inclusion criteria versus 82.8% for patients who did). However, due to the low number of patients, the confidence intervals are extremely wide. Figure 1.3.6 shows the Kaplan Meier curves of those pilot patients who received oxaliplatin, divided according to whether or not they fulfilled the inclusion criteria.

Table 1.3.14 Disease-free survival, Pilot versus MOSAIC oxaliplatin patients

	PILOT patients		MOSAIC patients
	All patients treated with oxaliplatin		
	ineligibles	**eligibles**	
	(N=42)	(N = 200)	(N = 672)
Probability of DFS at 2 year - % (95% CI)	56.7 (41.5 - 72.0)	78.4 (72.5 - 84.3)	79.5

Figure 1.3.6 Disease-free survival curve of pilot patients treated with oxaliplatin stratified by eligibility for MOSAIC



Costs: comparison with existing literature

The combination of 5FU/LV and oxaliplatin was observed to be the most expensive treatment option. Treatment with FOLFOX in periods 1 and 2 was € 21,759 more expensive than 5FU/LV without oxaliplatin (Kruskal Wallis test: $p < 0.001$), predominantly owing to hospitalisation and chemotherapy costs. Earlier studies, most of them based on the MOSAIC trial, have also demonstrated lower costs for 5FU/LV without oxaliplatin over FOLFOX, although to a varying degree. In comparison with 5FU/LV, the life-time costs of the combination 5FU/LV and oxaliplatin were estimated to be about € 5,000 more expensive from the perspective of the NHS in the United Kingdom (€ 28,500 versus € 23,500) [20] and about € 16,000 more expensive from the perspective of Medicare in the United States (€ 52,850 versus € 36,900).[21]

Furthermore, treatment with FOLFOX in periods 1 and 2 was € 13,662 more expensive than treatment with CAPOX (Kruskal Wallis test: $p < 0.001$). Maniadakis et al. (2009), whose study was carried out in Greece, determined the total treatment cost of FOLFOX as an adjuvant treatment for high risk colon cancer patients to be about € 5,000 greater than that of CAPOX ($p < 0.001$; follow up duration: ≈ 13 months). The higher costs for FOLFOX were almost entirely due to higher hospitalisation costs. The FOLFOX group was hospitalised for an average of 10.7 inpatient days (versus 20.3 in our study) where the CAPOX group was hospitalised for an average of 2.2 inpatient days (versus 4.3 in our study).[36]

3.7 Cost-effectiveness of oxaliplatin

Base case results

The Markov model simulated the transitions of a hypothetical colon cancer stage III patient cohort through the clinical states.

The undiscounted ICER results, using LY gained and QALY gained as effectiveness measures, are presented in table 1.3.15 (oxaliplatin MOSAIC/PILOT/combined versus control MOSAIC). For example, the incremental costs were € 13,316 for oxaliplatin combined versus control treatment. Oxaliplatin combined resulted in a QALY gained of 1.18 compared to the control treatment. The ICER of oxaliplatin combined was €11,266 per QALY gained compared with control treatment, meaning that € 11,266 would have to be spent to gain an additional QALY with oxaliplatin treatment combined.

In general, the control treatment without oxaliplatin leads to the lowest costs (€ 17,142 for periods 1+2+3) and lowest effectiveness (13.12 LY and 11.56 QALY). Treatment with oxaliplatin results in higher costs (varying from € 30,415 in MOSAIC patients to € 30,606 in PILOT patients) and greater effects (varying from 14.19 LY and 12.60 QALY in PILOT patients to 14.37 LY and 12.78 QALY in MOSAIC patients). Essentially there is no big difference between MOSAIC oxaliplatin and PILOT oxaliplatin patients. Moreover, ICER results based on QALYs are very similar to ICER results based on LYs. Table 1.3.16 shows the discounted base case results. Discounting leads to ICERs that are € 4,629 to € 5,659 higher than undiscounted ICERs.

Table 1.3.15 Base Case results, Not Discounted

Base case results over a lifetime horizon

Incremental cost per life year gained

	Total Costs period 1+2	Total Costs period 1+2+3	Life Years (LY)		Incremental costs (1+2)	Incremental costs (1+2+3)	LY gained	ICER per LY gained (1+2)	ICER per LY gained (1+2+3)
1 Control treatment MOSAIC	€ 9,077	€ 17,142	13.12						
2 Oxaliplatin treatment MOSAIC	€ 23,825	€ 30,415	14.37	2 vs 1	€ 14,748	€ 13,273	1.26	€ 11,723	€ 10,551
3 Oxaliplatin treatment PILOT	€ 23,800	€ 30,606	14.19	3 vs 1	€ 14,723	€ 13,464	1.07	€ 13,747	€ 12,571
4 Oxaliplatin treatment combined	€ 23,819	€ 30,458	14.33	4 vs 1	€ 14,742	€ 13,316	1.22	€ 12,123	€ 10,951

Incremental costs per QALY gained

	Total costs period 1+2	Total Costs period 1+2+3	Quality Adjusted (LY)		Incremental costs (1+2)	Incremental costs (1+2+3)	QALY gained	ICER per QALY gained (1+2)	ICER per QALY gained (1+2+3)
1 Control treatment MOSAIC	€ 9,077	€ 17,142	11.56						
2 Oxaliplatin treatment MOSAIC	€ 23,825	€ 30,415	12.78	2 vs 1	€ 14,748	€ 13,273	1.22	€ 12,069	€ 10,862
3 Oxaliplatin treatment PILOT	€ 23,800	€ 30,606	12.60	3 vs 1	€ 14,723	€ 13,464	1.04	€ 14,157	€ 12,946
4 Oxaliplatin treatment combined	€ 23,819	€ 30,458	12.74	4 vs 1	€ 14,742	€ 13,316	1.18	€ 12,472	€ 11,266

Table 1.3.16 Base Case results, Discounted

Base case results over lifetime horizon

Incremental cost per life year gained

	Total Costs period 1+2	Total Costs period 1+2+3	Life Years (LY)		Incremental costs (1+2)	Incremental costs (1+2+3)	LY gained	ICER per LY gained (1+2)	ICER per LY gained (1+2+3)
1 Control treatment MOSAIC	€ 8,893	€ 16,350	9.95						
2 Oxaliplatin treatment MOSAIC	€ 23,626	€ 29,719	10.82	2 vs 1	€ 14,733	€ 13,369	0.87	€ 16,857	€ 15,296
3 Oxaliplatin treatment PILOT	€ 23,603	€ 29,895	10.69	3 vs 1	€ 14,710	€ 13,545	0.74	€ 19,798	€ 18,230
4 Oxaliplatin treatment combined	€ 23,620	€ 29,758	10.80	4 vs 1	€ 14,727	€ 13,408	0.85	€ 17,428	€ 15,867

Incremental costs per QALY gained

	Total costs period 1+2	Total Costs period 1+2+3	Quality Adjusted (LY)		Incremental costs (1+2)	Incremental costs (1+2+3)	QALY gained	ICER per QALY gained (1+2)	ICER per QALY gained (1+2+3)
1 Control treatment MOSAIC	€ 8,893	€ 16,350	8.69						
2 Oxaliplatin treatment MOSAIC	€ 23,626	€ 29,719	9.55	2 vs 1	€ 14,733	€ 13,369	0.86	€ 17,072	€ 15,491
3 Oxaliplatin treatment PILOT	€ 23,603	€ 29,895	9.42	3 vs 1	€ 14,710	€ 13,545	0.73	€ 20,068	€ 18,479
4 Oxaliplatin treatment combined	€ 23,620	€ 29,758	9.52	4 vs 1	€ 14,727	€ 13,408	0.83	€ 17,658	€ 16,077

Sensitivity analyses

In the base case the average life-expectancy of relapsed patients was assumed to be 1.7 years for all treatment alternatives. The effect of a lower life-expectancy was tested, using a worst case scenario, i.e. life-expectancy is equal to zero. Life years gained has increased by changing the life-expectancy. As a consequence the ICER per LY gained decreased somewhat, varying from € 1,792 to € 2,105 compared to the base case results. We therefore concluded that a lower life-expectancy has no major impact on our result, since we used the worst case scenario which is not very likely to occur in reality.

Probabilistic sensitivity analyses were conducted for the outcome measure of QALY gained (oxaliplatin MOSAIC, oxaliplatin PILOT, and oxaliplatin combined, all versus control treatment). The uncertainty surrounding the ICER is related to the uncertainty surrounding the costs and effects used in the model. Table 1.3.17 shows the mean difference in costs and QALYs as well as their 95% confidence intervals.

Table 1.3.17 Mean (95% CI) values of the total Δ Costs and Δ QALYs of the sensitivity analysis

		Δ Costs	95% CI		Δ QALY	95% CI		ICER
		Mean	Min	Max	Mean	Min	Max	Median
1 Control treatment MOSAIC								
2 Oxaliplatin treatment MOSAIC	2 vs 1	13,369	2,175-	28,984	0.86	0.26	1.45	€ 15,491
3 Oxaliplatin treatment PILOT	3 vs 1	13,545	2,648-	30,229	0.73	-1.78	2.79	€ 18,479
4 Oxaliplatin treatment combined	4 vs 1	13,408	2,400-	29,168	0.83	0.26	1.28	€ 16,077

The 95% confidence interval of the difference in costs between control treatment and oxaliplatin treatment (MOSAIC and PILOT patients combined) varied from - € 2,400 to € 29,168. The 95% confidence interval of the difference in QALYs between control treatment and oxaliplatin treatment varied from 0.26 to 1.45 when the MOSAIC oxaliplatin patients were used. However, when using only PILOT oxaliplatin patients, the 95% confidence interval was much wider (from -1.78 to 2.79).

Furthermore, the results of the simulations are shown in the three scatter plots below, where the simulated estimates in incremental costs and effects (i.e., QALYs) are plotted on a cost-effectiveness plane. Each dot on the scatter plot represents one estimate of the incremental costs and effectiveness of oxaliplatin vs. control treatment. The graphs illustrate again the much wider 95% confidence interval

regarding the effectiveness of only PILOT oxaliplatin patients. The 95% confidence ellipse of the PILOT patients is much wider, covering three quadrants of the cost-effectiveness plane. The ICER of only PILOT oxaliplatin patients is less robust.

Figure 1.3.7 Scatter plot of MOSAIC oxaliplatin versus control treatment based on Monte Carlo results (10,000 simulations)

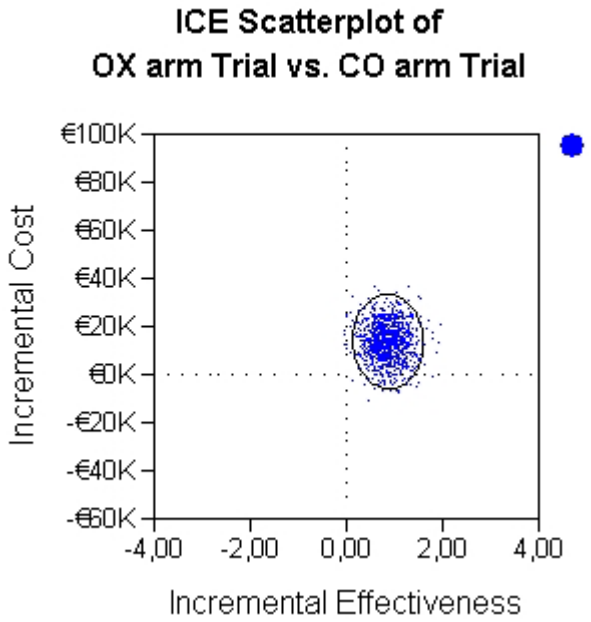


Figure 1.3.8 Scatter plot of PILOT oxaliplatin (eligibles) versus control treatment based on Monte Carlo results (10,000 simulations)

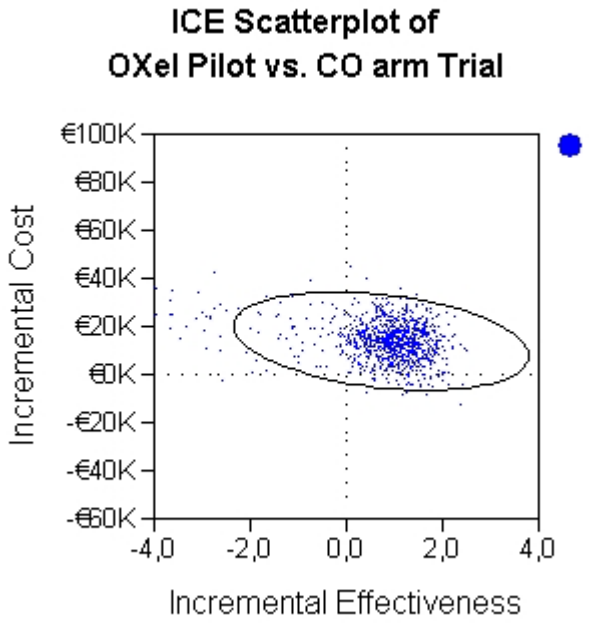
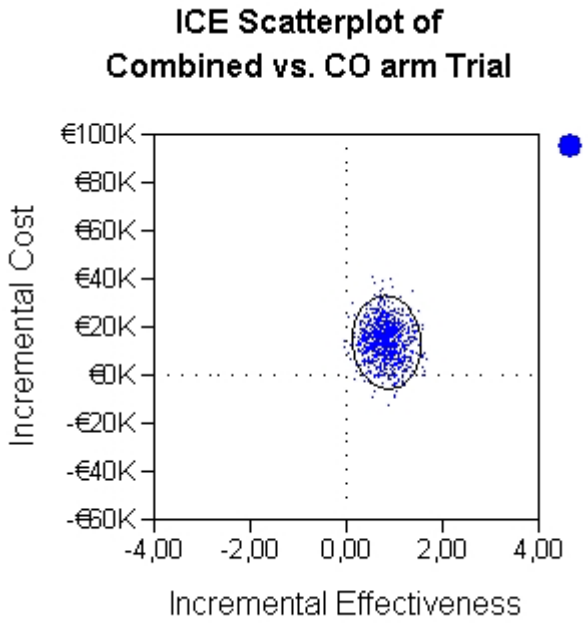


Figure 1.3.9 Scatter plot of combined oxaliplatin versus control treatment based on Monte Carlo results (10,000 simulations)



Since oxaliplatin was associated with both increased costs and increased effectiveness vs. control therapy, it is important to consider whether or not the additional costs are worth incurring in order to gain the additional effectiveness. Cost-effectiveness threshold curves (CEACs) show the probability that a treatment will be cost-effective at any given willingness-to-pay threshold. Figs. 1.3.7, 1.3.8 and 1.3.9 show the three CEACs from the base-case analyses.

Figure 1.3.10 cost-effectiveness acceptability curve for MOSAIC oxaliplatin versus control treatment

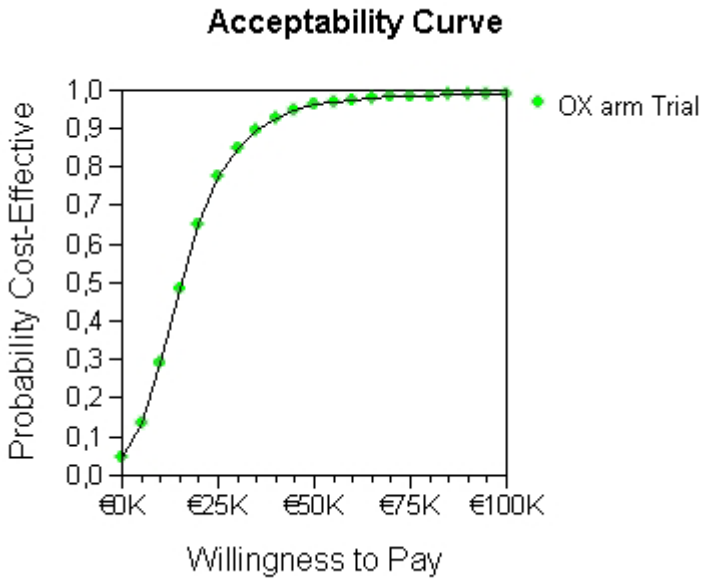


Figure 1.3.10 shows that for oxaliplatin MOSAIC vs. control treatment, there was a 98% probability that oxaliplatin would be cost-effective at a willingness-to-pay threshold of € 65,000.

Figure 1.3.11 Cost-effectiveness acceptability curve for PILOT oxaliplatin (eligibles) versus control treatment

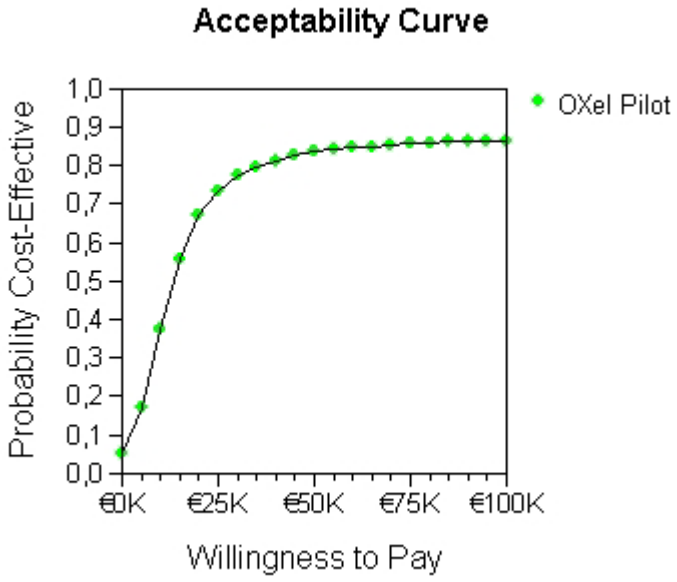


Figure 1.3.11 shows that for oxaliplatin PILOT vs. control treatment, there was a 85% probability that oxaliplatin would be cost-effective at a willingness-to-pay threshold of € 65,000.

Figure 1.3.12 Cost-effectiveness acceptability curve for combined oxaliplatin versus control treatment

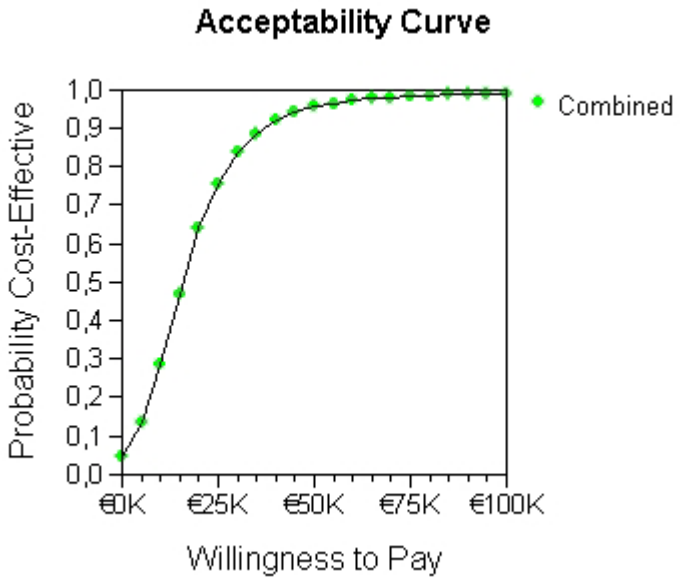


Figure 1.3.12 shows that for oxaliplatin PILOT vs. control treatment, there was a 98% probability that oxaliplatin would be cost-effective at a willingness-to-pay threshold of € 65,000.

Scenario analyses

Scenario 1: FOLFOX versus CAPOX'

Table 1.3.18 shows the impact of regimen choice. When oxaliplatin was combined with 5FU/LV (FOLFOX), the total costs were € 11,951 higher (PILOT oxaliplatin versus MOSAIC control) compared to the combination treatment with capecitabine (CAPOX). The resulting incremental costs per QALY gained are € 26,958, more than twice as high as the ICER of € 10,653 seen for scenario FOLFOX versus CAPOX.

Scenario 2: Ineligible patients integrated

Table 1.3.19 shows the impact of incorporating into the model the 18% of PILOT oxaliplatin patients who did not fulfil the MOSAIC eligibility criteria. Different scenarios can be made about the actual treatment benefit of oxaliplatin for these patients. One scenario is to assume that oxaliplatin is just as beneficial for these patients as it is for patients who fulfil the MOSAIC eligibility criteria. Another scenario is to assume that oxaliplatin has absolutely no treatment effect of oxaliplatin in this ineligible subpopulation. Although this would be viewed as an extremely unlikely scenario, we nevertheless examined the impact that this assumption would have on the ICER. Table 1.3.19 shows that the impact of these assumptions about benefit to ineligible patients is limited. For example, the incremental costs per QALY gained for the total population (eligible + ineligible patients) are € 22,836 in the worst-case scenario, only slightly higher than the ICER found in the base case scenario.

Table 1.3.18 FOLFOX versus CAPOX treatment

Discounted results over lifetime horizon

All oxaliplatin patients receive FOLFOX

	Total Costs period 1+2+3	Life Years (LY)	Quality Adjusted (LY)	Incremental costs (1+2+3)	LY gained	QALY gained	ICER per LY gained	ICER per QALY gained
1 Control treatment MOSAIC	€ 16,350	9.95	8.69					
2 Oxaliplatin treatment MOSAIC	€ 35,934	10.82	9.55	2 vs 1 € 19,584	0.87	0.86	€ 22,407	€ 22,693
3 Oxaliplatin treatment PILOT	€ 36,110	10.69	9.42	3 vs 1 € 19,760	0.74	0.73	€ 26,595	€ 26,958
4 Oxaliplatin treatment combined	€ 35,973	10.80	9.52	4 vs 1 € 19,623	0.85	0.83	€ 23,222	€ 23,529

All oxaliplatin patients receive CAPOX

	Total Costs period 1+2+3	Life Years (LY)	Quality Adjusted (LY)	Incremental costs (1+2+3)	LY gained	QALY gained	ICER per LY gained	ICER per QALY gained
1 Control treatment MOSAIC	€ 16,350	9.95	8.69					
2 Oxaliplatin treatment MOSAIC	€ 23,983	10.82	9.55	2 vs 1 € 7,633	0.87	0.86	€ 8,733	€ 8,845
3 Oxaliplatin treatment PILOT	€ 24,159	10.69	9.42	3 vs 1 € 7,809	0.74	0.73	€ 10,510	€ 10,653
4 Oxaliplatin treatment combined	€ 24,022	10.80	9.52	4 vs 1 € 7,672	0.85	0.83	€ 9,079	€ 9,199

Table 1.3.19 Impact of including patients not fulfilling the MOSAIC eligibility criteria

Discounted results over lifetime horizon

Incremental cost per life year and QALY gained

		Total Costs period 1+2+3	Life Years (LY)	Quality Adjusted (LY)	Incremental costs	(1+2+3)	LY gained	QALY gained	ICER per LY gained	ICER per QALY gained
1	Control treatment MOSAIC	€ 16,350	9.95	8.69						
2	Oxaliplatin treatment MOSAIC	€ 29,719	10.82	9.55	2 vs 1	€ 13,369	0.87	0.86	€ 15,296	€ 15,491
3	Oxaliplatin treatment PILOT	€ 29,895	10.69	9.42	3 vs 1	€ 13,545	0.74	0.73	€ 18,230	€ 18,479
4	Oxaliplatin treatment combined	€ 29,758	10.80	9.52	4 vs 1	€ 13,408	0.85	0.83	€ 15,867	€ 16,077
5	Control ineligibles Full effect	€ 21,562	5.89	4.66	7 vs 5	€ 13,233	1.20	1.18	€ 11,055	€ 11,205
6	Control ineligibles Zero effect	€ 20,244	7.09	5.84	7 vs 6	€ 14,551	0.00	0.00	∞	∞
7	Oxaliplatin ineligibles PILOT	€ 34,795	7.09	5.84						
8	Control el (82%) + inel (18%) Full	€ 17,288	9.22	7.96	10 vs 8	€ 13,489	0.82	0.81	€ 16,356	€ 16,578
9	Control el (82%)+ inel (18%) Zero	€ 17,051	9.44	8.18	10 vs 9	€ 13,726	0.61	0.60	€ 22,529	€ 22,836
10	Oxaliplatin PILOT el + inel	€ 30,777	10.04	8.78						

4 Discussion

4.1 Data collection

Data collection was based on three sources: data obtained via the Dutch Cancer Registry, data obtained via the 'minimal' CRF and data obtained via the 'maximal' CRF.

Dutch Cancer registry

The Dutch Cancer Registry (NKR) is a registry that provides important data for epidemiological research, clinical studies, evaluation of preventive programmes and health care policy. The NKR collects data of all cancer patients who are admitted to a hospital or whose disease has been confirmed by means of tissue examination. This amounts to more than 95% of all cases of cancer in the Netherlands.

Information from the NKR formed the basis for the data collection and was used to identify patients with stage III colon carcinoma. This guaranteed that a representative sample of the population was included which contributes to the external validity of the study. Furthermore, using this existing database allowed a simple method of supplying data on large numbers of patients. However, a disadvantage was the time-lag because of regular updates of the NKR database: new patients are often entered in the database a couple of months after their treatment has started. This is a problem particularly when a study is set up prospectively. Since our pilot study had a retrospective study design, this disadvantage was less important in our study. Nevertheless, it did take seven months before the data became available. We expect this to be much quicker in the future. Furthermore, it turned out that the database of the NKR contains insufficient data to form a complete basis for outcomes research. Firstly, extra information was needed for further patient selection. For the outcomes research on oxaliplatin it was important to know which type of chemotherapy patients had received. The NKR database does not contain this information. Secondly, for more detailed information, for example, on clinical effects and costs, additional data had to be collected from hospitals.

Minimal versus maximal CRF

It was possible to screen a large number of patients (in total 463) effectively via 'minimal' data collection (minimal CRF). This method is particularly effective when one does not know in advance whether all patients are relevant to the study. A disadvantage is that the collected data provide insufficient details to be able to assess dose schedules, toxicity and costs of treatments. This required a form of 'maximal' data collection (maximal CRF). This type of data collection was extremely time-consuming.

Prospective versus retrospective data collection

The set-up for data collection in this pilot study was retrospective. This means that at the moment of data collection the entire follow-up period was already in the past. In this pilot study we followed patients from 2005 up to the moment of inspecting the patient files. With prospective studies the follow-up time begins at the moment that data collection begins. The researcher subsequently follows the patients during the follow-up period. Both types of studies have advantages and disadvantages.[37] The advantage of using retrospective data collection in this pilot study was the possibility of making use of the NKR. Furthermore, data could be collected in a relatively short period of time, as each patient file only needed to be examined once. A major disadvantage was that we were utterly dependent on what could be found in the patient files. For example, an important prognostic factor, the WHO performance score, was often not recorded. In addition it was sometimes difficult to determine the chemotherapy dose schedules and doctors' considerations in choosing a particular therapy. Nor was there any information about quality of life, which is often only available in prospective studies. However, the price of this advantage is loss of efficiency: repeated measurements have to be made over a number of years.

4.2 Use of oxalilatin

This study has shown that, since 2005, the conventional treatment with 5FU/LV has been almost fully replaced by either capecitabine monotherapy (24%) or a combination therapy with oxaliplatin (72%). Over the time period 2005-2006 a preference started to develop for a combination therapy with CAPOX rather than FOLFOX. This is probably closely linked to implantable devices required by long-term intravenous administration of 5FU/LV, whilst capecitabine is given orally.

The prescription of oxaliplatin was significantly lower for elderly patients and patients with comorbidities. The negative impact of age and comorbidity on the prescription of adjuvant therapy for stage III colon carcinoma has been described earlier.[26] During 2005 and 2006 the prescription pattern of doctors was reasonably stable. This is probably a result of the extensive experience with both capecitabine and oxaliplatin in the treatment of metastatic colorectal carcinoma.[38]

The observed dose schedules correspond with current guidelines. The results, both of dose modifications and toxicities, suggest that oxaliplatin may be less well tolerated when given in the CAPOX schedule than in the FOLFOX schedule. A direct comparison of these two schedules for the treatment of stage III colon carcinoma had never been done before. There was only one study published on the use of CAPOX for stage III colon carcinoma, and it

reported that oxaliplatin dose had to be reduced for 35% of the patients and that on average 87% of the planned doses were received.[39] This differs considerably from the results in this pilot study (70% and 71%, respectively). Comparing the FOLFOX schedules in the pilot and MOSAIC studies shows that in Dutch daily practice dose adjustments are less frequently performed, but treatment is discontinued earlier. This difference may be explained by strict instructions for dose adjustments and treatment continuation within the trial protocol.

4.3 Clinical efficacy

Patients treated with oxaliplatin

In our study, after 2 years 72% of all the patients treated with oxaliplatin were still disease-free. 78.4% of the pilot patients who fulfilled the inclusion criteria of the MOSAIC trial were still disease-free after 2 years. This percentage is comparable to the percentage of patients being disease-free in the MOSAIC trial (79%). This outcome, which is supported by the finding that the baseline characteristics and the FOLFOX dosages are comparable in the pilot and MOSAIC patients, can be interpreted as a positive sign for the generalisability of the results of the MOSAIC trial to Dutch daily practice. However, these results obviously apply only for the 82% of the pilot oxaliplatin patients who fulfilled the MOSAIC eligibility criteria. The prognosis of the patients who did not fulfil these inclusion criteria was considerably poorer. This can be explained by the fact that these patients had significantly higher CEA-values, which is a strongly negative prognostic factor.

Patients treated without oxaliplatin

Patients who did not receive oxaliplatin were significantly older and had more comorbidities than patients who were treated with oxaliplatin. Patients who did not receive oxaliplatin were also significantly older than the patients in the MOSAIC trial, resulting in incomparability of the pilot and MOSAIC populations regarding the control treatment. This may be explained by the fact that oxaliplatin adds toxicity to treatment, and elderly patients and patients with comorbidities are therefore often considered to be poor candidates for this treatment.

Incremental efficacy of treatment with oxaliplatin versus treatment without oxaliplatin

Due to limitations in study design, caution is required when interpreting the results on incremental efficacy. The retrospective, observational nature of the pilot study is fundamentally different from a prospective, randomized design. In our study, the treating physicians determined which patients would be treated with oxaliplatin and which would not. This resulted in patients who did not receive oxaliplatin being older and having more comorbidities. For this reason, the uncorrected disease-free survival curves of the patients with and without oxaliplatin cannot be directly compared. Even after correction for baseline

characteristics, it is uncertain whether a valid estimate of the hazard ratio (HR) of the treatment effect of oxaliplatin was calculated. This is because it is uncertain whether the model has taken all relevant factors into account. For example, no information was available on the state of health of the patients (WHO performance score or Karnofsky index). It is not a standard procedure to record this in the medical files. However, we know that a poor state of health is a prognostic factor for a poor outcome, irrespective of comorbidity.[40] Apart from this, other factors may have played a role in the decision-making between doctors and patients, which have not been documented and therefore cannot be incorporated into the analysis. The selection of historical control patients diagnosed in 2004, before the rapid uptake of oxaliplatin had taken place, could result in more comparable groups of patients.

The median duration of the follow-up in our study approximated 2 years. This was 1 year less than what is usual in adjuvant colon carcinoma trials. Nevertheless, the literature indicates that extending from 2 to 3 years has only a limited effect on the outcomes of studies in this setting.[9]

4.4 Costs

In 2005 and 2006, 2,284 newly diagnosed patients with stage III colon cancer in the Netherlands received adjuvant chemotherapy. Of these, 4% received 5FU/LV, 24% received capecitabine, 35% received FOLFOX and 37% received CAPOX. In general, the diversity of treatment agents and regimens applied in daily practice results in a wide cost variation between patients.[41] Especially new expensive drugs, such as oxaliplatin, have placed a serious economic burden on the health care system, not only because of higher costs per drug but also because of their expanded use.[41, 42] The lower costs of CAPOX in comparison with FOLFOX may relieve the economic burden of stage III colon cancer in the future.

Costs are preferably determined from a societal perspective in which all relevant costs are included.[43]. However, considering limited time and information, it was impossible to collect retrospective data on societal costs for our cost analyses. Therefore, our cost analyses were conducted from the hospital perspective. As stage III colon carcinoma often occurs in the elderly unemployed population, productivity losses are expected to only have a minor impact on the results. Ignoring patients' out-of-pocket expenses may have affected the relative cost difference in favour of patients treated with oxaliplatin. In comparison with patients treated with capecitabine, more inpatient days and daycare treatments were registered for the FOLFOX group because the administration of 5FU/LV with oxaliplatin is an inpatient procedure. However, it should be noted that these admissions regarding the administration

of FOLFOX might not have been necessary since we found hospitals where the 48-hour infusion was given via day-care treatment or outpatient visits only.

Previous studies examining the costs of stage III colon cancer treatment based their cost assessment on resource use obtained from RCTs. However, the potentially limited generalisability of RCT-based economic evaluations may seriously restrict their relevance to policy-making. On the other hand, RCTs guarantee comparability between treatment groups, which was not the case in our observational study. Patients who received oxaliplatin were significantly younger and had fewer comorbidities than patients who did not receive oxaliplatin. This has a substantial impact when calculating the incremental cost-effectiveness of oxaliplatin. However, on the cost side, we have shown that differences in baseline characteristics do not have a significant impact on the total costs. This makes it considerably easier to arrive at a valid estimate of the incremental costs.

4.5 Cost-effectiveness model

The cost-effectiveness of oxaliplatin as an adjuvant treatment in stage III colon cancer was determined using a probabilistic Markov model. In order to evaluate the cost-effectiveness of oxaliplatin, the two arms (oxaliplatin containing regimens versus regimens without oxaliplatin) were evaluated separately. The model contains three Markov states for each arm: disease-free state, relapsed state and death. The Markov model simulated the transitions of a hypothetical cohort through the clinical states. Three categories of parameters are used as inputs to the model: transition probabilities between the Markov states, costs and utility values.

The process of model development and parameterisation requires making choices and assumptions. Each of these choices introduces additional uncertainty. Assumption 1 states that the disease-free survival data of the PILOT oxaliplatin population beyond the PILOT study follow-up period can be derived from the probabilities of the MOSAIC oxaliplatin patients. The hazard of relapsing was assumed to be equal to the hazard of relapsing in the oxaliplatin arm of the MOSAIC trial. This assumption is realistic since the hazard of relapsing was similar during the first 30 months as well. Furthermore, a large uncertainty surrounding the 6-monthly hazard is incorporated in the sensitivity analyses via the beta distributions.

Secondly it is assumed that all adverse events resulting in dose modifications are significant and have an impact on the patient's quality of life. This assumption might lead to an overestimation of the impact of dose modifications on quality of life, which would lead to a

conservative estimate of the cost-effectiveness of oxaliplatin, since patients receiving oxaliplatin experienced a higher number of dose modifications.

Thirdly it is assumed that deaths due to adverse events did not influence the results during the first 5 years following treatment. This assumption was based on the results of the MOSAIC trial that the number of deaths (possibly) due to adverse events was similar in both control and oxaliplatin arms (0.5% in each group). Furthermore, background mortality was assumed not to influence the incremental effectiveness results. This is plausible because ages were similar between the groups and the number of deaths was expected not to be higher than 5% during the first 5 years[5].

Assumption 5 says that the average life-expectancy of relapsed patients is equal for all treatment alternatives. This assumption was based on the findings of the MOSAIC trial that disease-free survival turned out to be an excellent predictor of overall survival. This finding supports the use of DFS not only as a surrogate endpoint for survival, but also as a full endpoint in colon cancer adjuvant studies.[9, 16]

In the MOSAIC study, adjuvant treatment with additional oxaliplatin was demonstrated to be more effective than adjuvant treatment with 5FU/LV or capecitabine alone, resulting in 0.863 QALY gain over a lifetime horizon. The oxaliplatin patients in the PILOT study show similar results, resulting in 0.733 QALY gained when compared with the MOSAIC control patients. The costs of treatment with oxaliplatin were higher than treatment with 5FU/LV or capecitabine alone, resulting in a lifetime incremental cost/QALY gained of € 15,491 and € 18,479 for MOSAIC and PILOT oxaliplatin patients respectively. When combining both MOSAIC and PILOT oxaliplatin patient groups, the incremental cost/QALY becomes € 16,077. The base case results were expressed in costs per life-year gained and costs per QALY gained. The difference in ICER based on life-years versus QALYs is < € 300, showing only a limited impact of the inclusion of quality-of-life in the analyses.

The impact of the model parameters was evaluated through probabilistic sensitivity analyses. The 95% confidence interval of the difference in costs between control treatment and oxaliplatin treatment (MOSAIC and PILOT patients combined) varied from - € 2,400 to € 29,168. The 95% confidence interval of the difference in QALYs between control treatment and oxaliplatin treatment varied from 0.26 to 1.45 when the MOSAIC oxaliplatin patients were used. However, when only PILOT oxaliplatin patients were used, the 95% confidence interval was much wider (from -1.78 to 2.79). The reason for this increased uncertainty surrounding the incremental QALY estimate is the lower number of patients and the limited

follow-up time in the PILOT study (200 patients and median follow-up of 24 months in the PILOT study versus 672 patients and median follow-up of 60 months in the MOSAIC study).

Sensitivity analyses were performed using different sources of cost and effectiveness data. Overall we found only minimal differences in the estimated incremental cost-effectiveness in our analyses, showing the robustness of the model results. The CEAC for MOSAIC oxaliplatin versus control treatment showed that in 98% of the 10,000 iterations, the incremental cost per QALY was < € 65,000. The CEAC for PILOT oxaliplatin versus control treatment showed that in 85% of the 10,000 iterations, the incremental cost per QALY was < € 65,000.

Two scenario analyses were performed to evaluate the cost-effectiveness of oxaliplatin in settings that better reflect the current Dutch daily practice setting. In the first scenario the cost of FOLFOX was compared to that of CAPOX. If all patients use CAPOX rather than FOLFOX, the incremental cost per QALY gained would decrease by € 16,305 (ICER of € 26,958 for FOLFOX versus € 10,653 for CAPOX). Figure 1.3.3 shows a trend towards the use of CAPOX rather than FOLFOX during the course of 2005-2006. As a consequence the ICER decreased as well during the course of 2005-2006; this lower ICER might better reflect the cost-effectiveness of Dutch daily clinical practice from 2006 to the present. The second scenario also included patients who did not fulfil the MOSAIC trial eligibility criteria. The PILOT study showed that 18% of the patients receiving oxaliplatin did not fulfil these criteria. The prognosis of these patients was worse than the prognosis of patients who fulfilled the criteria. Since the ineligible patients were not included in the MOSAIC trial at all, no information was available regarding ineligible patients receiving control treatment. Two additional options were explored: one option assumed that oxaliplatin is just as beneficial for these patients as it is for patients who fulfil the MOSAIC eligibility criteria, and one option assumed no effect of oxaliplatin at all. The latter forms the most conservative assumption. The scenario analyses showed that if there is no treatment effect of oxaliplatin in the ineligible patient group (18%), the resulting incremental cost per QALY gained is € 22,836.

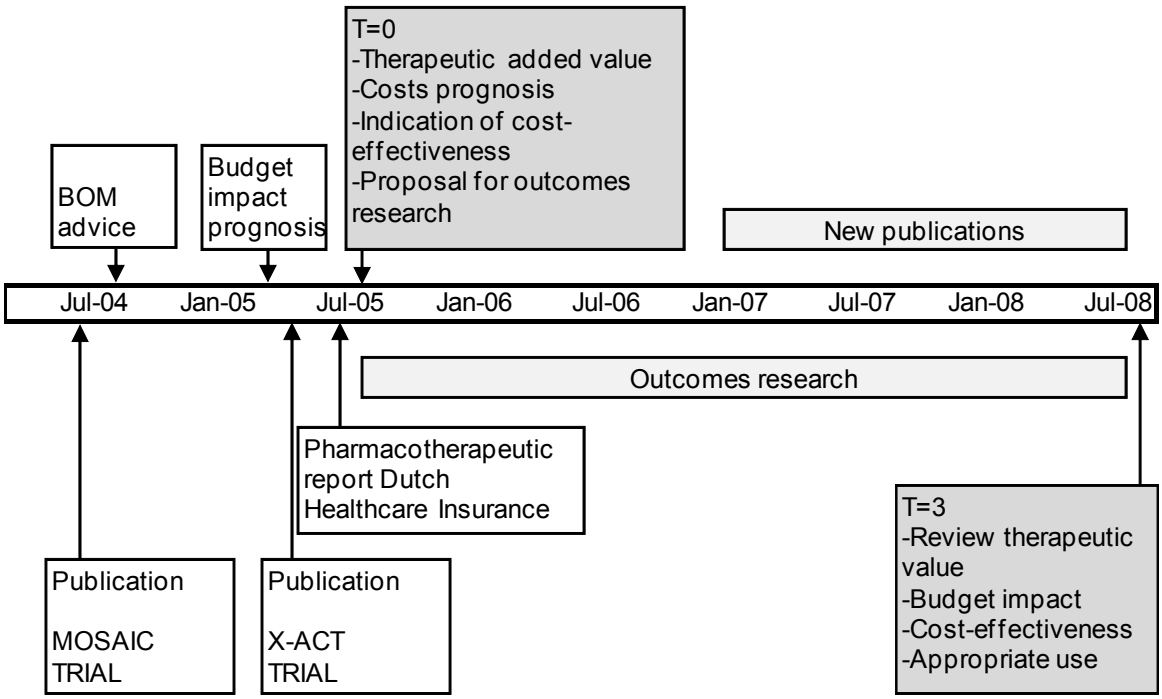
A similar cost-effectiveness model was used by Pandor et al., 2006.[12] In their analysis a comparable cost-effectiveness analysis was used based on the MOSAIC trial. In our cost-effectiveness analysis we used a slightly simplified version of their model. Pandor et. al reported 1.61 undiscounted QALYs (1.33 discounted) gained in the base case analysis. Our study found 1.22 undiscounted QALYs (0.86 discounted) gained when considering only MOSAIC patients. The difference between these two estimates is probably caused by our more conservative estimate regarding the overall survival of the patients. Furthermore, Pandor et al. (2006) only reported discounted incremental costs of £ 3,941 where this is €

13,369 (Euro 2009) in our study (€ 13,273 discounted). This difference is due to the higher costs of the control treatment in the study of Pandor et al. In current Dutch daily practice, capecitabine is indicated rather than 5FU/LV. Therefore the costs of the control treatment are mainly based on the cost of capecitabine, which is a less costly alternative compared to 5FU/LV.

4.6 Cost-effectiveness in daily clinical practice

Figure 1.4.1 reflects the passage of time in relation to treatment of stage III colon carcinoma with oxaliplatin. Based on the knowledge at T = 0 oxaliplatin was accepted into the policy regulation 'expensive medicines'. A first indication of its cost-effectiveness was provided at that moment. At T = 3 knowledge will have to be obtained on the cost-effectiveness of oxaliplatin in daily practice.

Figure 1.4.1 Time-plan for oxaliplatin



Knowledge at T = 0

Knowledge relating to clinical efficacy

Oxaliplatin was included in the policy regulation based on the results of the MOSAIC trial. This trial found a significantly lengthened disease-free survival when using FOLFOX in

comparison with 5FU/LV alone. There are no data available relating to overall survival and quality of life.

Knowledge relating to costs

Based on the costs of the new medicine itself, the extra costs that would be involved in using oxaliplatin were estimated at T = 0. The duration of treatment, as agreed by protocol, and the expected dose schedules were taken into account.

Provisional inclusion in the policy regulation takes place in the event of positive advice which follows if a medicine has a therapeutic added value, it achieves the cost threshold and the research protocol for cost-effectiveness has been sufficiently elaborated. The latter means that the provisional data regarding cost-effectiveness provide an indication of efficiency (t=0) and that a properly substantiated proposal for outcomes research is submitted.[1] As oxaliplatin was accepted into the policy regulation before this new policy was implemented, no such CVZ-report was available at T=0.

Knowledge via outcomes research at T = 3

Knowledge relating to clinical efficacy

Oxaliplatin is used both in combination with 5FU/LV (FOLFOX) and in combination with capecitabine (CAPOX). There was no difference in efficacy between these two combinations. Based on their baseline characteristics, a large majority (82%) would have been eligible for the MOSAIC trial. Furthermore, the entire group of oxaliplatin-users show a similar disease-free survival to the MOSAIC trial. These similarities can be regarded as a positive sign of the generalisability of the results from the MOSAIC trial into daily practice. However, due to its rapid diffusion, most of the patients who were eligible for oxaliplatin, were actually treated with it, which has resulted in a control group that is not comparable with the group of patients that received oxaliplatin as far as baseline characteristics are concerned. In the meantime 5FU/LV has actually been replaced by capecitabine monotherapy. Correction for dissimilarities is hampered by the small numbers of patients (problems of precision) and possible “residual confounding” (problems with internal validity). As a result, there is a great deal of uncertainty regarding the estimated incremental disease-free survival in daily practice. There are no data on overall survival and quality of life from daily practice in the Netherlands.

Knowledge relating to costs

The total costs of treatment and follow-up were calculated per treatment group. However, there was considerable variation in these costs. This was due to the large variation in costs and the small numbers of patients. The patients from the various treatment groups did differ

with regard to baseline characteristics, but this had no impact on the total costs. This finding suggests there is no threat to the internal validity of incremental cost estimation in daily practice.

Knowledge via literature study at T = 3

Knowledge relating to clinical efficacy

Various publications were available at T=3. The results of a 6-year follow-up of the MOSAIC study show that the use of oxaliplatin leads to a significantly improved overall survival (83). No data are available involving a comparison with capecitabine monotherapy. There are no publications on the efficacy of CAPOX in stage III colon carcinoma available at T = 3. Nor is any information available relating to quality of life.

Knowledge relating to costs

Various publications were available at T = 3. These were mainly cost studies that had piggy-backed on the MOSAIC trial. There are no publications on Dutch costs.[12, 20, 21]

Cost-effectiveness at T =3

Knowledge on clinical effectiveness from outcomes research alone does not supply a valid and reliable estimate of the incremental cost-effectiveness of oxaliplatin. We have described how the oxaliplatin patients who fulfilled the inclusion criteria of the MOSAIC study with respect to baseline characteristics and disease-free survival correlate highly with the MOSAIC patients who received oxaliplatin. Furthermore, new results of the MOSAIC study had been published at T = 3. In order to arrive at the best possible valid and reliable estimate of cost-effectiveness, a model study of clinical effectiveness and knowledge was carried out that combined knowledge at T = 0, knowledge at T = 3 obtained from outcomes research, and knowledge at T = 3 from the literature. Only data from the outcomes research was used for calculating the incremental costs.

Cost-effectiveness model of oxaliplatin

The aim of the cost-effectiveness model was to establish the cost-effectiveness of oxaliplatin in the treatment of stage III colon carcinoma. The base case results showed an incremental cost-effectiveness per QALY gained that varied from € 15,491 for patients from the MOSAIC trial to € 18,479 when only the pilot oxaliplatin patients were taken into account. Sensitivity and scenario analyses were subsequently carried out using various sources of cost and effectiveness data. Overall we found only minimal differences in the estimated ICERs in our analyses, showing the robustness of the model results. In the most conservative scenario,

i.e., incorporating PILOT patients who were not eligible for the MOSAIC study and assuming no treatment effect of oxaliplatin in this subpopulation, the incremental cost per QALY gained was estimated to be € 22,836. We feel confident that the effects of the model's assumptions are limited. Based on our results, one can conclude that the addition of oxaliplatin combination therapy as adjuvant treatment of stage III colon carcinoma is a cost-effective alternative.

General conclusion on cost-effectiveness

The model makes use of both the results of the outcomes research and the published literature. All cost data used in the model were based entirely on the outcomes research. Data relating to clinical efficacy on patients treated with oxaliplatin were based both on the outcomes research and on the MOSAIC study. Due to the impossibility of comparing patients who received oxaliplatin treatment in daily practice and those who did not, with respect to clinical cost-effectiveness, we were forced to limit ourselves to the control arm of the MOSAIC study as sole comparator in the model. We feel that this choice provides a sufficiently precise and accurate estimate of the cost-effectiveness of oxaliplatin in daily practice. The claim is justified that the cost-effectiveness of oxaliplatin has been sufficiently substantiated in daily practice.

4.7 Appropriate use in daily clinical practice

This pilot outcomes research studied the appropriate use of oxaliplatin. The aim was to provide insight into the dynamics of clinical practice. *Dynamics of clinical practice* is defined as the differences between the requirements for registering oxaliplatin and the information on its use in daily practice. These differences may result from differences in the use of oxaliplatin or differences in the observed effectiveness or adverse events.[1] The following is a short summary of the aspects relevant to the dynamics of clinical practice.

Population treated in clinical practice versus population from the MOSAIC study
A large proportion of the patients (82%) treated with oxaliplatin in daily practice were similar to the population from the MOSAIC study. The patients who did not fulfil the MOSAIC eligibility criteria (18%) had significantly higher CEA-values, which is a strongly negative prognostic factor.

Selective prescription
As a result of the rapid diffusion of oxaliplatin, the baseline characteristics of patients who received oxaliplatin and those who did not remained unaltered during 2005 and 2006.

Therefore we do expect that the patients groups studied are representative of the total patient populations for whom oxaliplatin was prescribed after 2006.

Prescribing outside the registered indication

Oxaliplatin is registered for the indication adjuvant treatment of stage III colon carcinoma. This is the indication examined in this pilot study. The professionals involved have already indicated that oxaliplatin can also be considered for high-risk stage II patients. We did not investigate this shift in indication and the degree to which this existed during the timeframe of this pilot study is unclear.

The use of oxaliplatin in practice versus use in the MOSAIC study

The observed dose schedules in daily practice demonstrated a good adherence to existing guidelines which, with respect to FOLFOX, are based on the MOSAIC study. Regarding FOLFOX, the total cumulative dose of oxaliplatin received by patients in daily practice was also similar to the dosages reported in the MOSAIC study. In daily practice, in addition to the FOLFOX, the CAPOX regimen was also often prescribed. The observed CAPOX dose schedules are also consistent with existing guidelines. In daily practice, however, dose modifications were seen more frequently. On average patients in daily practice received 71% of the planned dose, whilst the literature reports this to be 87%. In there Netherlands, extensive experience has been obtained with the use of CAPOX for treating metastatic colorectal carcinoma.

Effectiveness of oxaliplatin in practice versus effectiveness in the MOSAIC study

The 82% oxaliplatin patients from daily practice who fulfilled the inclusion criteria of the MOSAIC study show a similar disease-free survival to that of the oxaliplatin patients in the MOSAIC study. Although on the basis of the pilot study no conclusions can be drawn with regard to overall survival, due to the short follow-up (median 24 months), the outcome, with a median 2-year follow-up, appears to be a good predictor for overall survival.[9] No comparative trial data are available on the patients who did not fulfil the inclusion criteria of the MOSAIC study (18%). Daily practice shows that these patients have a less favourable prognosis. This is mainly explained by the significantly higher CEA-values of these patients. Although it is uncertain whether adjuvant therapy with oxaliplatin might have an added value here, it is unlikely that oxaliplatin would be unfavourable for this group of patients as oxaliplatin also plays an important role in the treatment of metastatic colon carcinoma.

Toxicity of oxaliplatin in practice versus toxicity in the MOSAIC study

The adverse events of FOLFOX in daily practice are similar to the pattern of side effects described in the MOSAIC study. Side effects seem to occur more frequently with CAPOX.

The hand-foot syndrome often plays a role in adjustments in the CAPOX dose. This side effect occurs frequently in patients treated with capecitabine (such as CAPOX). Although the hand-foot syndrome is burdensome for patients, this side effect is not life-threatening.

General conclusion on appropriate use

It is difficult to compare patients who have been treated in daily practice without oxaliplatin with patients who have been treated with oxaliplatin. It has proven impossible to correct satisfactorily for differences in baseline characteristics. Nevertheless, proper correction is essential for calculating the incremental cost-effectiveness based only on data from daily practice.

Providing insight into the dynamics of clinical actions makes it clear that patients who are treated with oxaliplatin in daily practice, with respect baseline characteristics, use of oxaliplatin, efficacy and toxicity, comply well with the requirements for registering oxaliplatin at T = 0. Lastly, one can say that oxaliplatin, when prescribed within the registered indication, is used appropriately in daily practice.

Section 2 Oxaliplatin in metastatic colorectal cancer

1 Introduction

For patients with distant irresectable metastatic CRC there are no curative treatment options and palliative systemic treatment is the treatment of choice, with the goal to prolong overall survival and maintain quality of life for as long as possible. The median overall survival of patients with metastatic colorectal cancer (mCRC) is significantly increased by the use of chemotherapy.

The paper of Miriam Koopman and Cornelis JA Punt, titled “Chemotherapy, which drugs and when”, published in the European Journal of Cancer 2009[44], gives an overview of the most relevant data concerning, among others, the efficacy of each of these drugs, their use in combination chemotherapy, their sequential versus combined use as well as their preferred sequence. Parts of the findings are mentioned in this introduction.

For this pilot study a cohort of metastatic CRC patients diagnosed in 2003 and 2004 was used. Consequently, the data collection of this retrospective pilot study went back to January 2003. In order to focus on published literature relevant for the timeframe of the pilot study, we used different time periods; 1) Published literature until January 2003, since this was the only information available at T=0, 2) published literature until January 2006, since this was the information available at T=3, and 3) Results of the CAIRO and FOCUS studies.[45, 46] Furthermore, a summary of the cost-effectiveness of different chemotherapy regimens will be provided and drugs that became available more recently will be mentioned briefly.

Published literature until January 2003 (T=0)

Fluoropyrimidines (FL)

For many decades, 5-FU with or without leucovorin (LV) was the only available treatment for patients with mCRC, which resulted in a median overall survival of approximately 11-12 months.[47] Its main toxicities are diarrhoea, stomatitis, neutropenia, and hand-foot syndrome, depending on the type of schedule used. Since 2001, oral fluoropyrimidines have become available of which capecitabine and UFT have been tested in mCRC. In comparison to bolus 5FU/LV, both oral agents have shown comparable results in overall and progression-free survival but an improved tolerability. [48-53]

Irinotecan

Irinotecan, available since 2000, is a topo-isomerase I inhibitor, and its main toxicities are nausea/vomiting, diarrhoea, alopecia, myelosuppression, and a cholinergic syndrome. It first showed efficacy in second-line treatment in 5-FU refractory mCRC patients.[54, 55] Subsequently two studies with irinotecan plus either bolus or infusional 5FU/LV compared to 5FU/LV alone showed a significant absolute benefit in median overall survival of 2.2 and 3.3 months, respectively.[56 57] However, these studies have been criticised for the fact that effective second-line treatment with irinotecan in the control arm was not a prospective part of the study design.[58]

Oxaliplatin

Oxaliplatin is an alkylating agent of the platinum family, and its main toxicities are a (often reversible) sensory neuropathy, nausea/vomiting, diarrhoea, and myelosuppression. Given its synergistic activity with fluoropyrimidines (FL) it is usually administered in combination with a fluoropyrimidine.[59] Two studies, published in 2000, in which the addition of oxaliplatin to 5FU/LV was compared to 5FU/LV alone in first-line treatment did show a benefit in response rate and progression-free survival for the combination, but not in overall survival as these studies were not designed to demonstrate a benefit in overall survival.[60, 61]

In conclusion, newer chemotherapy agents such as irinotecan and oxaliplatin already became available in 2000, both showing a benefit over the use of monotherapy with FL. However, in 2003 there were no good data on the optimal strategy to use these drugs.

Table 2.1.1 Possible (equivalent) treatment combinations

first-line	second-line	third-line
FL	FL+ oxaliplatin	(FL+) irinotecan
FL	(Fl +) irinotecan	FL+ oxaliplatin
FL+ oxaliplatin	(Fl +) irinotecan	
(FL +) irinotecan	FL+ oxaliplatin	

The first two treatment combinations can be referred to as “sequential treatment” since both treatments start with fluoropyrimidines only, followed by either oxaliplatin or irinotecan in second- and third-line. The latter two are “combination treatments” as they directly start with a combination of fluoropyrimidines and oxaliplatin or irinotecan in the first-line treatment.

Published literature until January 2006 (T=3)

In 2003 it became apparent that the combination of fluoropyrimidines with oxaliplatin had efficacy as a second-line treatment after failure on 5-FU and irinotecan.[62]. In 2004, a combination of infusional 5FU/LV and oxaliplatin (FOLFOX) was shown to significantly prolong the median overall survival compared with a bolus 5FU/LV/irinotecan (IFL)[63]. In many countries these results have shifted the preference to FOLFOX as first-line regimen. However, as with studies on first-line irinotecan-based combination therapy, second-line treatment was not a prospective part of the study design. In this study there was an imbalance in the use of salvage treatment, since 60% of patients received second-line irinotecan after failure on FOLFOX, but, due to its limited availability at the time this study was conducted, only 24% of the patients failing IFL received oxaliplatin. The finding that the absolute difference in medial overall survival (4.5 months) was greater compared to the absolute difference in median time to progression (1.8 months) also suggests that salvage treatment had a significant impact on survival outcome.[58] Furthermore, the different modes of 5FU administration between the two treatment arms (continuous versus bolus infusion) may have been responsible for the higher incidence of severe toxicities as well as the decreased efficacy in the IFL arm. This latter view is supported by the results of another randomised study in which FOLFOX and infusional 5FU/LV plus irinotecan (FOLFIRI) had comparable overall survival results, although it should be noted that overall survival was not the primary endpoint of this study.[64]. Regarding toxicities, this study showed that the incidence of serious adverse events was higher in patients treated with FOLFIRI (14% versus 5%), but the overall incidence of grade 3-4 toxicities as well as the percentage of patients that had to discontinue treatment for reasons of toxicities was greater upon treatment with FOLFOX (74% versus 53%, and 11% versus 6%, respectively). Based on this and other comparative studies it could be concluded that there is no preference for irinotecan or oxaliplatin in the first-line treatment in terms of efficacy, and that the choice can be made on individual patient preferences.[65] However, despite the fact that combination treatment of 5FU with either irinotecan or oxaliplatin was widely accepted as the new standard in first-line treatment of mCRC, the question whether its benefit would have been maintained if patients would have received appropriate salvage treatment in the control arm of these studies was left unanswered. The validity of this question first came from a retrospective analysis that showed a correlation between survival and the number of effective drugs to which patients had been exposed.[66] In other words, it may be more important that patients are exposed to these drugs during the course of their disease, rather than receiving these drugs in first-line.

Two important studies with a novel design have provided a better insight in this issue: the CAIRO and FOCUS studies.

CAIRO and FOCUS studies

Although not published before 2007, we will discuss the CAIRO and FOCUS studies as they were already conducted during the timeframe of our pilot study. The results of the CAIRO study are particularly of interest because its study population was selected from the same source population as the pilot study. The CAIRO study of the DCCG was the only study that prospectively evaluated the sequential versus concomitant use of all three effective cytotoxic drugs, i.e. a fluoropyrimidine, irinotecan and oxaliplatin.[6745] In this study the treatment with first-line capecitabine, second-line irinotecan and third-line capecitabine plus oxaliplatin was compared with first-line capecitabine plus irinotecan, and second-line capecitabine plus oxaliplatin. Upfront combination treatment did not result in a significant overall survival benefit compared to sequential treatment. The FOCUS study of the Medical Research Council UK confirmed this finding.[46] In this study the sequential versus concomitant use of either irinotecan or oxaliplatin with infusional 5FU/LV was tested in separate treatment arms, and no advantage was demonstrated for combination therapy. Therefore, the CAIRO and FOCUS studies demonstrate that the sequential use of cytotoxic agents remains a valid treatment option in mCRC patients.

Cost-effectiveness

The paper of Marieke Krol, Miriam Koopman, Carin Uyl-de Groot and Cornelis JA Punt, published in Expert Opinion 2007, presents a systematic review of economic analyses of pharmaceutical therapies for advanced colorectal cancer.[42] The selected publication date limit was from 01 January 2000 to 15 May 2006, which reflects literature until T = 3. The main cost-effectiveness findings of this paper will be summarized here.

Cost-effectiveness of orally versus intravenously administered fluoropyrimidine

Two selected articles have compared the cost (-effectiveness) of capecitabine with traditional 5FU/LV regimes. One study analysed 89 fee-listings from 26 patients with advanced colorectal cancer treated with 5FU/LV.[68] Projected quarterly costs for capecitabine were € 2,338. The potential savings of replacing 5FU/LV with capecitabine were € 310 – 10,500/quarter depending on the treatment setting and the 5FU/LV regimen. Another study examined the files of 33 patients who were treated with 5FU/LV for metastatic disease. Capecitabine costs were projected in this study as well resulting in a mean total cost of

capecitabine treatment of € 4,004 and a mean total cost of 5FU/LV of € 5,614.[69] Both studies used projections to calculate costs of capecitabine treatment and have limited sample sizes.

Cost-effectiveness of irinotecan

Three selected articles studied the cost and cost-effectiveness of irinotecan in the treatment of advanced colorectal cancer. The first compared the economic implications of differences in clinical benefit between irinotecan plus 5-FU/LV versus 5-FU/LV as first-line therapy among 385 patients.[54]. The analyses resulted in an incremental cost-effectiveness ratio of £ 14,794/life year gained. Based on these findings, the authors conclude that the use of irinotecan plus 5-FU/LV in the first-line is strongly supported. Another study compared irinotecan to infusional 5-FU regimens when given as second-line treatment among 256 patients.[70] The cost-effectiveness ratios varied from $ 9344 – 10,137/life year gained (depending on the infusional 5-FU regimen chosen). The authors concluded that the additional costs of irinotecan were balanced by the added months of survival, with a cost-effectiveness ratio close to that of other cancer treatments. Lastly, a study compared 2 schedules of second-line irinotecan: a weekly and a 3-weekly schedule.[71] The results show a cost–utility ratio associated with the 3-weekl arm of $ 78,627/QALY. Because of the large uncertainty of this study, no conclusion could be drawn on the incremental cost-effectiveness.

Cost-effectiveness of oxaliplatin

No studies of the cost-effectiveness of oxaliplatin plus fluoropyrimidines versus fluoropyrimidines alone could be found. Two articles reported on the cost-effectiveness of oxaliplatin versus irinotecan. Hillner *et al.*[72] calculated the costs and effects of oxaliplatin plus infusional fluorouracil (FOLFOX) compared to irinotecan plus bolus fluorouracil (IFL) in first-line therapy. Total costs were $ 94,693 for FOLFOX and $ 66,231 for IFL at a 5-year end point. Their baseline results indicate that FOLFOX would provide a survival benefit of 4.4 months at an incremental cost-effectiveness ratio of $ 80,410/life year gained and $ 111,890/QALY gained. Limat et al.[73] undertook a cost-minimisation analysis to compare the costs related to the standard de Gramont regimen and to the simplified de Gramont regimen combined with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) as first-line treatment.

Overall costs appeared to be similar between FOLFOX and FOLFIRI, with the exception of hospital admissions related to adverse effects (these admission were more expensive for FOLFIRI within the standard regimen and in the simplified regimen for FOLFOX). For now, it seems that similar to the clinical viewpoint, there is no clear preference for either irinotecan or oxaliplatin as first-line treatment from an economical point of view.

No cost-effectiveness analysis was performed piggy-backed on the CAIRO trial. For this reason it is impossible to comment on the cost-effectiveness of fluoropyrmidines, irinotecan and oxaliplatin when consequently used in either sequential or combination therapy.

Newer targeted therapies

The median overall survival of the treatment of advanced colorectal cancer has been further improved by the addition of a new class of drugs (targeted therapy) to chemotherapy, which include the inhibitors of signal transduction through VEGF or EGFR. Currently available drugs are bevacizumab, cetuximab and panitumumab. Adding bevacizumab to a fluoropyrimidine-containing chemotherapy regimen is considered the standard of care in first-line treatment for patients with advanced colorectal cancer, at present.

Bevacizumab, cetuximab and panitumumab are relatively new drugs in the treatment of colorectal cancer. It is clear that these drugs will greatly increase the costs of treatment for advanced colorectal cancer. To be able to assess the cost-effectiveness of these therapies results of ongoing research needs to be awaited.

Oxaliplatin in daily practice

Economic evaluations piggy-backed on a randomized clinical trial are generally regarded as the most scientific basis to determine the cost-effectiveness of pharmaceutical treatments. Data based on clinical trials may not be representative of daily practice, as clinical trials are conducted under controlled conditions.

Outcomes research collects data from daily clinical practice that are useful for determining appropriate use and cost-effectiveness of pharmaceutical treatments. This section describes the results of outcomes research that investigated the appropriate use and cost-effectiveness of oxaliplatin as first-line treatment of metastatic colorectal cancer.

- **How is oxaliplatin used in daily practice?** (sections 2.2 and 3.2)
- **What clinical effects does the use of oxaliplatin involve?** (sections 2.3 and 3.3)
- **What costs are involved in the use of oxaliplatin?** (sections 2.4 and 3.4)
- **What is the relationship between the results of this outcomes research and the results of clinical trials?** (sections 2.5 and 3.5)
- **What is the cost-effectiveness of oxaliplatin?** (2.6 and 3.6)

2 Methods

2.1 Patient population and data collection

All patients newly diagnosed with stage IV colorectal cancer (pTany,Nany,M1, ICD-O C18 C20) in 2003 or 2004 were eligible for this outcomes research provided that they received palliative chemotherapy. Similar to the stage III colon cancer pilot study, patients were identified retrospectively in June 2007 via the database of the Dutch Cancer Registry. Subsequently, using 'minimal' case record forms (CRFs), additional information was collected from the medical records of all patients identified in 29 selected hospitals. Afterwards, further selection of patients took place based on the information obtained via the 'minimal' CRFs.

Patients were excluded from the analyses if their medical records revealed that they did not have colorectal cancer, had clinical disease stage III, did not receive any chemotherapy, or did not start chemotherapy at the selected hospitals. Moreover, patients included in trials and patients whose medical file was not available were excluded. Lastly patients were excluded if their tumour could not be evaluated or if the patients received bevacizumab as first-line therapy.

A randomly selected representative sub-group was selected from the patient population thus defined. Additional data regarding this subgroup of patients were collected from medical records by means of 'maximal' CRFs.

Some of the patients identified via the Dutch Cancer Registry participated in the CAIRO trial.[45] In the CAIRO study 820 patients were included between January 1st 2003 and December 31st 2004 in 74 hospitals in the Netherlands. They were randomly allocated to one of the following treatment strategies: 1) first-line capecitabine, second-line irinotecan, and third-line capecitabine + oxaliplatin (sequential treatment arm); or 2) first line capecitabine + irinotecan and second-line capecitabine + oxaliplatin (combination treatment arm).

All patients included in the CAIRO trial fulfilled certain eligibility criteria. The patients included in the PILOT study were categorized according to these CAIRO eligibility criteria in order to facilitate comparisons between the CAIRO and PILOT studies. Tables 2.2.1 and 2.2.2 give

an overview of the inclusion and exclusion criteria of the CAIRO trial. Subsequently patients were categorized according to administered chemotherapy regimens.

Table 2.2.1 Inclusion criteria CAIRO study

Histological proven Colorectal Cancer; advanced disease, not amenable to curative surgery

In case of a single metastasis, hystological or cytological proof should be obtained prior to randomization

Measurable or evaluable disease

Serum CEA as only parameter for disease activity is not allowed

Adequate bone marrow function

WBC ≥ 3.0 x 10^9 / L
Platelets ≥ 100 x 109 / L
Hb ≥ 6.0 mmol /L

Adequate hepatic function

Tot. Bilirubin ≤ 1.5 x ULN
ASAT ≤ 3 x ULN (in case of liver mets's ≤ 5 x ULN)
ALAT ≤ 3 x ULN (in case of liver mets's ≤ 5 x ULN)

Adequate renal function: creat clearance (Cockroft) ≥ 50 ml /min

Age ≥ 18

Table 2.2.2 Exclusion criteria CAIRO study

Any prior chemotherapy for advanced disease; prior adjuvant therapy completed ≤ 6 months prior randomisation
Serious concomitant disease preventing the safe administration of chemotherapy or likely to interfere with the study assessment
Central nervous system metastases (in asymptomatic patients no screening required)
Serious active infections
Inflammatory bowel disease or other disease associated with chronic diarrhoea
Previous radiation of the pelvis or abdomen (excl. 5x5 Gy in case of rectal carcinoma)
Other malignancies in the past 5 years with the exception of adequately treated carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin
Concomitan (or within 4 weeks of randomisation) administration of any other experimental drug under investigation
pregnancy or lactation
Patients with reproductive potential not implementing adequate contraceptive measurses

Data collection of both stage III and metastatic colorectal cancer pilots took place in a similar way. An extensive description of the data collection methodology can be found in section 1, 2.2. The data collection took place via three sources: the Dutch Cancer Registry, the 'minimal CRF', and the 'maximal CRF'. A detailed overview of the data obtained from the Dutch Cancer Registry and via the minimal and maximal CRFs can be found in Annex IV. The original versions of the minimal and maximal CRFs are also enclosed in Annexes VII and VIII.

2.2 Use of oxaliplatin

The use of oxaliplatin in daily practice was examined by considering five different parameters. Each of those parameters provides an indication of who received oxaliplatin or how much oxaliplatin they received.

Treatment patterns

All treatments observed in Dutch clinical practice were illustrated for each line, per separate first-line treatment group.

CAIRO eligibility status

Reasons for not being eligible for the CAIRO trial were analysed

Baseline characteristics

The baseline patient and tumour characteristics provide a pointer for the 'profile' fulfilled by a patient being treated with oxaliplatin in daily practice. Among other things, the effect of age distribution and WHO performance score were examined in order to explain significant differences between the different treatment groups as well as between CAIRO eligible versus non eligible patients.

Considerations in choice of treatment regimen

Possible predictors for receiving combination therapy in first-line were analysed.

Dose schedules

The number of patients receiving specific drugs, median number of cycles and total cumulative dosages were recorded and compared between the treatment groups.

2.3 Clinical efficacy of oxaliplatin

The clinical efficacy of oxaliplatin in daily practice was assessed by examining its impact on overall survival, since this was also the primary endpoint in the CAIRO trial. Overall survival was calculated as the interval from the date of start of the first treatment line until date of death from any cause or until the date of last follow-up.

Statistical analyses of clinical data

We first assessed the frequency of administration of treatment. To compare baseline characteristics, the administered regimens were firstly grouped into "patients receiving first-line monotherapy" and "patients receiving first-line combination therapy". Subsequently baseline characteristics were compared in patients grouped according to CAIRO eligibility status. Continuous data were expressed in terms of the mean value and categorical data as a percentage, unless otherwise denoted. The Student's t-test and the chi-square test with the Fisher's exact correction for frequencies less than five were used for continuous and categorical variables, respectively. Reasons for not being eligible for the CAIRO trial were explored using descriptive statistics. A multivariate logistic regression analysis was performed to identify independent predictors of non-prescription of first-line combination

therapy. Survival curves were visualised according to the Kaplan-Meier methods, including comparisons by means of the log rank test. A total of 130 patients were selected for further more extensive analyses. For patients eligible for inclusion in the CAIRO study, this selection took place at random. Only 11 patients ineligible for CAIRO were evaluated. These numbers were based on practical limitations in terms of time and finance and on experience with previous iMTA studies. An evaluation of dose schedules per treatment regimen was performed in this selected subset of patients. For this evaluation, the tests for continuous and categorical variables mentioned above were used. Significant variables are reported with their respective p-value. In all analyses, statistical significance was assumed if the two-tailed probability value was < 0.05. The SAS computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA, 1999).

2.4 Costs of oxaliplatin

This section describes the methods of the cost analyses which were conducted from the hospital perspective. Use of this perspective meant that some cost categories like productivity costs and costs associated to informal care were not taken into account. However, as explained before, we believe that the exclusion of those cost components from the analyses had no important impact on the estimate of the real-world cost-effectiveness of oxaliplatin. The following costs were calculated separately for:

- patients receiving monotherapy (n=57)
- patients receiving oxaliplatin combination therapy (n=51)
- patients receiving irinotecan combination therapy (n=11)
- patients who did not meet the CAIRO eligibility criteria (see section 2.1) (n=11)

For the interpretation of results, one should keep in mind that patients who did not meet the CAIRO eligibility criteria could either have received monotherapy (n=7), oxaliplatin combination therapy (n=2) or irinotecan combination therapy (n=2).

Total costs for individual patients were determined by the identification of resource use and unit costs of the following cost components: inpatient hospital days, intensive care days, outpatient visits, consultations by telephone, daycare treatments, emergency room visits, radiotherapy, surgical procedures, laboratory services, medical imaging services, chemotherapy and concomitant medications.

Table 2.2.3 Unit costs (Euro 2009)

5-Fluorouracil (mg)	€ 0.01
Leucoforin (mg)	€ 0.28
Capecitabine (mg)	€ 0.01
Oxaliplatin (mg)	€ 4.35
Irinotecan (mg)	€ 1.83
Bevacizumab (mg)	€ 3.78
Cetuximab (mg)	€ 2.15
Uracil/tegafur (mg)	€ 0.05

mg = milligram

Table 2.2.3 presents the unit costs per milligram for chemotherapy. Methods on the unit cost calculation of other cost components as well as methods on sensitivity and statistical analyses are identical to those of stage III colon cancer (see section 1, 2.5).

2.5 Daily practice versus clinical trials

We examined the relationship between the results of our outcomes research and the results of the CAIRO trial by comparing results in the following categories: baseline characteristics, treatment patterns, dose schedules, and the clinical effects of oxaliplatin. These subjects were chosen to determine whether the patients treated in the CAIRO trial were similar to those in the pilot population, whether oxaliplatin use in the CAIRO study was similar to the oxaliplatin use in the pilot population and whether the clinical effects of oxaliplatin were similar in the two populations.

2.6 Quality of life

Our retrospective study design made it impossible to use Health Related Quality of Life (HRQOL) as an outcome measure. As a consequence, we did not collect real-world HRQOL data of pilot patients. However, the CAIRO trial provided disease specific quality of life data on Dutch patients, which meant that there was little need to collect real-world quality of life data. The CAIRO study measured the disease specific quality of life by means of the QLQ-C30 questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC). A model to convert QLQ-C30 values into utilities in haematological cancers has recently been developed, but has not yet been validated.[74] To enable us to compare Quality adjusted life years (QALYs) rather than life years between the mono and combination

therapy treatment groups, we applied this model on patient-level CAIRO disease specific quality of life data. The validity of such a model for use across diseases has the attention of researchers in this field as it needs further exploration. However, due to the characteristics of the QLQ-C30, which is a generic quality of life questionnaire, the specific influences of disease type are assumed to be small. The model applied is the only model capable of estimating Dutch EQ-5D utility values at this moment.

Quality of life measurement in the CAIRO study

The QLQ-C30 questionnaire was used to assess the patients' wellbeing during the study. Participation in this part of the study was proposed to the first 620 patients entered in the study. Questionnaires were to be completed within 1 week before randomisation and at every 9 weeks thereafter until the end of study treatment.

Model converting QLQ-C30 values into utilities

The 30 items of the QLQ-C30 can be divided in three categories: Functional scales (physical, role, emotional, cognitive and social functional, total of 15 items), symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, sleep, appetite, constipation, diarrhea and financial difficulties, total of 13 items) and a global health status scale (two items). The regression coefficients of the model we used to convert these QLQ-C30 values into utilities are:

```
EQ-5D index (Dutch tariff)= 0.985 + (1*-.037)+ (2*-.025) + (3*-.059) +
(4*-.033) + (5*-.134) + (6_level2*-.033) + (6_level3*-.067) +
(6_level4*-.180) + (7_level2*-.013) + (7_level3*-.037) +
(7_level4*-.012) + (9_level2*-.065) + (9_level3*-.053) +
(9_level4*-.189) + (16_level2*-.038) + (16_level3*-.045) +
(16_level4*-.126) + (23_level2*-.028) + (23_level3*-.049) +
(23_level4*-.456) + (24_level2*-.053) + (24_level3*-.140) +
(24_level4*-.232) + (27_level2*-.027) + (27_level3*-.091) +
(27_level4*-.110).
```

3 Results

3.1 Patient population

A patient flowchart is shown in Figure 2.3.1. Between January 2003 and December 2004, 4201 patients were diagnosed with stage IV colon cancer, of whom 1962 (47%) were treated with palliative chemotherapy. Of these identified patients, 400 were included in the CAIRO trial and 1562 patients were treated outside the CAIRO trial. A total of 433 patients were treated at one of the 29 hospitals included in our study; 314 of these patients met our initial inclusion criteria. After evaluation of the CAIRO eligibility criteria in the PILOT population, 224 patients would and 90 patients would not have been eligible for the CAIRO trial. Figure 2.3.2 shows the different first-line treatment combinations found in Dutch practice. A total of 312 patients were included for further analyses. As to the administered first-line chemotherapy regimens, 197 patients (63%) received first-line monotherapy with fluoropyrimidines, of which 64% fulfilled the CAIRO eligibility criteria. The remaining 116 patients (37%) received combination therapy with either oxaliplatin (N = 91) or irinotecan (N = 24) in first-line. In total, 84% of the patients receiving combination therapy would have been eligible for the CAIRO trial (87% in the oxaliplatin group and 72% in the irinotecan group), which is significantly higher compared to patients receiving first-line monotherapy ($p < 0.001$).

Figure 2.3.1 Patient flowchart

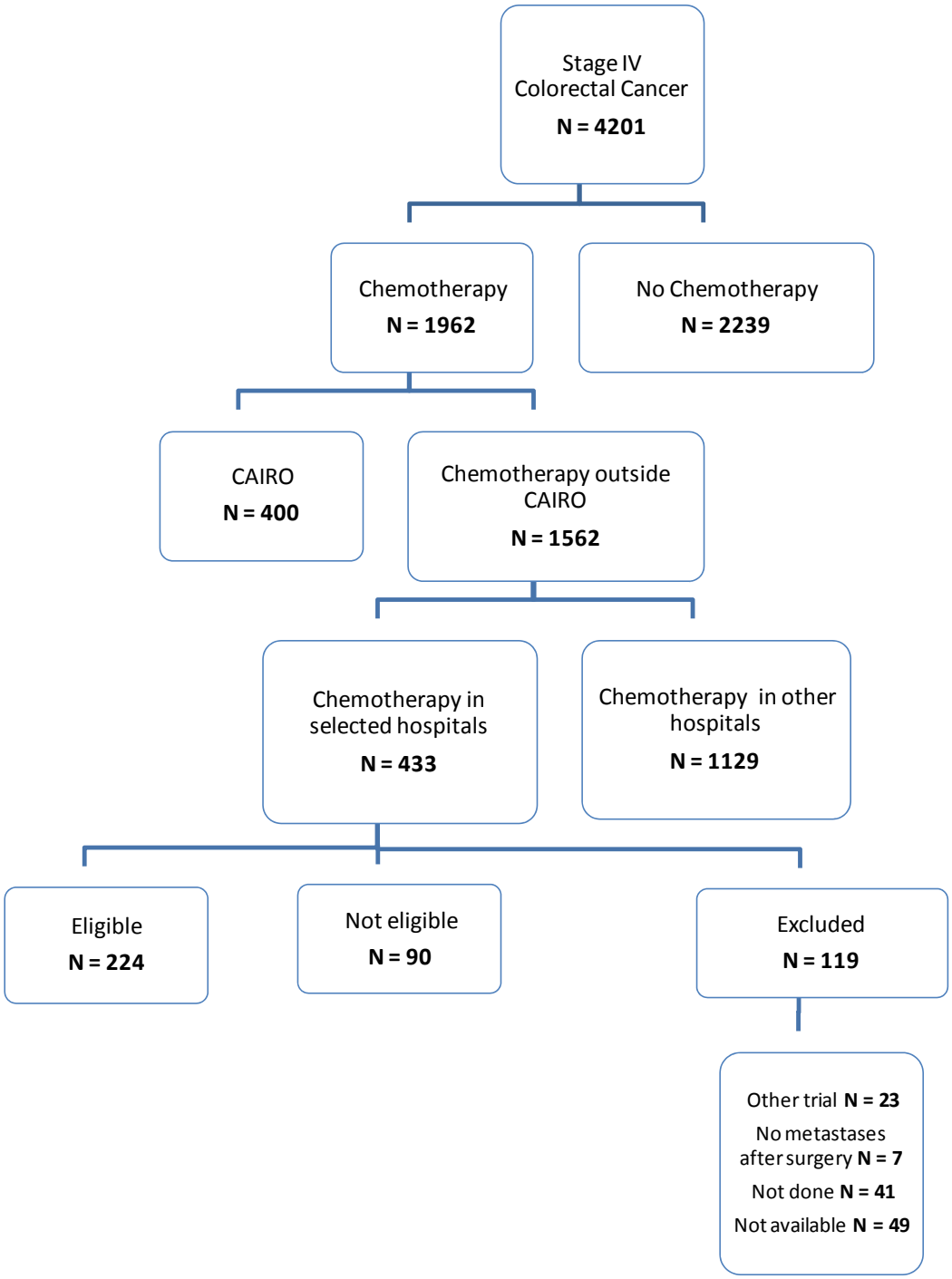
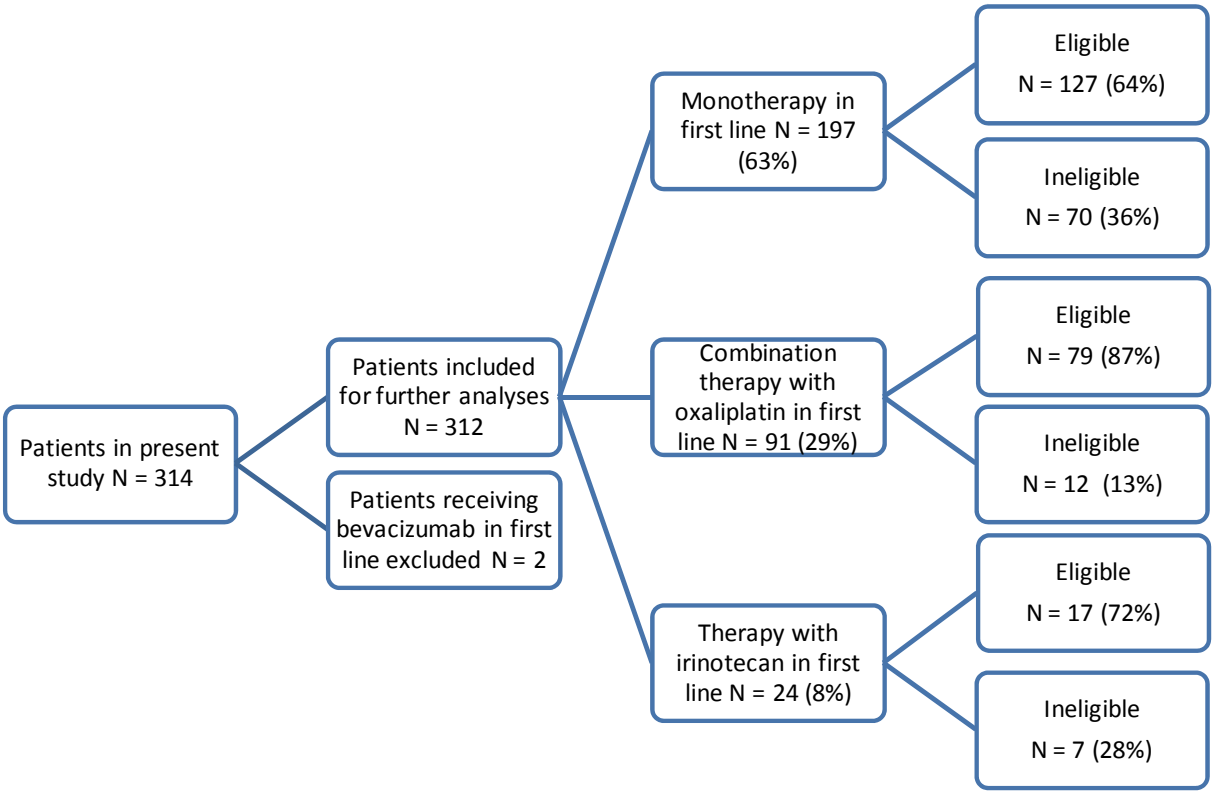


Figure 2.3.2 Flowchart of first-line treatment combinations found in Dutch practice



3.2 Use of oxaliplatin

CAIRO eligibility status

We explored the reasons why patients in the PILOT study would not have been eligible for the CAIRO trial. These reasons, shown in Table 2.3.1, included: poor patient condition (32%), comorbidity (17%), second tumour (11%), abnormal lab values (13%), brain metastases (3%), no evaluable disease (8%), unclear histology (7%) and other factors (9%).

Table 2.3.1 Reasons for not being eligible for CAIRO (N = 90)

Reasons for not being eligible for CAIRO study	Number of patients (%)
Patient condition	29 (32%)
Comorbidity	15 (17%)
Second tumor diagnosed < 5 years ago	10 (11%)
Abnormal liver/renal function	12 (13%)
Brainmetastases	3 (3%)
No evaluable disease	7 (8%)
Histology of tumor unclear	6 (7%)
Other	8 (9%)

Baseline characteristics

The baseline patient characteristics of the total included PILOT population, categorized by first-line chemotherapy regimen and CAIRO eligibility status, are summarized in table 2.3.2a. Subsequently, table 2.3.2b presents the results of the statistical comparisons of baseline characteristics. Statistically significant findings are highlighted in this table. Patients receiving combination therapy with either oxaliplatin or irinotecan were significantly younger than patients who did receive first-line monotherapy ($p < 0.0001$). This is also illustrated by the percentages of patients older than 70 years old (32% in mono therapy patients versus 13% in patients receiving combination therapy, $p = 0.0002$). However, there was no difference in age between patients who would have been eligible for the CAIRO study and patients who would not have been eligible. This seems logical considering that age was not a selection criterion in the CAIRO study. Regarding performance score, a significant difference is observed in both comparisons. Firstly, 90% of the patients receiving combination therapy has a good performance score (WHO PS 0-1), versus 78% in the group of patients receiving mono therapy ($p = 0.0426$). The non-randomised assignment of treatments in the pilot patients can explain this finding, since combination therapy is generally associated with an increased risk of toxicity. Therefore, patients having a worse performance score (WHO 2-3)

might be less likely to receive the more aggressive combination treatment regimen. Furthermore, we found a significant difference in WHO performance scores between CAIRO-eligible patients versus CAIRO-ineligible patients as well (WHO PS 0-1: 92% versus 60%, respectively, $p < 0.0001$). This difference can be explained by the CAIRO selection criteria, since patients having a poor performance score (WHO 3) and severe comorbidities were excluded. However, it should be noted that up to 62% of this variable was missing, since physicians do not routinely document a patients' performance status. No other differences in baseline characteristics were found when comparing the mono and the combination therapy groups. Regarding eligible versus ineligible patients we found that eligible patients more often had a resection of their primary tumour (65% versus 52% $p = 0.0255$). No other statistically significant differences were found although there was a trend towards a higher frequency of extrahepatic metastases and white blood count abnormalities in ineligible patients.

Table 2.3.2a Baseline characteristics of patients receiving chemotherapy in Dutch practice

	First-line chemotherapy					
	Monotherapy N = 197		Combinationtherapy with oxaliplatin N = 91		Combinationtherapy with irinotecan N = 25	
Baseline Characteristics	Eligible N = 127 (64%)	Ineligible N = 70 (36%)	Eligible N = 79 (87%)	Ineligible N = 12 (13%)	Eligible N = 18 (72%)	Ineligibe N = 7 (28%)
Age - yr						
Median	64	64	59	61	58	59
Range	39-84	30-92	29-81	35-75	39-70	41-73
Age group - no. (%)						
≥ 70	42 (33%)	21 (30%)	12 (15%)	1 (8%)	1 (6%)	1 (14%)
Performance status						
PS 0-1	71 (91%)	23 (55%)	41 (91%)	6 (75%)	11 (100%)	4 (80%)
PS 2-3	7 (9%)	19 (45%)	4 (9%)	2 (25%)	0 (0%)	1 (20%)
Missing	50 (39%)	28 (40%)	34 (43%)	4 (33%)	7 (39%)	2 (29%)
Sex - no. (%)						
male	72 (57%)	43 (61%)	55 (70%)	7 (58%)	5 (28%)	5 (71%)
female	55 (43%)	27 (39%)	24 (30%)	5(42%)	13 (72%)	2 (29%)
Predominant localisation of metastases						
Liver	111 (93%)	54 (86%)	65 (93%)	9 (82%)	15 (94%)	5 (100%)
Extrahepatic	8 (7%)	9 (14%)	5 (7%)	2 (18%)	1 (6%)	0 (0%)
Missing	8 (6%)	7 (10%)	9 (11%)	1 (8%)	2 (11%)	2 (29%)
LDH at randomisation						
Normal	51 (49%)	26 (47%)	36 (54%)	7 (58%)	9 (60%)	2 (40%)
Abnormal	53 (51%)	29 (53%)	31 (46%)	5 (42%)	6 (40%)	3 (60%)
Missing	23 (18%)	15 (21%)	12 (15%)		3 (17%)	2 (29%)
WBC at randomisation						
Normal	79 (68%)	35 (57%)	49 (70%)	8 (67%)	17 (94%)	3 (60%)
Abnormal	38 (32%)	26 (43%)	21 (30%)	4 (33%)	1 (6%)	2 (40%)
Missing	10 (8%)	9 (13%)	9 (11%)			2 (29%)
AF at randomisation						
Normal	47 (44%)	12 (26%)	23 (36%)	4 (36%)	6 (38%)	2 (40%)
Abnormal	59 (56%)	34 (74%)	41 (64%)	7 (64%)	10 (62%)	3 (60%)
Missing	21 (17%)	24 (34%)	15 (19%)	1 (8%)	2 (11%)	2 (29%)
Site of primary tumor						
Rectosigmoid	10 (8%)	9 (13%)	10 (13%)	1 (8%)	0 (0%)	3 (43%)
Rectum	27 (21%)	19 (27%)	2 (30%)	3 (25%)	5 (28%)	2 (29%)
Colon	90 (71%)	42 (60%)	45 (57%)	8 (67%)	13 (72%)	2 (29%)
Resection of primary tumor						
Yes	79 (65%)	33 (47%)	451(67%)	7 (58%)	10 (63%)	2 (29%)
No	43 (35%)	37 (53%)	25 (33%)	5 (42%)	6 (38%)	5 (71%)
Missing	5 (4%)		3 (4%)		2 (11%)	

Table 2.3.2b Comparison of baseline characteristics of patients receiving chemotherapy in Dutch practice

	First-line chemotherapy					
	All patients			All therapies		
	N = 313		T or X2 tests	N = 313		T or X^2 tests
Baseline Characteristics	mono therapy N = 197 (63%)	combi therapy N = 116 (37%)	p-value m vs c	Eligible N = 224 (72%)	Ineligible N = 89 (28%)	p-value el vs inel
Age - yr						
Median	64	59	<0.0001	61	63	0.96
Range	30-92	29-81		29-84	30-92	
Age group - no. (%)						
≥ 70	63 (32%)	15 (13%)	0.0002	23 (26%)	55 (25%)	0.8123
Performance status						
PS 0-1	93 (78%)	62 (90%)	0.0426	122 (92%)	33 (60%)	<0.0001
PS 2-3	26 (22%)	7 (10%)		11 (8%)	22 (40%)	
Missing	78 (40%)	69 (41%)		91 (41%)	55 (62%)	
Sex - no. (%)						
male	115 (58%)	72 (62%)	0.5206	132 (59%)	55 (62%)	0.6411
female	82 (42%)	44 (38%)		92 (41%)	34 (38%)	
Predominant localisation of metastases						
Liver	165 (91%)	94 (92%)	0.6697	191 (93%)	68 (86%)	0.0591
Extrahepatic	17 (9%)	8 (8%)		14 (7%)	11 (14%)	
Missing	15 (8%)	14 (12%)		19 (8%)	10 (11%)	
LDH at randomisation						
Normal	77 (48%)	54 (55%)	0.3401	96 (52%)	35 (49%)	0.6659
Abnormal	82 (52%)	45 (45%)		90 (48%)	37 (51%)	
Missing	38 (19%)	17 (15%)		38 (17%)	38 (43%)	
WBC at randomisation						
Normal	114 (64%)	77 (73%)	0.1077	145 (71%)	46 (59%)	0.0596
Abnormal	64 (36%)	28 (27%)		60 (29%)	32 (41%)	
Missing	19 (10%)	11 (9%)		19 (8%)	11 (12%)	
AF at randomisation						
Normal	59 (39%)	35 (36%)	0.7099	76 (41%)	18 (29%)	0.0971
Abnormal	93 (61%)	61 (64%)		110 (59%)	44 (71%)	
Missing	45 (23%)	20 (17%)		38 (17%)	27 (30%)	
Site of primary tumor						
Rectosigmoid	19 (10%)	14 (12%)	0.157	20 (9%)	13 (15%)	0.3758
Rectum	46 (23%)	34 (29%)		56 (25%)	24 (27%)	
Colon	132 (67%)	68 (59%)		148 (66%)	52 (58%)	
Resection of primary tumor						
Yes	116 (60%)	70 (63%)	0.649	140 (65%)	46 (52%)	0.0255
No	76 (40%)	41 (37%)		74 (35%)	43 (48%)	
Missing	5 (3%)	5 (5%)		10 (5%)		

Considerations in choice of treatment regimen

We next tried to identify independent predictors of non-prescription of combination therapy. We performed a multivariate logistic regression on baseline characteristics and initially included all variables present in the baseline characteristics table. The multivariate analysis identified only age and eligibility status as being independent predictors of non-prescription of combination therapy (OR [95CI] of 0.956 [0.932 – 0.980] and 3.269 [1.632 – 6.548] for age and eligibility, respectively).

Treatment patterns

Since several chemotherapies were available at the time this study was conducted, we expected that patients in daily practice might receive one of several different treatment regimens. Therefore, chemotherapy treatments during the course of different treatment lines were explored for each first-line therapy group (mono versus oxaliplatin versus irinotecan). Table 2.3.3a, describes the numbers of patients who received available treatments by line for patients receiving first-line monotherapy. Table 2.3.3b, describes the same for patients receiving first line combination therapy with oxaliplatin and Table 2.3.3c for patients receiving first-line irinotecan. Fifty-two percent of the patients receiving first-line monotherapy received chemotherapy in second-line as well; most of these patients received either oxaliplatin or irinotecan. In the third line, 22% of the patients still received chemotherapy. It is very likely that the patients who did not receive oxaliplatin in previous lines receive it in third line, and likewise this also applies to irinotecan.

Table 2.3.3a Treatments given to pilot patients who received first-line monotherapy

	patients receiving first line monotherapy				
Treatment	Line 1	Line 2	Line 3	Line 4	Line 5
Number of patients (% of patients)	197 (100%)	103 (52%)	44 (22%)	12 (6%)	5 (3%)
5FU/LV	83	18	9	-	-
capecitabine	109	36	21	3	3
UFT	5	1	-	-	-
Raltitrexed	-	-	-	-	-
oxaliplatin	-	43	26	2	3
irinotecan	-	49	14	4	1
bevacizumab	-	-	1	-	-
cetuximab	-	-	2	2	-
experimental	-	-	-	5	1

Regarding patients receiving oxaliplatin combination therapy in the first-line, all patients received the oxaliplatin in combination with either 5FU/LV or capecitabine. There was no clear preference for either fluoropyrimidine. In second-line therapy the majority of the patients received irinotecan, but bevacizumab was also administered to some patients. Patients receiving irinotecan combination therapy in the first line who received a second-line therapy were mostly treated with oxaliplatin in the second line. In general, 20-22% of the patients in all groups received at least three treatment lines.

Table 2.3.3b Treatments given to pilot patients who received first-line oxaliplatin combination therapy

	patients receiving first line oxaliplatin				
Treatment	Line 1	Line 2	Line 3	Line 4	Line 5
Number of patients (% of patients)	91 (100%)	53 (57%)	20 (22%)	4 (4%)	0 (0%)
5FU/LV	40	4	1	-	-
capecitabine	51	17	9	3	-
UFT	-	-	-	-	-
Raltitrexed			1		
oxaliplatin	91	10	5	1	-
irinotecan	-	36	10	1	-
bevacizumab	-	6	2	1	-
cetuximab	-	-	4	-	-
experimental	-	-	1	1	-

Table 2.3.3c Treatments given to pilot patients who received first-line irinotecan combination therapy

	patients receiving first line irinotecan				
Treatment	Line 1	Line 2	Line 3	Line 4	Line 5
Number of patients (% of patients)	24 (100%)	18 (32%)	5 (20%)	1 (4%)	1 (4%)
5FU/LV	11	4	-	-	-
capecitabine	9	11	1	1	-
UFT	-	-	-	-	-
Raltitrexed	-	-	-	-	-
oxaliplatin	-	16	2	1	-
irinotecan	24	2	-	-	-
bevacizumab	-	-	1	-	-
cetuximab	-	-	-	-	-
experimental	-	-	2	-	1

Dose schedules

Treatment details of the most frequently used treatment regimens in the Netherlands during the study period are presented in table 2.3.4, where eligible patients receiving first-line monotherapy were compared to eligible patients receiving first-line combination therapy. Most (98%) of the eligible combination therapy patients were treated with oxaliplatin at one time or another; 54% of them received irinotecan. In the monotherapy group the percentages were significantly lower (44% for oxaliplatin and 30% for irinotecan) than those seen in the monotherapy group ($p < 0.001$ for both oxaliplatin and irinotecan). This is easily explained by the fact that in monotherapy, both irinotecan and oxaliplatin are being administered only after first line treartment, and after each treatment line a subgroup of patients are not able to receive further treatment. No significant differences were found in the percentages of patients receiving fluoropyrimidines, which corresponds to the inclusion of fluoropyrimidines as part of the standard first line treatment. Regarding the mean total cumulative dosages, a significant difference was only found for the fluorouracil regimen ($p < 0.05$). This can be explained by the large variety in administration schedules of fluorouracil. We also compared the median numbers of cycles of the different treatment regimens and found no significant differences between the monotherapy and combination therapy groups. We also found no differences in the median number of cycles (of any treatment) per line. The median total time on therapy was 6 months (range 1-37) for the monotherapy group versus 8 months (range 1-44) in the combination therapy group. Since we had only limited detailed treatment data of ineligible patients, comparisons by treatment group in ineligible patients were not feasible. In general, the ineligible patients received less chemotherapy than eligible patients.

Table 2.3.4 cycles and dosages received in clinical practice

	First-line therapy, Eligibles only		Ineligibles
	monotherapy	combination therapy	All
	N = 57	N = 62	N = 11
5FU/LV			
patients receiving drug - nr (%)	34 (60%)	39 (62%)	3 (27%)
Median nr of cycles	9	10	3
Fluorouracil			
Mean total cumulative dose - mg	18901*	35971*	8000
Leucovorin			
Mean total cumulative dose - mg	7848	4729	299
Capecitabine			
patients receiving drug - nr (%)	39 (68%)	36 (57%)	8 (73%)
Median nr of cycles	6	6	6
Mean total cumulative dose - mg	352910	319450	363688
Oxaliplatin			
patients receiving drug - nr (%)	25 (44%)**	62 (98%)**	3 (27%)
Median nr of cycles	5	6	4
Mean total cumulative dose - mg	1176	1274	661
Irinotecan			
patients receiving drug - nr (%)	17 (30%)**	33 (53%)**	3 (27%)
Median nr of cycles	2	6	4
Mean total cumulative dose -mg	2866	3277	1950
Median nr of cylcles per line			
Line 1	6	6	3
Line 2	6	5	4
Line 3	3	3	2
Total time on therapy (months)			
Median	6	8	3
Range	1 - 37	1 - 44	1 - 22

3.3 Clinical efficacy of oxaliplatin

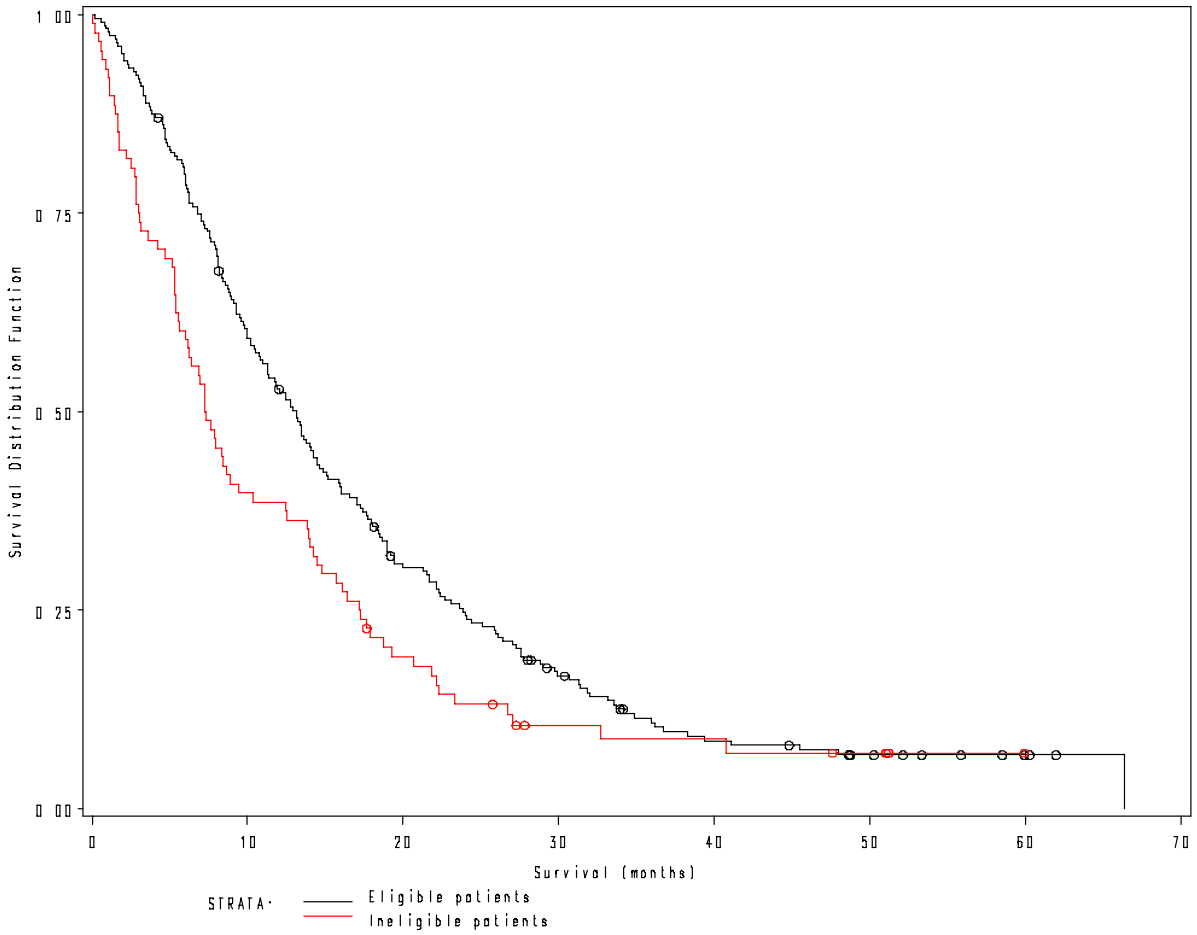
Overall survival of patients eligible for CAIRO versus ineligible patients

We found that pilot patients who would have been eligible for the CAIRO study were different from ineligible patients regarding certain baseline characteristics. Based on this, ineligible patients are expected to have a worse prognosis compared to eligible patients. Possible unfavourable parameters that can be present in ineligible patients include: worse

performance score, no resection of primary tumour, inadequate organ functions, presence of brainmetastases, comorbidities, or presence of second tumours.

Median overall survival was 13.1 (95% CI 10.8 – 14.4) months for the patients who would have been eligible for the CAIRO trial and, as expected much lower, 7.3 (95% CI 6.0 – 9.4) months for the ineligible patients. Figure 2.3.3 shows the Kaplan Meier overall survival curves of both eligible and ineligible patient groups.

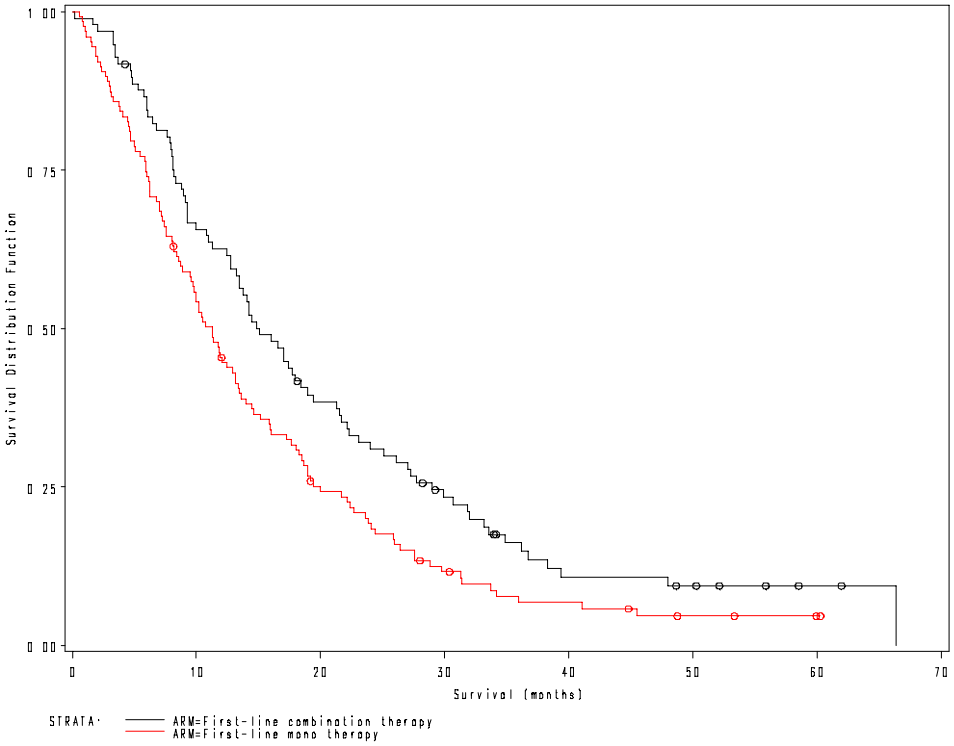
Figure 2.3.3 Overall survival by CAIRO eligibility status



Overall survival of patients receiving first-line mono therapy versus first-line combination

Next we compared the overall survival of patients receiving first-line monotherapy with fluoropyrimidines to patients receiving combination therapy with either oxaliplatin or irinotecan.Figure 2.3.4 shows the Kaplan Meier overall survival curves of monotherapy versus combination therapy in eligible patients. Median overall survival was 15.1 (95% CI 12.8 – 19.0) months for the patients who received first-line combination therapy and 11.2 (95% CI 9.5 – 13.3) months for patients receiving first-line monotherapy.

Figure 2.3.4 Overall survival by treatment group, eligible patients



It should be noted that the assignment of these treatments was not randomized. We found that patients who received monotherapy were significantly older than patients receiving first-line combination therapy. From this we can conclude that the patients in the two treatment groups are not comparable in terms of their prognosis. In order to able to comment on the efficacy of the combination treatment a randomized study like the CAIRO trial is needed. In section 3.5 our results will be compared to the CAIRO study.

Regarding ineligible patients, we have shown they have a worse overall survival than eligible patients. The small patient numbers in this subgroup, the differences in baseline characteristics between the monotherapy and combination therapy groups, and the inability to make comparisons with the CAIRO trial, where all patients were obviously eligible, made direct comparisons between the mono- and combination therapy inappropriate. However, we did observe trends in the ineligible patient population that were similar to the eligible population.

3.4 Costs of oxaliplatin

Table 2.3.5 presents the total mean costs per patient for the four treatment groups. Mean costs amounted to € 19,812 (SD 14,679) for monotherapy, € 28,200 (SD 19,470) for oxaliplatin combination therapy, € 44,664 (SD 24,367) for irinotecan combination therapy and € 13,899 (SD 11,860) for ineligible patients (Kruskal Wallis test: $p < 0.001$). Mean costs for monotherapy and oxaliplatin combination therapy were significantly different (Mann-Whitney U test: $p = 0.014$). A substantial cost variation was found in the total costs obtained for individual patients within treatment groups as well as in each individual cost component. Inpatient hospital days and chemotherapy (leucovorin, capecitabine, oxaliplatin and irinotecan) were the most important cost drivers.

Table 2.3.5 Total mean treatment costs for monotherapy, oxaliplatin combination therapy, irinotecan combination therapy and ineligibles

	Monotherapy n=57	Oxaliplatin combination n=51	Irinotecan combination n=11	Ineligibles n=11
Costs (Euro 2009)				
Inpatient hospital days	6,241	9,387	14,878	4,455
Intensive care unit days	0	0	0	378
Outpatient visits	1,154	1,355	2,013	1,007
Consultations by telephone	32	26	22	8
Day-care treatments	1,620	959	2,885	501
Emergency room visits	89	133	174	127
Radiotherapy	89	165	0	153
Intravenous access	0	70	216	36
Colonoscopy	101	244	283	162
Other surgical procedures	293	689	1,215	1,497
Laboratory	968	782	1,701	671
X ray	103	114	289	138
CT scan	613	870	815	493
PET scan	25	249	128	0
Ultrasound	76	79	282	102
Other radiological procedures	121	169	241	138
Other procedures	70	225	146	143
5-Fluorouracil (bolus)	28	18	97	8
5-Fluorouracil (infusion)	43	96	172	5
Leucovorin	1,237	576	2,210	28
Capecitabine	1,458	1,111	1,155	1,593
Oxaliplatin	2,440	6,123	5,946	928
Irinotecan	1,575	2,651	6,553	1,000
Bevacizumab	0	244	1,716	0
Cetuximab	860	1,396	0	0
Uracil/tegafur	264	0	0	71
Other chemotherapy	41	32	279	40
Concomitant medication	272	438	1,247	218
Costs (Euro 2009)	19,812	28,200	44,664	13,899
Median	17,650	23,172	40,039	10,327
Minimum	2,052	2,200	18,016	462
Maximum	65,288	95,118	109,139	40,305

CT = Computed Tomography
PET = Positron Emission Tomography

Inpatient stay costs were € 6,241 (SD 7,861) for monotherapy, € 9,387 (SD 9,971) for oxaliplatin combination therapy, € 14,878 (SD 12,756) for irinotecan combination therapy and € 4,455 (SD 5,602) for ineligible patients (Kruskal Wallis test: p = 0.014). Inpatient stay costs for monotherapy and oxaliplatin combination therapy were not significantly different (Mann-Whitney U test: p = 0.069). Of the inpatient admissions, 33% related to the administration of chemotherapy. Inpatient hospital days were especially important in irinotecan combination therapy, particularly owing to one patient whose inpatient stay was relatively long (97 days of which 87 days for the administration of 5FU/LV). 25% of the patients in the irinotecan combination therapy group had an inpatient stay of at least 30 days, compared to 9%, 10% and 9% of the patients in the other three treatment groups. Only one patient was admitted to

the intensive care unit. This patient did not meet the CAIRO eligibility criteria and was admitted for pneumonia, shock and wound infection following a low anterior resection.

Chemotherapy costs were € 7,946 (SD 9,459) for monotherapy, € 12,246 (SD 12,591) for oxaliplatin combination therapy, € 18,128 (SD 12,484) for irinotecan combination therapy and € 3,672 (SD 3,808) for ineligible patients (Kruskal Wallis test: $p < 0.001$). Mean costs for monotherapy and oxaliplatin combination therapy were significantly different (Mann-Whitney U test: $p = 0.003$). For oxaliplatin combination therapy, oxaliplatin alone accounted for 50% of the chemotherapy costs (compared to 31%, 33% and 25% for the other treatment groups) and 22% of the total treatment costs (compared to 12%, 13% and 7% for the other treatment groups). For irinotecan combination therapy, irinotecan alone accounted for 36% of the chemotherapy costs (compared to 20%, 22% and 27% for the other treatment groups) and 15% of the total treatment costs (compared to 8%, 9% and 7% for the other treatment groups).

Significant differences between the treatment groups were further observed in the costs of outpatient visits (Kruskal Wallis test: $p = 0.033$) day-care treatments (Kruskal Wallis test: $p = 0.006$), intravenous accesses ($p < 0.001$), colonoscopies ($p = 0.031$), laboratory services ($p = 0.005$), X ray (Kruskal Wallis test: $p = 0.027$), PET scans ($p = 0.039$), ultrasounds ($p = 0.001$), other procedures (Kruskal Wallis test: $p = 0.002$) and concomitant medications ($p = 0.001$). Significant differences between monotherapy and oxaliplatin combination therapy were observed in the costs of intravenous accesses (Mann-Whitney U test: $p = 0.001$), CT scans ($p = 0.018$) and PET scans ($p = 0.009$).

For patients receiving monotherapy, treatment costs ranged from € 2,052 to € 65,288, with the most expensive patient receiving 6 cycles of uracil/tegafur (€ 5,014), 4 cycles of irinotecan (€ 5,115), 6 cycles of capecitabine with oxaliplatin (€ 8,882) and 6 cycles of cetuximab with irinotecan (€ 28,959).

For patients receiving oxaliplatin combination therapy, treatment costs ranged from € 2,200 to € 95,118, with the most expensive patient receiving 6 cycles of capecitabine with oxaliplatin (€ 7,905), 8 cycles of irinotecan (€ 6,868) and 23 cycles of cetuximab with irinotecan (€ 64,572).

For patients receiving irinotecan combination therapy, treatment costs ranged from € 18,016 to € 109,139, with the most expensive patient receiving 15 cycles of 5FU/LV with irinotecan

(€ 15,102) and 14 cycles of 5FU/LV and bevacizumab with oxaliplatin (€ 34,392). 5FU/LV was administered to this patient during 87 inpatient days (€ 42,630).

Sensitivity analyses

Varying the unit costs of inpatient hospital days, day-care treatments and outpatient visits between 50% and 150% appeared to have a rather modest influence on the total mean costs with the greatest influence when varying the unit price for inpatient hospital days. Total mean costs varied from € 16,692 to € 22,933 for patients treated with monotherapy, from € 23,507 to € 32,893 for patients treated with oxaliplatin combination therapy and from € 37,225 to € 52,103 for patients treated with irinotecan combination therapy when inpatient hospital day unit costs were varied. Total mean costs varied from € 19,002 to € 20,623 for patients treated with monotherapy, from € 27,720 to € 28,680 for patients treated with oxaliplatin combination therapy and from € 43,222 to € 46,106 for patients treated with irinotecan combination therapy when day-care treatment unit costs were varied. Total mean costs varied from € 19,236 to € 20,389 for patients treated with monotherapy, from € 27,523 to € 28,877 for patients treated with oxaliplatin combination therapy and from € 43,657 to € 45,671 for patients treated with irinotecan combination when outpatient visit unit costs were varied.

3.5 Daily practice versus clinical trials

In the CAIRO study 820 patients with metastatic colorectal cancer were included between January 1st 2003 and December 31st 2004 in 74 hospitals in the Netherlands. They were randomized between first-line capecitabine, second-line irinotecan, and third-line capecitabine + oxaliplatin (sequential treatment arm) versus first line capecitabine + irinotecan and second-line capecitabine + oxaliplatin (combination treatment arm). It should be noted that the trial population consisted of patients with both synchronous and metachronous metatastases, which subgroups differ in their prognosis. Synchronous disease was defined as distant metastases occurring within 6 months of diagnosing CRC. In our pilot population, all patients were diagnosed with metastases and therefore having synchronous disease. Also the 400 CAIRO patients who were identified via the Dutch Cancer Registry (Figure 2.3.1) had synchronous disease. The result of the CAIRO study involving all included patients was published by Koopman et al, Lancet 2007.[45] This section shows the results of the comparison of our pilot study with the CAIRO trial. In this comparison we only included the 394 CAIRO patients who were part of the same source population as the pilot patients, i.e. patients diagnosed with stage IV colorectal cancer in 2003 or 2004, in the Netherlands, by making use of patient level data of this CAIRO subpopulation.

Comparison of baseline characteristics

A total 224 PILOT patients fulfilled the CAIRO eligibility criteria and were included in the comparison. Table 2.3.6 provides an overview of the baseline characteristics of the CAIRO and Pilot patients, the latter grouped by therapy choice.

Statistically significant findings are highlighted in gray in this table. Pilot study patients receiving monotherapy were significantly older than CAIRO patients ($p = 0.0002$). On the other hand, pilot patients receiving combination therapy were significantly younger than CAIRO patients ($p = 0.0258$). This is explained by the non-randomised assignment of treatments in the pilot patients. No other differences in baseline characteristics between the CAIRO and pilot patients were found, except for the earlier mentioned difference in synchronous/metachronous metastases.

Table 2.3.6 Baseline characteristics CAIRO and Pilot studies compared

	First-line chemotherapy				
	Pilot study, eligibles N = 224		CAIRO study, eligibles N = 394	T or X^2 tests p-value	T or X^2 tests p-value
Baseline Characteristics	mono therapy N = 127 (57%)	combi therapy N = 97(43%)	randomised patients	mono vs CAIRO	combi vs CAIRO
Age - yr					
Median	64	59	61	0.0002	0.0258
Range	39-84	29-81	27-82		
Age group - no. (%)					
≥ 70	42 (33%)	13 (13%)	73 (19%)	0.0006	0.2346
Performance status					
PS 0-1	71 (91%)	52 (93%)	373 (95%)	0.2023	0.5799
PS 2-3	7 (9%)	4 (7%)	21 (5%)		
Missing	50 (39%)	41 (42%)	0 (0%)		
Sex - no. (%)					
male	72 (57%)	60 (62%)	256 (65%)	0.0931	0.5660
female	55 (43%)	37 (38%)	138 (35%)		
Predominant localisation of metastases					
Liver	111 (93%)	80 (93%)	345 (88%)	0.1048	0.1804
Extrahepatic	8 (7%)	6 (7%)	47 (12%)		
Missing	8 (6%)	11 (11%)	2 (0.5%)		
LDH at randomisation					
Normal	51 (49%)	45 (55%)	208 (53%)	0.4960	0.7308
Abnormal	53 (51%)	37 (45%)	186 (47%)		
Missing	23 (18%)	15 (15%)	0 (0%)		
WBC at randomisation					
Normal	79 (68%)	66 (75%)	227 (72%)	0.3566	0.5851
Abnormal	38 (32%)	22 (25%)	88 (28%)		
Missing	10 (8%)	9 (9%)	79 (20%)		
AF at randomisation					
Normal	47 (44%)	29 (36%)	139 (44%)	0.9298	0.2196
Abnormal	59 (56%)	51 (64%)	178 (56%)		
Missing	21 (17%)	17 (18%)	77 (20%)		
Site of primary tumor					
Rectosigmoid	10 (8%)	10 (10%)	38 (10%)	0.4523	0.1740
Rectum	27 (21%)	29 (30%)	93 (23%)		
Colon	90 (71%)	58 (60%)	263 (67%)		
Resection of primary tumor					
Yes	79 (65%)	31 (34%)	140 (36%)	0.9539	0.7399
No	43 (35%)	61 (66%)	254 (64%)		
Missing	5 (4%)	5 (5%)	0 (0%)		

Comparison of treatment characteristics

A comparison of the treatment details is presented in table 2.3.7. Regarding the percentage of patients receiving subsequent lines, the results show that approximately 60% of all eligible patients receive second-line chemotherapy treatment. In third-line however, a larger percentage of the CAIRO patients who were randomised to the sequential (monotherapy first-line) arm is still on therapy (39% of CAIRO patients versus 28% of pilot patients, $p < 0.05$). The CAIRO patients receiving first-line combination therapy went off-protocol after two lines of therapy, making comparisons regarding the third line impossible in this group.

Table 2.3.7 Treatment characteristics CAIRO and Pilot studies compared

	First-line chemotherapy			
	Pilot study, eligibles N = 224		CAIRO study, eligibles N = 394	
Treatment Characteristics	mono therapy N = 127 (57%)	combi therapy N = 97(43%)	mono therapy N = 193 (49%)	combi therapy N = 201 (51%)
% of patients receiving line 1	100%	100%	100%	99%
% of patients receiving line 2	60%	59%	60%	58%
% of patients receiving line 3	28%*	NA	39%*	NA

** p < 0.05*

Overall survival of CAIRO patients; sequential versus combination therapy

First the results of the CAIRO study are presented here. Figure 2.3.5 shows the Kaplan Meier overall survival curves for the sequential (first-line monotherapy) versus combination therapy arms. Median overall survival was 13.4 (95% CI 11.5 – 15.2) months for the patients who received first-line monotherapy and 15.9 (95% CI 14.3 – 18.0) months for patients receiving first-line combination therapy. Comparison of the curves by the log-rank test showed that the difference was not significant (p = 0.0897). The corresponding hazard ratio was 0.84 (95% CI 0.68 – 1.029). Again, it should be noted that these survival curves reflect a CAIRO subpopulation with synchronous metastases only. The survival curves as presented in the paper of Koopman et al, 2007[45], reflect the total CAIRO population including metachronous patients as well (N = 820 in total versus N = 394 in our comparison). The median overall survival of the total CAIRO population is 16.3 months in patients receiving first-line monotherapy versus 17.4 months in patients receiving first-line combination therapy (HR 0.92 (95% CI 0.79 – 1.08) Log-rank statistics (p = 0.3281)).

Overall survival of CAIRO patients versus eligible pilot patients; first-line monotherapy

Figure 2.3.6 shows the Kaplan Meier overall survival curves of pilot versus CAIRO patients, all receiving first-line mono therapy. Median overall survival was 13.4 (95% CI 11.5 – 15.2) months for CAIRO patients receiving first-line monotherapy and 11.2 (95% CI 9.5 – 13.3) months for the Pilot patients who received first-line monotherapy. Comparison of the curves by the log-rank test showed that the difference was not significant (p = 0.2772). The corresponding hazard ratio was 0.88 (95% CI 0.70 – 1.11).

Overall survival of CAIRO patients versus eligible pilot patients; first-line combination therapy

Figure 2.3.7 shows the Kaplan Meier overall survival curves of pilot versus CAIRO patients, all receiving first-line combination therapy. Median overall survival was 15.9 (95% CI 14.3 – 18.0) months for CAIRO patients receiving first-line combination therapy and 15.1 (95% CI

12.8 – 18.9) months for the Pilot patients who received first-line combination. Comparison of the curves by the log-rank test showed that the difference was not significant (p = 0.5737). The corresponding hazard ratio was 1.077 (95% CI 0.83 – 1.34).

Figure 2.3.5 Overall survival by treatment group, CAIRO patients

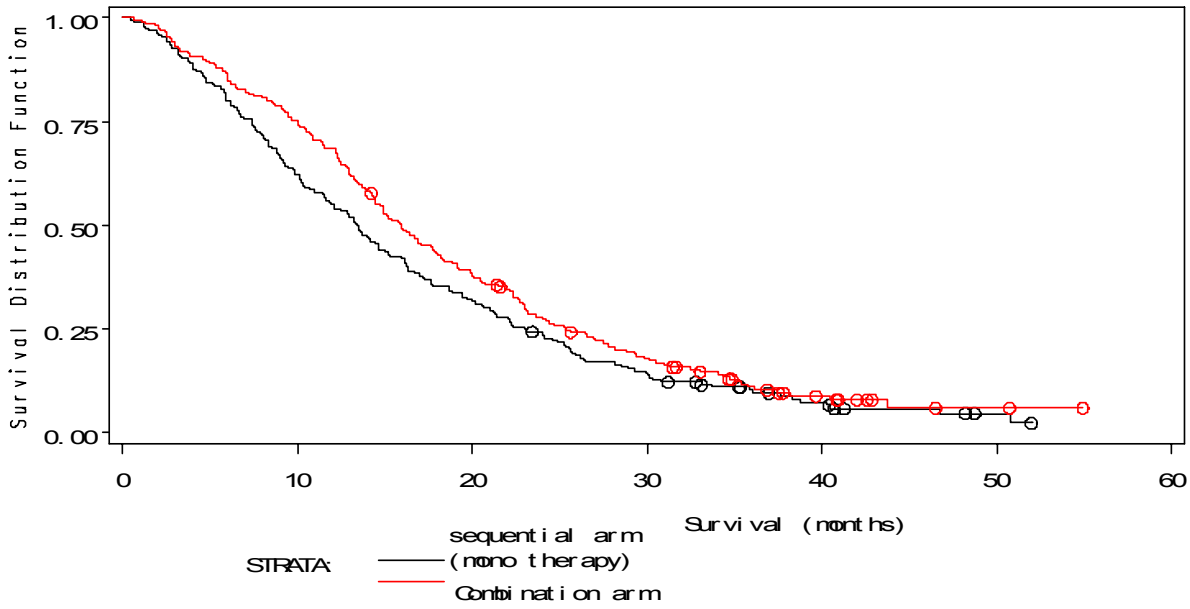


Figure 2.3.6 Overall survival by study, patients receiving first-line monotherapy only

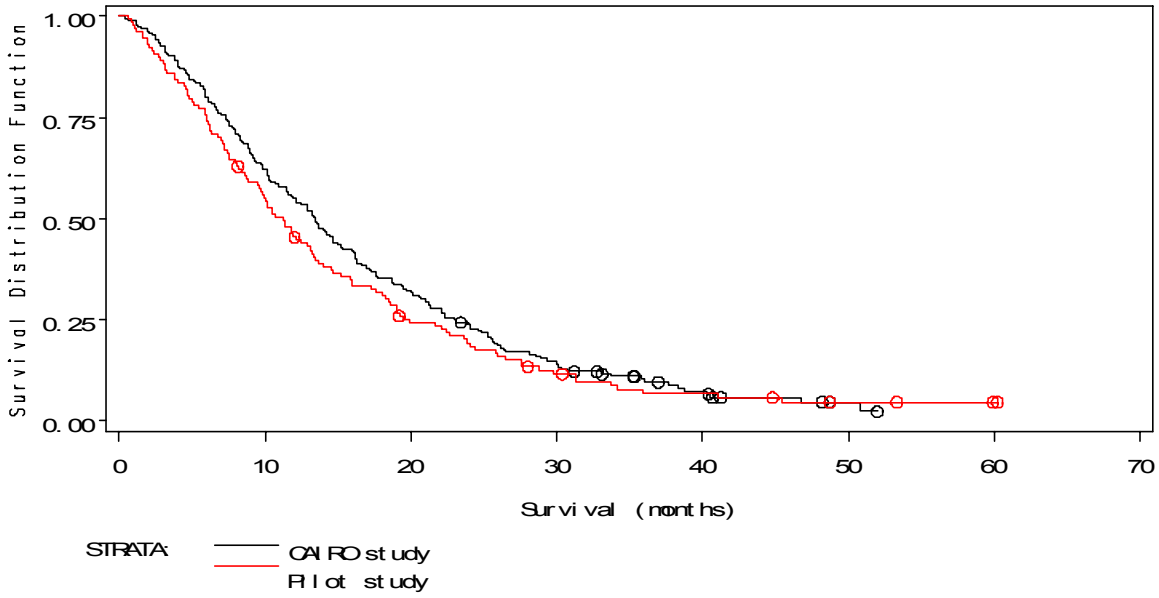
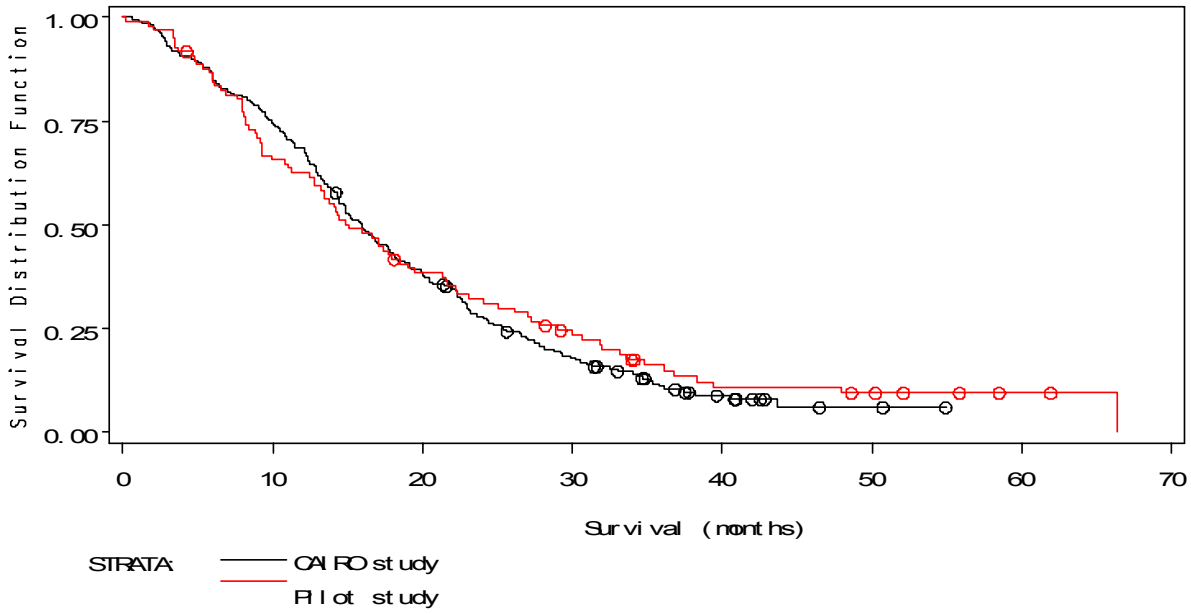


Figure 2.3.7 Overall survival by study, patients receiving first-line combination therapy only



We conclude that the eligible Pilot study patients are comparable to the patients included in the CAIRO study. This is reflected in the overall survival outcomes. No significant differences were found between the CAIRO study and the pilot patients treated in Dutch clinical practice. However, patients receiving monotherapy in the pilot study tend to have a slightly worse outcome compared to the CAIRO patients receiving first-line monotherapy and compared to patients receiving combination therapy. This can be explained by the non-random assignment of treatments in the pilot population. A significantly larger part of the pilot population receiving monotherapy was over 70 years of age (compared to pilot patients receiving combination therapy and compared to CAIRO patients). Besides this we found that these patients were significantly less often treated with a third-line therapy than were patients in the CAIRO sequential treatment arm. This may reflect a tendency towards a higher motivation for treatment in trial versus non-trial patients.

Costs: comparison with existing literature

From the systematic review of Krol et al. (2007)[42] on the cost (-effectiveness) of pharmaceutical therapies for advanced colorectal cancer, 5 papers discussed the cost-effectiveness of irinotecan.[54, 70-73] Of these, 2 made a comparison with oxaliplatin combinations.[72, 73]

Table 2.3.8 The cost assessment of Hillner et al. (2005) (Euro 2009)

	Hillner et al. (2005)		Our outcomes study	
	FOLFOX	IFL	FOLFOX	FOLFIRI
Initial semipermanent venous access	1,648	502		
First-line treatment	47,076	26,860		
First-line toxic deaths	317	566		
Nonfatal toxicities	3,342	4,380		
Second-line treatment	7,467	5,682		
Palliative care for advanced disease	23,907	20,591		
Total treatment costs	**83,757**	**58,582**	**28,533**	**50,166**

Hillner et al (2005). [72]compared the total treatment costs for patients receiving FOLFOX in the first treatment line to those of patients receiving 5FU (bolus) with irinotecan (IFL) in the first treatment line from the perspective of an American third party payer. Resource use was collected during 5 years and included hospitalisation for chemotherapy or adverse events, chemotherapy, concomitant medications, surgical procedures and some laboratory services (e.g. prothrombin time, complete blood count). Table 2.3.8 presents the cost assessment of Hillner et al. (2005). Total treatment costs were € 83,757 for FOLFOX and € 58,582 for IFL.

Total treatment costs for patients receiving IFL were comparable to those found for patients receiving FOLFIRI in our outcomes study. 7/12 patients of our irinotecan combination therapy group received FOLFIRI in the first treatment line; their total cost were € 50,166 (SD 27,390). Total treatment costs for patients receiving FOLFOX were much higher compared to those found in our outcomes study. 27/51 patients of our oxaliplatin combination therapy group received FOLFOX in the first treatment line; their total cost were € 28,533 (SD 18,257). There may be 3 explanations for this cost difference. Firstly, Hillner et al. (2005) used a unit cost price of € 14.95 per mg (versus € 4.35 in our outcomes study; table 2.2.3). Secondly, Hillner et al. (2005) made use of a model to simulate the observations and consequences of care over a 5-year period after initiating therapy with either FOLFOX or IFL. However, this Markov process model was based on various assumptions and projections (verified by expert opinion), while our outcomes study was based on actual patient level data. Thirdly, Hillner et al. (2005) included palliative care costs (at palliative care centers) because their study was conducted from the third party payer perspective. In contrast, our outcomes study excluded these palliative costs, because our study was conducted from the perspective of the hospital.

Limat et al. (2006)[73] compared the first treatment line costs for patients receiving FOLFOX to those for patients receiving FOLFIRI from the perspective of the French Health System.

Resource use included hospitalisation for chemotherapy or adverse events, chemotherapy, concomitant medications (including blood products), medical devices (e.g. disposal pumps) and patients' travel expenses. Laboratory services and radiological procedures were assumed to be identical in both treatment groups and therefore excluded from the cost analysis. Using standard de Gramont regimens, the per diem approach resulted in first treatment line costs of about € 14,000 for FOLFOX and € 15,500 for FOLFIRI. The DRG approach resulted in first treatment line costs of about € 21,000 for FOLFOX and € 21,500 for FOLFIRI. These results are fairly in agreement with the results of our outcomes study.

3.6 Quality of life

Table 2.3.9 gives an overview of the generated mean utility values per 9 week interval in CAIRO study patients. The overall mean utility value 0.77 in patients randomised to sequential therapy and 0.76 in patients randomised to combination therapy (p = 0.2599). In conclusion, the quality of life in patients treated with sequential therapy and combination therapy is comparable. This is in line with the conclusions of the CAIRO study based on the disease specific QLQ-C30 values, where only one significant difference in change between the two treatment arms was seen: 20 points for sequential versus 28 points for combination treatment change in the score for diarrhoea (p = 0.002).

Table 2.3.9 health utility values

	Sequential therapy					Combination therapy					
	Mean	±	sd	(N)		Mean	±	sd	(N)		
Baseline	0.76	±	0.20	(385)		0.75	±	0.22	(362)		
Wk 9	0.76	±	0.21	(208)		0.74	±	0.22	(199)		
Wk 18	0.79	±	0.18	(188)		0.74	±	0.20	(194)		
Wk 27	0.81	±	0.17	(149)		0.80	±	0.15	(135)		
Wk 36	0.75	±	0.22	(132)		0.75	±	0.24	(102)		
Wk 45	0.78	±	0.22	(105)		0.76	±	0.21	(84)		
Wk 54	0.78	±	0.17	(98)		0.76	±	0.17	(76)		
Wk 63	0.76	±	0.19	(68)		0.77	±	0.19	(58)		
Wk 72	0.77	±	0.18	(61)		0.82	±	0.15	(49)		
Wk 81	0.75	±	0.22	(33)		0.83	±	0.12	(33)		
Wk 90	0.71	±	0.21	(32)		0.76	±	0.16	(30)		
Wk 99	0.73	±	0.20	(27)		0.81	±	0.22	(19)		
Wk 108	0.80	±	0.22	(15)		0.89	±	0.10	(8)		
											p-value
Totals	0.77	±	0.20	(1501)		0.76	±	0.20	(1349)		0.2599

4 Discussion

4.1 Use of oxaliplatin

This study has shown that patients who started first-line chemotherapy treatment for metastatic colorectal cancer between January 2003 and January 2005 were treated with either monotherapy using fluoropyrimidines (63%) or combination therapy including oxaliplatin (29%) or irinotecan (8%). According to professional guidelines, these three options were all appropriate in the first-line treatment of metastatic colorectal cancer. No recommendations in regard to the choice and sequence of chemotherapy were available. In the CAIRO study, all patients randomised to first-line combination therapy received irinotecan. Therefore, the total percentage of patients receiving irinotecan as first-line chemotherapy in the Netherlands between January 2003 and January 2005 was actually higher than the 8% we found.

After evaluation of the CAIRO eligibility criteria in the PILOT population, 71% of the patients would have been eligible for the CAIRO study. Possible unfavourable parameters that can be present in ineligible patients include: poorer performance score, no resection of primary tumour, inadequate organ functions, presence of brain metastases, comorbidities, or presence of second tumours. Patients receiving first-line combination therapy were more likely to be eligible for the CAIRO study than patients receiving first-line monotherapy. This was to be expected since first-line combination therapy is considered to be associated with a slightly higher degree of side effects. Therefore, patients who would have been excluded from the CAIRO study because of patient condition, comorbidity or inadequate organ functions, would also have been less eligible to receive a more toxic chemotherapy regimen as first choice since the assignment of treatments was not randomised in our pilot study.

Physicians were less likely to prescribe combination therapy to patients with advanced age or decreased performance status. This finding was in line with the results of the stage III colon cancer pilot study (section 1) where physicians were less likely to prescribe oxaliplatin to patients with advanced age or serious comorbidities. However, in metastatic colorectal cancer most patients receive several treatment lines. Our results showed that at least half of the patients receiving monotherapy as first-line treatment received combination therapy with either oxaliplatin or irinotecan in second-line. In the third line 22% of the patients are still receiving chemotherapy. These percentages are in line with patients receiving first-line combination therapy although a larger part of these patients received both oxaliplatin and

irinotecan during the course of their disease compared to patients receiving first-line monotherapy. Furthermore, patients receiving first-line combination therapy were more often treated with other therapies such as bevacizumab or cetuximab during the course of their disease. This difference between the mono and combination therapy groups might be explained by the difference in baseline characteristics where elderly patients with a worse performance status will be less able to receive a long series of aggressive chemotherapies, especially when they start with monotherapy.

4.2 Clinical efficacy

In the pilot study, eligible patient population, the median overall survival was 15.1 (95% CI 12.8 – 19.0) months for the patients who received first-line combination therapy and 11.2 (95% CI 9.5 – 13.3) months for patients receiving first-line monotherapy. These results are comparable to the results of the CAIRO study where the median overall survival was 15.9 (95% CI 14.3 – 18.0) months for patients receiving first-line combination therapy and 13.4 (95% CI 11.5 – 15.2) months for the patients who received first-line monotherapy. This outcome, which is supported by the finding that the baseline characteristics and treatment patterns are comparable between eligible pilot and CAIRO patients, can be interpreted as a positive sign for the generalisability of the results of the CAIRO trial to Dutch daily practice.
However, patients receiving monotherapy in the pilot study tend to have a slightly worse outcome compared to the CAIRO patients receiving first-line monotherapy and compared to patients receiving combination therapy. This can be explained by the non-random assignment of treatments in the pilot population. A significantly larger part of the pilot population receiving monotherapy was over 70 years old (compared to pilot patients receiving combination therapy and compared to CAIRO patients). Besides this we found that these patients were significantly less often treated with a third-line therapy than were patients in the CAIRO sequential (first-line monotherapy) treatment arm. This may reflect a tendency towards a higher motivation for treatment in trial versus non-trial patients. These results obviously only apply for the eligible pilot patients. The prognosis of the patients who did not fulfil these inclusion criteria was considerably poorer.

Due to limitations in study design, caution is required when interpreting the results on incremental efficacy. The retrospective, observational nature of the pilot study is fundamentally different from a prospective, randomized design. In our study, the treating physicians determined which patients would be treated with first-line monotherapy and which would receive combination therapy. This resulted in an older population receiving

monotherapy. For this reason, the uncorrected disease-free survival curves of the patients with and without oxaliplatin are not directly comparable. Even after correction for baseline characteristics, it remains uncertain whether a valid estimate of the hazard ratio (HR) of the treatment effect can be calculated. This is because it is uncertain whether the model has taken all relevant factors into account. For example, up to 62% of the information on the health state of the patients was missing since physicians do not routinely document a patients' performance status. Apart from this, other factors may have played a role in the decision-making between doctors and patients, which have not been documented and therefore cannot be incorporated into the analysis.

4.3 Costs

Mean costs amounted to € 19,812 (SD 14,679) for monotherapy, € 28,200 (SD 19,470) for oxaliplatin combination therapy, € 44,664 (SD 24,367) for irinotecan combination therapy and € 13,899 (SD 11,860) for ineligible patients. In general the diversity of treatment agents and regimens applied in daily practice results in a wide cost variation between patients.[41] Another consequence of the diversity is the difficulty in comparing results to those of existing literature, as was partly demonstrated in section 3.5.

Costs are preferably determined from a societal perspective in which all relevant costs are included.[1, 43] However, considering limited time and information, it was impossible to collect retrospective data on societal costs for our cost analyses. Therefore, our cost analyses were conducted from the hospital perspective. As stage IV colon carcinoma often occurs in the elderly unemployed population, productivity losses are expected to only have a minor impact on the results. Inclusion of costs of informal care would increase total costs. However, there was no reason to expect any *difference* in costs of informal care between treatments. As a consequence, the inclusion of these costs would therefore have no impact on the difference in total costs. Given these arguments, we believe that the exclusion of those cost components from the analyses had no important impact on the estimate of the real-world cost-effectiveness of oxaliplatin.

4.4 Quality of life

Our retrospective study design made it impossible to use Health Related Quality of Life (HRQOL) as an outcome measure. However, The CAIRO study measured the disease

specific quality of life by means of the QLQ-C30 questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC). We used a recently developed model to convert these QLQ-C30 values into utilities to allow comparisons of Quality adjusted life years (QALYs) rather than life years between the treatment groups in metastatic colorectal cancer. This approach however has an important limitation. The model was developed and validated in patients having haematological cancers. The extent to which the model applies to colorectal cancer patients is uncertain. For this reason the validation of this model to colorectal cancer is currently under investigation by the institute for Medical Technology Assessment.

4.5 Cost-effectiveness in daily clinical practice

Knowledge at T = 0

Knowledge relating to clinical efficacy

Chemotherapy with a fluoropyrimidine was the only available treatment option for patients with metastatic colorectal cancer for many decades. In 2000 however, two novel chemotherapeutic agents, oxaliplatin and irinotecan were approved for the treatment of metastatic colorectal cancer as well. In 2003, which is the T=0 moment of this pilot study, both agents were completely diffused and used in first-, second- and third-line chemotherapy treatment. However, no recommendations from professional guidelines in regard to which chemotherapy to use when were available. At T = 0 it was unclear whether a combination therapy with either oxaliplatin or irinotecan should be preferred over monotherapy with fluoropyrimidines as first-line treatment option.

Knowledge relating to the costs

In 2003, no publications regarding costs of oxaliplatin in the treatment of metastatic colorectal cancer were available. Based on the costs of the new medicine itself, the extra costs that would be involved in using oxaliplatin were estimated at T = 0. The duration of treatment, as agreed by protocol and the expected dose schedules were taken into account.

The cost-effectiveness indication and a T = 0 model were not available for the reimbursement decision body due to the year of registration.

Knowledge via outcomes research at T = 3

Knowledge relating to clinical efficacy

See section 4.2

Knowledge relating to costs

The total costs of treatment and follow-up were calculated per treatment group. However, only limited information regarding costs from ineligible patients was available.

Knowledge via literature study at T = 3

Knowledge relating to clinical efficacy

Various new publications regarding were available at T=3. Based on these publications, combination therapy with either irinotecan or oxaliplatin had been widely accepted as the new standard in first-line treatment of mCRC. However, the question of whether the benefit of fist-line combination therapy with oxaliplatin or irinotecan would have been maintained if patients would have received appropriate salvage treatment in the control arm of these studies was left unanswered. In other words, it may be more important that patients are exposed to these drugs during the course of their disease, rather than receiving the drugs in the first-line. The CAIRO and the FOCUS studies were designed to provide a better insight in this issue. However their results were not available until T = 4.

Knowledge relating to costs

Various publications were available at T = 3. However, related to clinical efficacy, no results were known regarding the cost-effectiveness of fluoropyrimidines, irinotecan or oxaliplatin when consequently used in either sequential or combination therapy.

Cost-effectiveness at T =3

Knowledge of clinical effectiveness solely obtained via outcomes research was not sufficient to produce a valid estimate of the incremental effectiveness of oxaliplatin. The assignment of the treatments was not randomised. We found that patients who received monotherapy were significant older than patients receiving first-line combination therapy. From this we can conclude that the patients in the two treatment groups might not be comparable in terms of their prognosis. Randomised studies that are applicable to the daily practice setting are needed to compare the results from outcomes research with. The comparability between the pilot study and the CAIRO trial can be interpreted as a positive sign in support of the generalisability of the results of the CAIRO trial to Dutch daily practice. The hazard ratios regarding the treatment effect of combination therapy of the two studies were comparable. Therefore, both estimates could be used for the cost-effectiveness analysis. Similarly, we also feel confident in using the cost estimates obtained via outcomes research.

General conclusion on cost-effectiveness

Both the results of outcomes research and the CAIRO study could be used in the cost-effectiveness analyses. All cost data would be based entirely on outcomes research. In our opinion it would be possible to obtain a sufficiently precise and valid estimate of the cost-effectiveness of oxaliplatin in daily practice. However we should realise that the ability to compare our results to the CAIRO study has been of crucial importance in this pilot study. It remains questionable how often such trials will be available in other expensive drugs. Furthermore, the results of the CAIRO study were not available until T = 4.

4.6 Appropriate use in daily clinical practice

This section focused on the appropriate use of oxaliplatin as first-line treatment in metastatic colorectal cancer. The aim was to provide insight into the dynamics of clinical practice. *Dynamics of clinical practice* is defined as the differences between the requirements for registering oxaliplatin and the information on its use in daily practice. These differences may result from differences in the use of oxaliplatin or differences in the observed effectiveness or adverse events.[1] The following is a short summary of the aspects relevant to the dynamics of clinical practice.

Population treated in clinical practice versus population from the CAIRO study

A large proportion of the patients (71%) treated with oxaliplatin in daily practice were similar to the population from the CAIRO study with respect to their baseline characteristics. The patients who did not fulfil the CAIRO eligibility criteria (29%) had a significantly worse performance status.

Selective prescription

During the timeframe of this pilot study which started in 2003, oxaliplatin was completely diffused in clinical daily practice because this regimen was already registered for the indication of metastatic colorectal cancer since 2000. Moreover, professional guidelines approved the use of oxaliplatin in first-, second- and third-line treatment, without recommendation for one specific treatment line. In general, patients receiving oxaliplatin as a first-line treatment option were significantly younger and had a better performance score than patients receiving monotherapy with fluoropyrimidines as first-line therapy.

Prescribing outside the registered indication

In metastatic colorectal cancer, oxaliplatin is registered for first-, second- and third-line treatment. Given this broad registration, the problem of possible prescription outside the registered indication does not exist here.

The use of oxaliplatin in practice versus use in the CAIRO study

In the CAIRO study, patients were randomised to receive first-line chemotherapy with either capecitabine monotherapy or capecitabine + irinotecan combination therapy. In the pilot study, patients receiving combination therapy mostly received a combination with oxaliplatin as first-line treatment regimen. This is not surprising since professional guidelines did not recommend the use of a specific regimen as first-line treatment. We can conclude that the observed regimens as well as the observed dose schedules in daily practice demonstrated a good adherence to existing guidelines.

Effectiveness in practice versus effectiveness in the CAIRO study

Those patients from daily practice (71% of pilot study population) who fulfilled the inclusion criteria of the CAIRO study showed a similar overall survival to that of the patients in the CAIRO study. No comparative trial data are available on the patients who did not fulfil the inclusion criteria of the CAIRO study (29%). Daily practice shows that these patients have a less favourable prognosis. This is as expected since the exclusion criteria of the CAIRO trial mainly consisted of factors that would exclude patients with an unfavourable prognosis like patient condition, comorbidity, presence of a second tumour, abnormal organ function and brain metastases.

General conclusion on appropriate use

In regard to the insights gained from the dynamics in clinical practice, we observe that the pilot patients, with respect to baseline characteristics, use of oxaliplatin and efficacy comply well with the findings of the CAIRO study. We can conclude that oxaliplatin is used appropriately in metastatic colorectal cancer.

Conclusions

Oxaliplatin is an expensive medicine that was admitted under the Dutch policy regulation ‘expensive medicines’ in order to allow hospitals to obtain additional funding for this drug. Since 2006, the Dutch policy regulations for expensive hospital medicines require evidence from outcomes research for the assessment of appropriate use and real-world cost-effectiveness of expensive medicines after three years of temporary additional funding. Outcomes research in this particular context is new in Dutch policy making and therefore experience in the application of outcomes research is lacking. This report investigated how oxaliplatin is used in daily practice and explored real-world treatment effects and costs in stage III colon and metastatic colorectal cancer in Dutch daily practice. This pilot outcomes research study was conducted as part of a comprehensive study of methodological issues related to outcomes research. We conclude that outcomes research provides valuable information on the utilisation of oxaliplatin in daily practice. Via outcomes research we were able to obtain insight into the appropriate use of oxaliplatin. Results were comparable to the MOSAIC and CAIRO trials, allowing us to use these trials to obtain a valid and precise estimate of the incremental effectiveness. However it is important to note that the ability to use data from trials such as the MOSAIC and CAIRO was of crucial importance in this pilot study, along with a limited dynamics in daily practice (i.e., a limited amount of treatment variation). The combination of data sources used in this study is a cogent reminder that the assessment of the real-world effectiveness and cost-effectiveness of a medicine will make use of all available data. The actual approach to be taken will have to depend on the types of data and evidence available at the time of the final assessment (i.e., 3-4 years of use in daily practice).

References

1. Delwel, G. O. 2008. *Leidraad voor uitkomstenonderzoek.* Diemen: College voor Zorgverzekeringen, 270.

2. Landelijke richtlijn colon en colorectaal kanker. 2008.

3. Lemmens VEPP, Coebergh JWW. Epidemiologie van colorectale tumoren. IKR Bulletin 2006;30.

4. Greene FL. Current TNM staging of colorectal cancer. Lancet Oncol 2007 Jul;8(7):572-3.

5. Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. Dis Colon Rectum 1997 Jan;40(1):15-24.

6. Thirion P, Michiels S, Pignon JP, Buyse M, Braud AC, Carlson RW, O'Connell M, Sargent P, Piedbois P, Meta-Analysis Group in Cancer. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: An updated meta-analysis. J Clin Oncol 2004 Sep 15;22(18):3766-75.

7. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, Ungerleider JS, Emerson WA, Tormey DC, Glick JH, Veeder MH, Mailliard JA. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: A final report. Ann Intern Med 1995 Mar 1;122(5):321-6.

8. O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, Wieand HS. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol 1997 Jan;15(1):246-50.

9. Sargent DJ, Patiyil S, Yothers G, Haller DG, Gray R, Benedetti J, Buyse M, Labianca R, Seitz JF, O'Callaghan CJ, Francini G, Grothey A, O'Connell M, Catalano PJ, Kerr D, Green E, Wieand HS, Goldberg RM, de Gramont A, ACCENT Group. End points for colon cancer adjuvant trials: Observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT group. J Clin Oncol 2007 Oct 10;25(29):4569-74.

10. Twelves C, Wong A, Nowacki MP, Abt M, Burris H,3rd, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz JF, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J, Scheithauer W. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005 Jun 30;352(26):2696-704.

11. Twelves CJ, Scheithauer W, McKendrick J, Nowacki M, Seitz J, Van Hazel G, Wong A, Diaz-Rubio E, Cassidy J. 5-year overall survival update from the X-ACT trial of capecitabine vs. 5-FU/LV as adjuvant treatment for stage-III colon cancer. European Journal of Cancer Supplements;5(6).

12. Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: Systematic review and economic evaluation. Health Technol Assess 2006 Nov;10(41):iii,iv, xi-xiv, 1-185.

13. Eggington S, Tappenden P, Pandor A, Paisley S, Saunders M, Seymour M, Sutcliffe P, Chilcott J. Cost-effectiveness of oxaliplatin and capecitabine in the adjuvant treatment of stage III colon cancer. Br J Cancer 2006 Nov 6;95(9):1195-201.

14. Cassidy J, Douillard JY, Twelves C, McKendrick JJ, Scheithauer W, Bustova I, Johnston PG, Lesniewski-Kmak K, Jelic S, Fountzilas G, Coxon F, Diaz-Rubio E, Maughan TS, Malzyner A, Bertetto O, Beham A, Figer A, Dufour P, Patel KK, Cowell W, Garrison LP. Pharmacoeconomic analysis of adjuvant oral capecitabine vs intravenous 5-FU/LV in dukes' C colon cancer: The X-ACT trial. Br J Cancer 2006 Apr 24;94(8):1122-9.

15. Douillard JY, Tilleul P, Ychou M, Dufour P, Perrocheau G, Seitz JF, Maes P, Lafuma A, Husseini F. Cost consequences of adjuvant capecitabine, mayo clinic and de gramont regimens for stage III colon cancer in the french setting. Oncology 2007;72(3-4):248-54.

16. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009 Jul 1;27(19):3109-16.

17. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004 Jun 3;350(23):2343-51.

18. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. J Clin Oncol 2007 Jun 1;25(16):2198-204.

19. Sargent DJ, Goldberg RM, Bleiberg H, De Gramont A, Tournigand C, Andre T, Rothenberg ML, Tabah-Fisch IM. A pooled safety and efficacy analysis of the FOLFOX4 regimen (bi-monthly oxaliplatin plus fluorouracil/leucovorin) in elderly compared to younger patients with colorectal cancer. Journal of Clinical Oncology 2006;24(18).

20. Aballea S, Boler A, Craig A, Wasan H. An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the united kingdom (UK). Eur J Cancer 2007 Jul;43(11):1687-93.

21. Aballea S, Chancellor JV, Raikou M, Drummond MF, Weinstein MC, Jourdan S, Bridgewater J. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US. Cancer 2007 Mar 15;109(6):1082-9.

22. Gorner M, Riemer-Hommel P. Adjuvant chemotherapy for colon cancer--analysis of treatment costs from the perspective of statutory sickness funds. Z Gastroenterol 2008 Jul;46(7):681-8.

23. Committee Pharmacotherapeutical Aid (CFH), Health Care Insurance Board (CVZ): www.fk.cvz.nl. 2009. .

24. Punt CJ. Chemotherapy of patients with colorectal carcinoma. Ned Tijdschr Geneeskd 2005 Jun 25;149(26):1441-7.

25. Arkenau HT, Arnold D, Cassidy J, Diaz-Rubio E, Douillard JY, Hochster H, Martoni A, Grothey A, Hinke A, Schmiegel W, Schmoll HJ, Porschen R. Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: A pooled analysis of randomized trials. J Clin Oncol 2008 Dec 20;26(36):5910-7.

26. Lemmens VE, van Halteren AH, Janssen-Heijnen ML, Vreugdenhil G, Repelaer van Driel OJ, Coebergh JW. Adjuvant treatment for elderly patients with stage III colon cancer in the southern netherlands is affected by socioeconomic status, gender, and comorbidity. Ann Oncol 2005 May;16(5):767-72.

27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40(5):373-83.

28. The unit cost of inpatient hospital days, outpatient visits and daycare treatments in field of haematology and oncology .

29. Tan SS, Hakkaart-van Roijen L, Al MJ, Bouwmans CA, Hoogendoorn ME, Spronk PE, Bakker J. A microcosting study of intensive care unit stay in the netherlands. J Intensive Care Med 2008 Jul-Aug;23(4):250-7.

30. [Internet]; c2009. Available from: http://ctg.bit-ic.nl/Nzatarieven/top.do.

31. [Internet]; c2009. Available from: www.cbs.nl.

32. Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, van Groeningen CJ, Sinnige HA, Richel DJ, Voest EE, Dijkstra JR, Vink-Borger ME, Antonini NF, Mol L, van Krieken JH, Dalesio O, Punt CJ. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009 Feb 5;360(6):563-72.

33. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999 Jun;94(6):1650-7.

34. Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A, Urban N. Quality of life in survivors of colorectal carcinoma. Cancer 2000 Mar 15;88(6):1294-303.

35. Briggs AH, Goeree R, Blackhouse G, O'Brien BJ. Probabilistic analysis of cost-effectiveness models: Choosing between treatment strategies for gastroesophageal reflux disease. Med Decis Making 2002 Jul-Aug;22(4):290-308.

36. Maniadakis N, Fragoulakis V, Pectasides D, Fountzilas G. XELOX versus FOLFOX6 as an adjuvant treatment in colorectal cancer: An economic analysis. Curr Med Res Opin 2009 Feb 12.

37. Vandenbroucke JP, Hofman A. Grondslagen der epidemiologie. ; 1993. .

38. van Laarhoven HW, Punt CJ. Systemic treatment of advanced colorectal carcinoma. Eur J Gastroenterol Hepatol 2004 Mar;16(3):283-9.

39. Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, Price T, Lim R, Van Cutsem E, Park YS, McKendrick J, Topham C, Soler-Gonzalez G, de Braud F, Hill M, Sirzen F, Haller DG. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: A planned safety analysis in 1,864 patients. J Clin Oncol 2007 Jan 1;25(1):102-9.

40. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, Parodi S, Dal Lago D, Gioia F, Monfardini S, Aapro MS, Serraino D, Zagonel V. Comprehensive geriatric assessment adds information to eastern cooperative oncology group performance status in elderly cancer patients: An italian group for geriatric oncology study. J Clin Oncol 2002 Jan 15;20(2):494-502.

41. Ferro SA, Myer BS, Wolff DA, Poniewierski MS, Culakova E, Cosler LE, Scarpace SL, Khorana AA, Lyman GH. Variation in the cost of medications for the treatment of colorectal cancer. Am J Manag Care 2008 Nov;14(11):717-25.

42. Krol M, Koopman M, Uyl-de Groot C, Punt CJ. A systematic review of economic analyses of pharmaceutical therapies for advanced colorectal cancer. Expert Opin Pharmacother 2007 Jun;8(9):1313-28.

43. Drummond M. Methods for the economic evaluation of health care programmes. 2005.

44. Koopman M, Punt CJ. Chemotherapy, which drugs and when. Eur J Cancer 2009 Sep;45 Suppl 1:50-6.

45. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Slee PH, Werter MJ, Mol L, Dalesio O, Punt CJ. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): A phase III randomised controlled trial. Lancet 2007 Jul 14;370(9582):135-42.

46. Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ, FOCUS Trial Investigators, National Cancer Research Institute Colorectal Clinical Studies Group. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): A randomised controlled trial. Lancet 2007 Jul 14;370(9582):143-52.

47. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate. advanced colorectal cancer meta-analysis project. J Clin Oncol 1992 Jun;10(6):896-903.

48. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. meta-analysis group in cancer. J Clin Oncol 1998 Jan;16(1):301-8.

49. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. J Clin Oncol 2001 Apr 15;19(8):2282-92.

50. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P, Xeloda Colorectal Cancer Study Group. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol 2001 Nov 1;19(21):4097-106.

51. Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002 Sep 1;20(17):3605-16.

52. Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oza A, Skovsgaard T, Munier S, Martin C. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2002 Sep 1;20(17):3617-27.

53. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger U, Garin A, Graeven U, McKendric J, Maroun J, Marshall J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schilsky RL, Capecitabine Colorectal Cancer Study Group. First-line oral capecitabine therapy in metastatic colorectal cancer: A favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 2002 Apr;13(4):566-75.

54. Cunningham D, Falk S, Jackson D. Clinical and economic benefits of irinotecan in combination with 5-fluorouracil and folinic acid as first line treatment of metastatic colorectal cancer. Br J Cancer 2002 Jun 5;86(11):1677-83.

55. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998 Oct 31;352(9138):1407-12.

56. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 2000 Mar 25;355(9209):1041-7.

57. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. irinotecan study group. N Engl J Med 2000 Sep 28;343(13):905-14.

58. Punt CJ. New options and old dilemmas in the treatment of patients with advanced colorectal cancer. Ann Oncol 2004 Oct;15(10):1453-9.

59. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: A review of preclinical and clinical studies. Ann Oncol 1998 Oct;9(10):1053-71.

60. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without

oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000 Aug;18(16):2938-47.

61. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Levi F. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000 Jan;18(1):136-47.

62. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Bail N, Haller DG. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol 2003 Jun 1;21(11):2059-69.

63. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004 Jan 1;22(1):23-30.

64. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 2004 Jan 15;22(2):229-37.

65. Punt CJ. Irinotecan or oxaliplatin for first-line treatment of advanced colorectal cancer? Ann Oncol 2005 Jun;16(6):845-6.

66. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004 Apr 1;22(7):1209-14.

67. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Akkermans-Vogelaar JM, Punt CJ. Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer, an interim safety analysis. A dutch colorectal cancer group (DCCG) phase III study. Ann Oncol 2006 Oct;17(10):1523-8.

68. Hieke K, Kleeberg UR, Stauch M, Grothey A. Costs of treatment of colorectal cancer in different settings in germany. Eur J Health Econ 2004 Oct;5(3):270-3.

69. Jansman FG, Postma MJ, van Hartskamp D, Willemse PH, Brouwers JR. Cost-benefit analysis of capecitabine versus 5-fluorouracil/leucovorin in the treatment of colorectal cancer in the netherlands. Clin Ther 2004 Apr;26(4):579-89.

70. Levy-Piedbois C, Durand-Zaleski I, Juhel H, Schmitt C, Bellanger A, Piedbois P. Cost-effectiveness of second-line treatment with irinotecan or infusional 5-fluorouracil in metastatic colorectal cancer. Ann Oncol 2000 Feb;11(2):157-61.

71. Earle CC, Kwok A, Gazelle GS, Fuchs CS. Two schedules of second-line irinotecan for metastatic colon carcinoma. Cancer 2004 Dec 1;101(11):2533-9.

72. Hillner BE, Schrag D, Sargent DJ, Fuchs CS, Goldberg RM. Cost-effectiveness projections of oxaliplatin and infusional fluorouracil versus irinotecan and bolus

fluorouracil in first-line therapy for metastatic colorectal carcinoma. Cancer 2005 Nov 1;104(9):1871-84.

73. Limat S, Bracco-Nolin CH, Legat-Fagnoni C, Chaigneau L, Stein U, Huchet B, Pivot X, Woronoff-Lemsi MC. Economic impact of simplified de gramont regimen in first-line therapy in metastatic colorectal cancer. Eur J Health Econ 2006 Jun;7(2):107-13.

74. Versteegh MM, Leunis A, Luime JJ, Boggild M, Uyl-de Groot C, Stolk EA. Mapping QLQ-C30, HAQ and MSIS-29 on EQ-5D: Influence of overlap in dimenstions. Submitted (2010).

Annex I Collaboration with the DCCG in Nijmegen

For this outcomes research, the iMTA worked very closely with, in particular, the UMC St Radboud in Nijmegen, the core centre of the Dutch Colorectal Cancer Group (DCCG). In the DCCG a large number of hospitals work together in the field of clinical research on patients with a colorectal carcinoma. At the end of 2002 the 'CAIRO 1' study was initiated. In this study 820 patients with metastatic colorectal cancer were included between 1 January 2003 and 31 December 2004 in 74 hospitals in the Netherlands. They were randomized between first-line capecitabine, second-line irinotecan, and third-line capecitabine + oxaliplatin (sequential treatment arm) versus first line capecitabine + irinotecan and second-line capecitabine + oxaliplatin (combination treatment arm). Subsequently the 'CAIRO 2' and 'CAIRO 3' studies were initiated, of which the latter is still ongoing. Due to the national connections of the DCCG, permission for participation in the pilot study has been obtained in a large number of hospitals.

Prof. dr. C.J.A. Punt, chairman of the DCCG, and Dr. M. Koopman have been involved in the oxaliplatin pilot study since it's design. Furthermore, during the course of the pilot study, close collaboration took place with drs. L. Mol who is performing research into the quality of medical oncologic care and local data management. Efficiency gains were possible because this quality research and the pilot study were able to make use of the same patient population.

Annex II Systematic review of the clinical effectiveness of oxaliplatin for the adjuvant treatment of colon cancer

Identification of studies

A systematic literature search was performed to identify randomised controlled trials (RCTs) of oxaliplatin as adjuvant therapy in the treatment of colon cancer.

Sources searched

Pandor et al. published results of an extensive systematic review regarding the clinical effectiveness and cost-effectiveness of oxaliplatin, covering the literature until January 2005 (Pandor et al. 2006). In this literature review the publication date limit was set from January 2005 until February 2009 to cover the recent literature. A total of eight electronic databases were searched: Medline, Embase, Pubmed, Cochrane, Central, Dare-nhs eed-hta, Cinahl, and Web of science. In the searches of MEDLINE, EMBASE and Web of Science, search results were restricted to RCTs. Following Pandor et al. (2006), the search of PUBMED was restricted to the last 180 days to capture recent and unindexed MEDLINE references.

Key word strategies

Key word strategies were used similar to the ones reported by Pandor et al, Annex 3. These key word strategies were slightly adapted to fit other versions of the same databases.

Inclusion and exclusion criteria

The relevance of the studies was assessed according to the criteria set out below, largely identical to the criteria formulated by Pandor et al. (2006). Only English-language articles that were not incorporated in Pandor et al. (2006) were considered. All titles were screened and, when considered possibly relevant, abstracts were evaluated. Based on the abstracts, full copies of relevant papers were obtained.

Population	Patients (either gender at any age) with Stage III colon cancer after complete surgical resection of the primary tumour.
Interventions	Oxaliplatin (Eloxatin®, Sanofi-Aventis) used in combination with 5FU/LV, within its licensed indication.
Comparator	Chemotherapy as adjuvant therapy with an established FU-containing regimen.
Outcomes	Data on the following outcomes were included (as defined by Pandor, 2006):

Outcome	Definition
Overall survival	The interval from randomisation to death from any cause.
Disease-free survival	The time from trial entry or randomisation until recurrence of colorectal cancer or death from any cause.
Relapse-free survival	The time from trial entry or randomisation until recurrence of colorectal cancer or death from any cause, excluding deaths unrelated to disease progression or treatment.
Time to treatment failure	The interval from randomisation to discontinuation of treatment for any reason (including treatment toxicity and death).
Adverse effects of treatment/toxicity	Abstracted as reported, however defined.
Health-related QoL	Abstracted as reported, however defined.

Articles primarily focussing on safety/adverse events and/or drug administration were excluded.

Study design RCTs

Data abstraction and critical appraisal strategy

Since, no new studies were conducted from 2005 onwards, meeting the above-mentioned criteria, data relating to study design and quality, could be obtained from Pandor et al. (2006). New publications, mainly of extended follow-up results, were identified, data were extracted and incorporated into the initial outcomes reported by Pandor et al. (2006).

Results of clinical effectiveness review

Number and type of studies identified

A total of 1531 titles and abstracts were screened for inclusion. Based on this screening, 88 full papers were retrieved and assessed in detail. Three studies were identified, 2 of which covered the clinical effectiveness of oxaliplatin (MOSAIC and NSABP C-07). In our limited time period, 7 new and relevant publications on these studies were published (Kuebler, 2007; Wolmark, 2008; André, 2009; de Gramont 2007a; de Gramont, 2007b; Sargent, 2006; Goldberg, 2006).

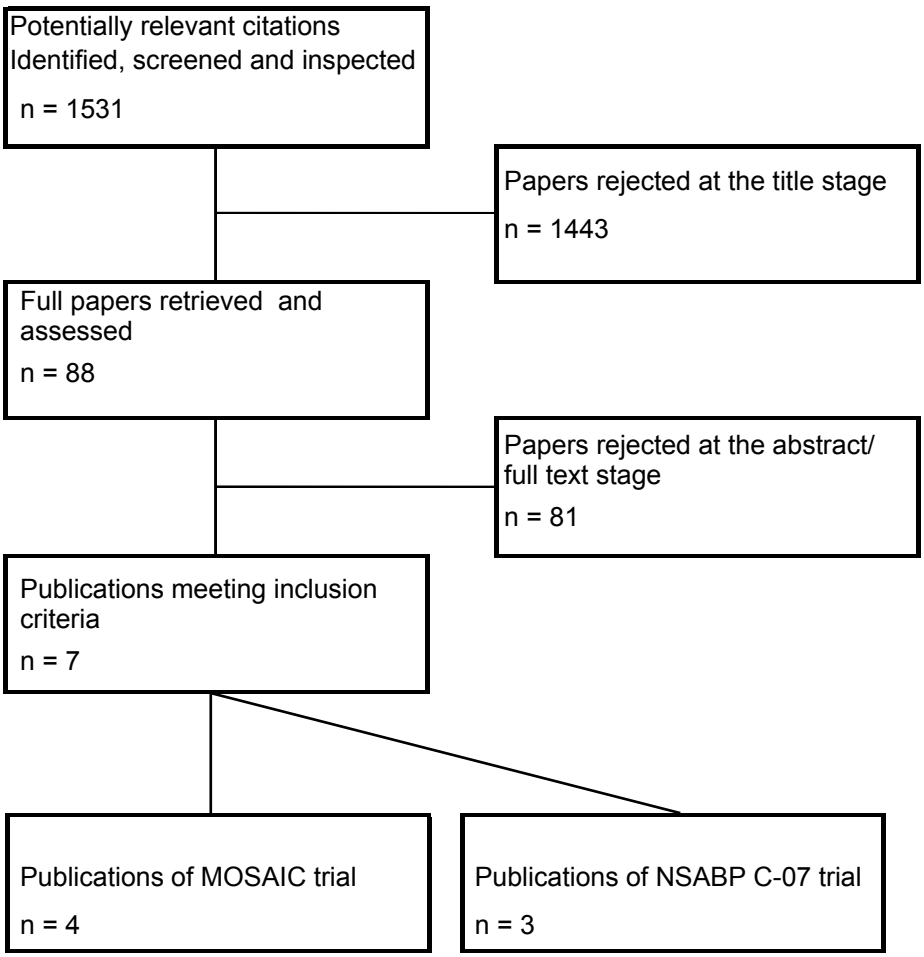
Number and type of studies included

Between 2005 and February 2009, no new studies were conducted comparing the efficacy of adjuvant therapy with oxaliplatin with the efficacy of adjuvant therapy with an established FU-containing regimen. However, while former results of the NSABP C-07 trial were only published in abstract-form, in 2007 the first full-text report of this study appeared (Kuebler, 2007). In 2008 these results were updated with overall survival results in an ASCO Annual Meeting Proceedings (Wolmark, 2008). Furthermore, in 2007 abstracts with updated results

from the MOSAIC study were presented, providing a median follow-up of six years for this trial (de Gramont 2007a; de Gramont, 2007b). Very recently, the MOSAIC 6-year overall survival was also published in a full-text article (André, 2009). Although this paper was published after the end of our search period, we included it since it elaborates on the limited information provided in the included abstracts. Two other articles, partly based on results from the MOSAIC trial, report the safety and efficacy of the FOLFOX4 regimen when given to elderly compared to younger patients with colorectal cancer (Sargent, 2006; Goldberg, 2006).

Number and type of studies excluded

A total of 80 papers were excluded. The main reason for exclusion was that the study presented no new data relating to efficacy. Most of the excluded articles were non-systematic reviews. A couple of these reviews did provide interesting comparisons between the MOSAIC and NSABP C-07 trial data. The review of Sharif et al. (2008) is quoted on various occasions for this reason. Several articles were excluded because they solely or primarily focussed on safety/adverse events.



Description of included studies

Tables 1 and 2 below – derived from Sharif et al. (2008) – provide a summary of the main characteristics of the MOSAIC trial and the NSABP C-07 trial. See Pandor et al. (2006) for more extensive information on study characteristics, including a quality assessment.

Table 1 Summary of design and study characteristics – MOSAIC trial and NSABP C-07 trial (Shardif, 2008).

Table 1. Comparison of study design, MOSAIC and NSABP C-07

	MOSAIC[a]	NSABP C-07[b]
Sample size	2246	2407
Study design	Randomized, phase III	Randomized, phase III
Tumor stage	Resected stage II, III	Resected stage II, III
Stratification	• T stage: 2, 3 vs. T4 • N stage: 0, 1, 2 • Perforation or obstruction or venous invasion	N stage: 0, 1, 2
Planned cumulative doses:		
Oxaliplatin	1020 mg/m^2	765 mg/m^2
5-FU	24,000 mg/m^2	9,000 mg/m^2
Primary endpoint	DFS	DFS
DFS defined[c]	Time to relapse or death, whichever comes first (non-colorectal cancers were disregarded in the analysis)	Time to first recurrence, death or second primary cancer
Primary analysis cut-off	3 years from enrollment of last patient or 303 events (relapse or death) in test arm, whichever comes later	675 events on the combined arms (estimated to be at approximately 3 years from enrollment of last patient)
Secondary endpoints	Safety, overall survival, long-term adverse events	Safety, overall survival, and recurrence- free interval
Statistical power	90% to detect a 6% increase in DFS at 3 years	89% to detect a 5.4% increase in DFS at 3 years

[a] André, T et al. N Eng J Med. 2004, 350:2343–2351.
[b] Kuebler, JP et al. J Clin Oncol. 2007, 25:2198–2204.
[c] Primary efficacy variable definition was different between the two trials.

Table 2 Summary of patient characteristics – MOSAIC trial and NSABP C-07 trial (Shardif, 2008).

Table 2. Patient characteristics

Characteristics, All patients	MOSAIC[a]		NSABP C-07[b]	
	FOLFOX (N = 1123)	FL (N = 1123)	FLOX (N = 1200)	FULV (N = 1207)
Age				
Median, years	61	60	59.0	59.0
<65 years, %	64.4	66.2	68.9	67.0
Sex, %				
Male	56.1	52.4	55.3	57.8
Female	43.9	47.6	44.7	42.2
T stage, %[c]				
T1	0.0	0.0	2.8	2.5
T2	4.5	4.8	8.6	10.0
T3	76.0	75.9	81.8	79.6
T4	19.0	18.5	6.8	6.9
Unknown	0.5	0.8	0.3	0.7
Nodal status, %[c]				
0 (stage II)	40.2	39.9	28.8	28.8
1–4	44.4	45.7	52.6	51.5
5+	15.1	14.2	18.0	19.5
Unknown	0.2	0.2	0.2	0.3

[a] André, T et al. N Eng J Med. 2004, 350:2343–2351.
[b] Kuebler, JP et al. J Clin Oncol. 2007, 25:2198–2204.
[c] The distribution of positive nodes and T stage are the only patient characteristics significantly different between the two trials ($p < 0.0001$ for each).

Efficacy of oxaliplatin

Disease-free survival (DFS) and overall survival (OS) data of the MOSAIC trial were published before, with a median follow-up of 37.9 months and 48.6 months (Pandor, 2006). In 2007, these OS results were updated for a median follow-up of six years, reported in abstract form (de Gramont 2007a; de Gramont, 2007b). In 2009 these abstracts were followed by a full-text article (André, 2009). MOSAIC trial results were reported for the patient group as a whole, as well as for subgroups based on disease stage. Since we are particularly interested in patients with stage III colon cancer, outcomes for this group are reported separately here as well. For the NSABP C-07 study, outcomes for the stage III patient subgroup were limited: they were available online, only for DFS at 4 years. The recent publications did extend formerly reported DFS-results for the whole patient group, whereby the DFS and OS results had a median follow-up of 42.5 (Kuebler, 2007) and 67 months (Wolmark, 2008). The following table shows that the MOSAIC trial and the NSABP C-07 trial both demonstrate the superiority of oxaliplatin-containing regimens (FOLFOX and FLOX) compared to FL and FULV, respectively. Adding oxaliplatin to 5FU/LV improves the DFS and OS of patients with resected colon cancer.

Table 3 Disease-free and overall survival for the MOSAIC[a] and NSABP C-07[b] trial.

Study/outcome	Median follow-up (months)	Event rate		Hazard ratio[d] (95% CI)	p-value for superiority
		Oxaliplatin (plus 5FU/LV)[c]	5FU/LV[c]		
Disease-free survival					
All patients (Stage II and III colon cancer)					
MOSAIC *	37.9	237/1123 (21.1%)	293/1123 (26.1%)	0.77 (0.65 to 0.91)	p = 0.002
MOSAIC +	48.6	267/1123 (23.8%)	332/1123 (29.6%)	0.76 (0.65 to 0.90)	p = 0.0008
MOSAIC #	72.0	Not reported	Not reported	Not reported	Not reported
MOSAIC %	73.4	304/1123 (27.1%)	360/1123 (32.1%)	Not reported	Not reported
NSABP C-07 &	34.0	272/1200 (22.7%)	332/1207 (27.5%)	0.79 (0.67 to 0.93)	p = 0.004
NSABP C-07 @	42.5	308/1200 (25.7%)	369/1207 (30.6%)	0.80 (0.69 to 0.93)	p = 0.0034
NSABP C-07 ^	67.0	Not reported	Not reported	Not reported	Not reported
Patients with stage III colon cancer only					
MOSAIC *	37.9	181/672 (26.9%)	226/675 (33.5%)	0.76 (0.62 to 0.92)	Not reported
MOSAIC +	48.6	200/672 (29.8%)	252/675 (37.3%)	0.75 (0.62 to 0.90)	p = 0.002
MOSAIC #	72.0	Not reported	Not reported	Not reported	Not reported
MOSAIC %	73.4	226/672 (33.6%)	271/675 (40.1%)	Not reported	Not reported
NSABP C-07 &	34.0	Not reported	Not reported	Not reported	Not reported
NSABP C-07 @	42.5	Not reported	Not reported	Not reported	Not reported
NSABP C-07 ^	67.0	Not reported	Not reported	Not reported	Not reported
Overall survival					
All patients (Stage II and III colon cancer)					
MOSAIC *	37.9	133/1123 (11.8%)	146/1123 (13.0%)	0.90 (0.71 to 1.13)	Not significant
MOSAIC +	48.6	176/1123 (15.7%)	194/1123 (17.3%)	0.89 (0.72 to 1.09)	p = 0.236
MOSAIC #	72.0	241/1123 (21.5%)	272/1123 (24.2%)	0.85 (0.71 to 1.01)	Not reported
MOSAIC %	81.9	245/1123 (21.8%)	283/1123 (25.2%)	Not reported	Not reported
NSABP C-07 &	34.0	Not reported	Not reported	Not reported	Not reported
NSABP C-07 @	42.5	187/1200 (15.6%)	198/1207 (16.4%)	Not reported	Not reported
NSABP C-07 ^ [e]	67.0	259/1200 (21.6%)	301/1209 (24.9%)	0.853 (0.723 to 1.008)	p = 0.061
Patients with Stage III colon cancer only					
MOSAIC *	37.9	104/672 (15.5%)	119/675	0.86 (0.66 to 1.11)	Not

			(17.6%)		significant
MOSAIC (*ad hoc* analysis) +	48.6	Not reported	Not reported	0.86 (0.68 to 1.08)	p = 0.196
MOSAIC #	72.0	182/672 (27.1%)	214/675 (31.7%)	0.80 (0.66 to 0.98)	Not reported
MOSAIC %	81.9	182/672 (27.1%)	220/675 (32.6%)	Not reported	Not reported
NSABP C-07 &	34.0	Not reported	Not reported	Not reported	Not reported
NSABP C-07 @	42.5	Not reported	Not reported	Not reported	Not reported
NSABP C-07 ^	67.0	Not reported	Not reported	Not reported	Not reported

* André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004 Jun 3;350(23):2343-51.
+ Gramont Ad, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years. Journal of Clinical Oncology. 2005;23(16S):3501.
# Gramont Ad, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with median follow-up of six years. Journal of Clinical Oncology. 2007;25(18S):4007.
% André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. J Clin Oncol. 2009 May 18.
& Wolmark N, Wieand S, Kuebler J, Colangelo L, Smith R. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07. Journal of Clinical Oncology. 2005;23(16S).
@ Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007 Jun 1;25(16):2198-204.
^ Wolmark N, Wieand S, Kuebler P, Colangelo L, O'Connel M, Yothers G. A phase III trial comparing FULV to FULV+oxaliplatin in stage II or III carcinoma of the colon: Survival results of NSABP C-07. Journal of Clinical Oncology. [2008 ASCO Annual Meeting Proceedings]. 2008;26(15S).
[a] ITT analysis.
[b] Per protocol analysis.
[c] MOSAIC trial, infusional 5FU/LV (de Gramont regimen); NSABP C-07 trial, bolus 5FU/LV (Roswell Park regimen).
[d] Hazard ration <1.0 favors oxaliplatin (plus 5FU/LV).
[e] Because the number of deaths (560) was fewer than anticipated (700), the power to detect de protocol specified effect size was reduced from 0.89 to 0.81.

Disease-free survival

The DFS-estimates of the MOSAIC trial and the NSABP C-07 trial do not differ greatly. Adding oxaliplatin to the 5FU/LV regimens significantly reduces a patient's risk of relapse or death by about 20%. The DFS at 3 years in the MOSAIC trial was 78.2% for FOLFOX compared to 72.9% for FL. Treatment with FOLFOX reduced the relative hazard of relapse or death by 23% (HR 0.77, 95% CI, 0.65-0.91, p=0.002). The DFS at 3 years in the NSABP C-07 trial was 76.1% for FLOX versus 71.8% for FULV. Treatment with FLOX reduced the relative hazard of relapse or death by 20% (HR 0.80, 95% CI 0.69-0.93, p=0.0034) (Shardif, 2008). Four-year en five-year DFS rates are similar. The MOSAIC trial shows five-year DFS rates of 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups respectively (HR=0.80, 95% CI 0.68-0.93, p=0.003) (André, 2009). The NSABP C-07 trial shows four-year DFS rates of 73.2% and 67.0% in the FLOX and FULV groups respectively: an absolute difference of 6.2% (Kuebler, 2007). The impact of oxaliplatin on DFS is even better for the subgroup of patients with stage III disease only. In this case, the absolute difference in four-year DFS rates between the FLOX and FULV groups is 7.8% (68.9% with FLOX, 61.1% with FULV).

The MOSAIC trial shows us the probabilities of DFS events at 5 years for this subgroup: 66.4% with FOLFOX4 and 58.9% with LV5FU2 (André, 2009).

Overall survival

While former results of the MOSAIC trial already showed a (non-significant) survival benefit with the addition of oxaliplatin, longer follow-up confirms this. At a median follow-up of six years, 24.2% of the patients in the LV5FU2 group died, versus 21.5% of the patients in the FOLFOX4 group (HR 0.85, 95% CI 0.71-1.01). When looking at stage III patients only, at a median follow-up of six years, 31.7% of the patients in the LV5FU2 group died, versus 27.1% of the patients in the FOLFOX4 group (HR 0.80, 95% CI 0.66-0.98). Adding oxaliplatin to adjuvant treatment significantly increases the probability that these patients will survive at 6 years by reducing their risk of death by 20% (de Gramont, 2007a; de Gramont, 2007b). The NSABP C-07 results do not provide survival information about the stage III subgroup of patients. For the total patient group, however, results are quite similar to the MOSAIC results. At a follow-up of 67 months, 24.9% of the patients on FULV died, versus 21.6% of the patients treated with FLOX (HR 0.85, 95% CI 0.72-1.01, p = 0.06) (Wolmark, 2008). Although the difference is not yet significant, there seems to be a trend towards improved survival.

Adverse events (toxicities)

Although the efficacy of FL (infusion schedule) appears to be similar to the efficacy of FULV (bolus schedule), their toxicity profiles are different. The same is true for FOLFOX versus FLOX. The rate of severe diarrhoea is 7% with FL versus 32% with FULV. Addition of oxaliplatin increases these rates of severe diarrhoea to 11% with FOLFOX and 38% with FLOX. Thus, although oxaliplatin improves DFS, it also increases the rate of severe diarrhoea. Oxaliplatin is also associated with an increase in other side effects, the most important one being severe peripheral neuropathy. In the NSABP C-07 trial, severe neurosensory toxicity was noted in 8.2% of patients receiving FLOX and in 0.7% of those receiving FULV (P<0.001) (Kuebler, 2007). Different oxaliplatin-containing regimens have different toxicity profiles (Shardif, 2008). For example: more diarrhoea was reported with FLOX than with FOLFOX4, but more severe neurotoxicity was reported with FOLFOX4 (12%) than with FLOX (8.2%) (Kuebler, 2007). The choice between FOLFOX and FLOX (and/or other oxaliplatin-containing regimens) should be made for each patient individually, based on toxicity as well as practical considerations (André, 2004). André et al. show that in the MOSAIC trial, the majority of deaths were a result of relapse or recurrence, with six deaths in each group being a result of adverse events. The incidence of secondary cancers was 5.5% in the FOLFOX4 group and 6.1% in the LV5FU2 group (André, 2009).

Oxaliplatin for elderly patients with colorectal cancer

The results of the MOSAIC trial and three other clinical trials were used to analyse the efficacy and safety of oxaliplatin plus FU/LV in elderly patients. Grade ≥3 adverse events, response rate, progression or relapse free survival, dose-intensity and OS were compared in patients aged younger than 70 years (n=3128) versus patients of at least 70 years old (n=614). Results demonstrate that FOLFOX4 maintains its efficacy and safety ratio in selected elderly patients with colorectal cancer. Old age was associated with slightly higher rates of neutropenia and thrombocytopenia but no other grade ≥3 adverse events. The relative benefit of FOLFOX4 versus control did not differ by age for response rate, progression or recurrence-free survival or OS. These results are not specific to FOLFOX4 in the adjuvant setting. Data from the MOSAIC trial were pooled with results from other clinical trials, testing FOLFOX4 in a combination of adjuvant, primary and secondary care settings (Sargent, 2006; Goldberg, 2006).

Observational studies

In the searches of MEDLINE, EMBASE and Web of Science, a methodological filter was used, aimed at restricting search results to RCTs. Since we were curious about observational research on the clinical effectiveness of oxaliplatin as well, we undertook another search to obtain these studies. PUBMED (including MEDLINE) was searched again for any citation (2005-2009, in English) concerning the clinical effectiveness of oxaliplatin, disregarding research type. 1126 titles were screened. Studies comparing oxaliplatin to (non-FU/LV) therapies, like irinotecan, were excluded. Studies focussing solely or primarily on safety/adverse events were also excluded. No additional, non-RCT studies on the clinical effectiveness of oxaliplatin were found. More specifically: we could not find any observational study on oxaliplatin fulfilling our criteria. Thus, this review provides a complete account of the recent literature on the efficacy of oxaliplatin.

Annex III Systematic review of the cost-effectiveness of oxaliplatin for the adjuvant treatment of colon cancer

Identification of studies

A systematic literature search was performed to identify economic evaluations of oxaliplatin in combination with 5FU/LV as adjuvant therapy in the treatment of completely resected stage III colon cancer. The comparator therapy was adjuvant chemotherapy with an established 5FU/LV-containing regimen.

Sources searched

Pandor et al. published results of an extensive systematic review regarding the clinical effectiveness and cost-effectiveness of oxaliplatin covering the literature until January 2005 (Pandor et al. 2006). In this review publication date limit was set from January 2005 until the month our search was undertaken, April 2009. Six electronic databases were searched, providing coverage of the biomedical and health technology assessment literature: Medline, Embase, Pubmed, Dare-nhs eed-hta, Cinahl, and Web of science. Following Pandor et al. (2006), the search of PUBMED was restricted to the last 180 days to capture recent and unindexed MEDLINE references.

Key word strategies

As reported by Pandor et al. (2006), the key word strategies developed in the review of clinical effectiveness were used, with the RCT methodological filter being replaced by a filter aimed at restricting search results to economic and cost-related studies. The key word strategies used by Pandor et al. (2006) were slightly adapted to fit other versions of the same databases.

Inclusion and exclusion criteria

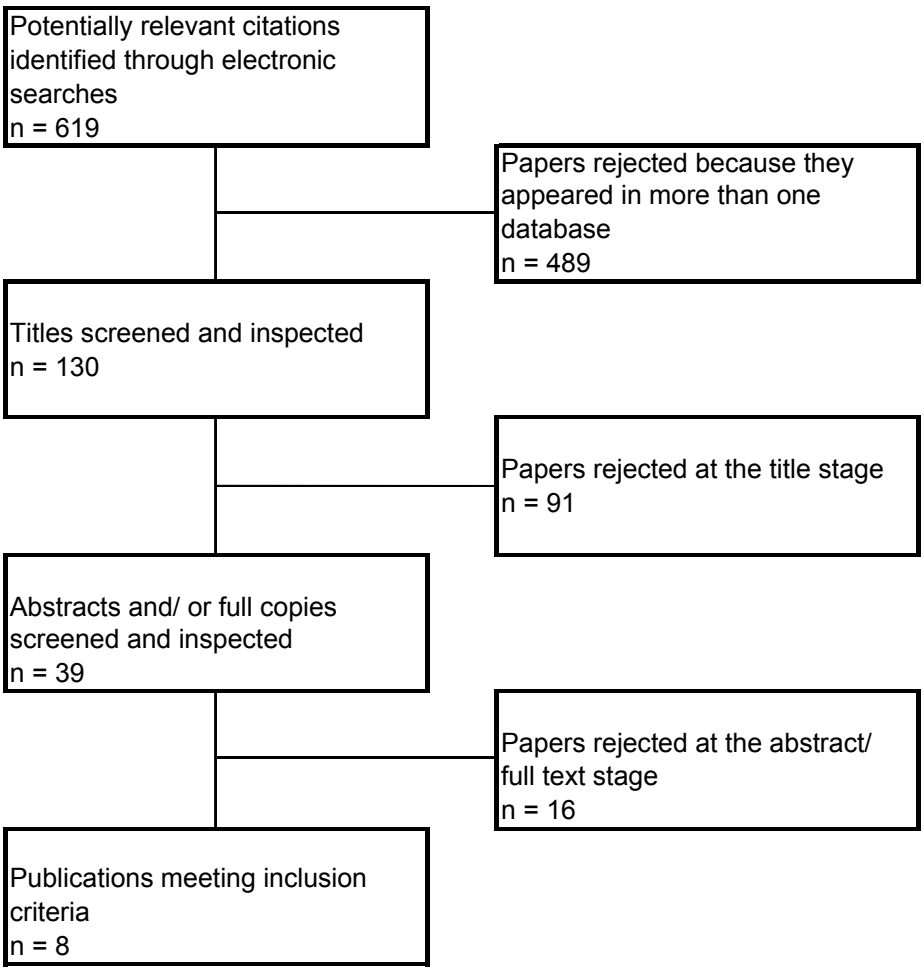
The relevance of the studies was assessed according to the criteria formulated by Pandor et al. (2006). Studies were included if they reported the cost-effectiveness of oxaliplatin in the adjuvant treatment of colon cancer. Only English-language articles that were not incorporated in Pandor et al. were considered. All titles were screened and, when considered possibly relevant, abstracts were evaluated. Based on the abstracts, full copies of relevant papers were obtained.

Results of the cost-effectiveness review

Systematic searches of the various databases resulted in a total of 619 relevant titles, representing 489 unique publications. Based on screening of titles and abstracts, 39 studies were identified. Full papers of these studies were retrieved and assessed in detail. Eight studies met the review criteria and were included. These 8 publications reported on the cost-effectiveness of oxaliplatin. First, an overview of the methods and results of the identified studies is presented. The subsequent section highlights important conclusions and compares the results to the findings of Pandor et al. (2006).

Two of the eight included publications on oxaliplatin were meeting-abstracts of economic evaluations which were later reported in more detail. Both the meeting-abstracts and the more recent full-text articles of the same analyses were included in the review. An overview of the methods and results of all included economic evaluations on oxaliplatin is presented below.

One full-text article, written by Maniadakis et al. (2009), is included in the review, despite the fact that it would formally be excluded according to our inclusion/exclusion guidelines. Maniadakis et al. report on a trial comparing XELOX (capecitabine/oxaliplatin) with FOLFOX6 (5FU/LV/oxaliplatin) in the adjuvant treatment of colorectal cancer patients in Greece. We do report the results of the economic analysis, since it provides an interesting addition to the rest of our review's results.


Potentially relevant citations identified through electronic searches
n = 619
Papers rejected because they appeared in more than one database
n = 489
Titles screened and inspected
n = 130
Papers rejected at the title stage
n = 91
Abstracts and/ or full copies screened and inspected
n = 39
Papers rejected at the abstract/ full text stage
n = 16
Publications meeting inclusion criteria
n = 8

Aballea and colleagues (2007). An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the United Kingdom (UK).

1. Overview

This article evaluates the long-term cost-effectiveness of oxaliplatin in combination with 5FU/LV. It uses patient level data from the MOSAIC trial, which compared oxaliplatin/5FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Aballea et al. restricted their analysis to stage III colon cancer. The primary outcome they estimated was the cost of adjuvant treatment with FOLFOX4 per QALY gained over a lifetime. The perspective of the analysis was that of the UK NHS.

2. Effectiveness analysis

DFS and OS in the first 4 years following randomisation were derived from the MOSAIC trial. As the trial data were not mature, survival in the 5th year was extrapolated from the first four using Weibull distributions. No further relapses were assumed to occur beyond 5 years from diagnosis and survival in subsequent years was assumed to match the general mortality of the UK as observed in standard life tables. The lifetime analyses were curtailed after 50 years.

Utility estimates were obtained from literature. QALYs, DFYs and LY gained were calculated and discounted at 3.5% per annum.

3. Cost analysis

Resource utilisation data were derived from the MOSAIC trial, supplemented with data from the literature and validated by UK clinical experts. Unit costs were sourced from the literature. Costs were for the year 2003. The perspective considered was direct costs to the UK NHS. Costs were discounted at 3.5% per annum.

4. Results and conclusion

See table 4.

Total unit cost per relapse was estimated to be £12.687.

5. Comments

- Analyses were reported for a time horizon of 4 years as well as for a time horizon of 50 years.
- Aballea et al. reported that the availability of relevant values for the calculation of QALYs was limited. Sensitivity analysis suggest that the impact of this parameter on long-term results is modest.
- Eleven sensitivity analyses were carried out to explore the effect of conceivable changes in some of the assumptions and data inputs. Ten of these analyses produced results similar to the base case scenario. One analysis, limiting benefits and costs to short term follow-up, resulted in substantially higher ICERs.
- Uncertainty surrounding efficacy data was explored using a bootstrapping approach.

Aballea and colleagues (2005). Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in the UK.

1. Overview

This meeting abstract outlines a cost-effectiveness analysis of oxaliplatin in combination with 5FU/LV. It uses patient level data from the MOSAIC trial, which compared oxaliplatin/5–FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Aballea et al. restricted their analysis to stage III colon cancer. They estimated the cost of adjuvant treatment with FOLFOX4 per QALY gained over a lifetime. The perspective of the analysis was that of the UK NHS.

2. Effectiveness analysis

The median follow-up of the used MOSAIC trial data was 44.2 months. DFS and OS were estimated up to 4 years from randomisation. A Weibull function was fitted to the DSF-curve and extrapolated to 5 years post-randomisation, with no further relapses assumed to occur beyond this time. A life table was used for survival of the UK general population, adjusting for age and gender. OS beyond 4 years was predicted using the extrapolated DSF-estimates and data on observed survival in relapsing patients.

To estimate QALYs, life-years accrued in both arms were assigned weights depending on occurrence of chemotherapy-related toxicities, disease status, and age. The number of QALYs were discounted at 3.5% per annum.

3. Cost analysis

Costs were calculated from trial data up to relapse, accounting for censoring. Costs for periods after relapse or 4 years were estimated using literature. The cost analysis was performed from a UK NHS perspective. Costs were discounted as well, probably at 3.5% per annum (not reported).

4. Results and conclusion

See table 4.

Expected cost of treatment following relapse was under £11.000.

5. Comments

- Uncertainty was explored using a bootstrapping approach.
- No breakdown of the costs is given.
- A full text article on the analyses outlined in this abstract was published in 2007 and has been discussed previously (37).

Aballea and colleagues (2005). Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in Germany.

1. Overview

This meeting abstract outlines a cost-effectiveness analysis of oxaliplatin in combination with 5FU/LV. It uses patient level data from the MOSAIC trial, which compared oxaliplatin/5–FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Aballea et al. restricted their analysis to stage III colon cancer. They estimated the cost of adjuvant treatment with FOLFOX4 per LY gained over a lifetime. The perspective of the analysis was that of the German public health payer.

2. Effectiveness analysis

The median follow-up of the used MOSAIC trial data was 44.2 months. DFS and OS were estimated up to 4 years from randomisation. A Weibull function was fitted to the DSF-curve and extrapolated to 5 years post-randomisation, with no further relapses assumed to occur beyond this time. A life table was used for the US general population. OS beyond 4 years was predicted using the extrapolated DSF-estimates and data on observed survival in relapsing patients. Outcomes were discounted at 5% per annum.

3. Cost analysis

Costs were calculated from trial data up to relapse, accounting for censoring. Costs for periods after relapse or 4 years were estimated using literature. The cost analysis was performed from a German public health payer perspective. Costs were discounted at 5% per annum.

4. Results and conclusion

See table 4.

Expected cost of treatment following relapse was close to *21.000 in both arms.

5. Comments

- Uncertainty was explored using a bootstrapping approach.
- No breakdown of the costs is given.
- The analysis is presented only in abstract form, hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

Aballea and colleagues (2007). Cost-Effectiveness Analysis of Oxaliplatin Compared With 5-Fluorouracil/Leucovorin in Adjuvant Treatment of Stage III Colon Cancer in the US.

1. Overview

This article evaluates the long-term cost-effectiveness of oxaliplatin in combination with 5FU/LV. It uses patient level data from the MOSAIC trial, which compared oxaliplatin/5–FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Aballea et al. restricted their analysis to stage III colon cancer. The outcome measures they estimated were the cost of adjuvant treatment with FOLFOX4 per LY, DFY and QALY gained over a lifetime. The perspective of the analysis was that of the US Medicare system.

2. Effectiveness analysis

The median follow-up of the used MOSAIC trial data was 44.2 months. DFS and OS were estimated up to 4 years from randomisation. A Weibull function was fitted to the DSF-curve and extrapolated to 5 years post-randomisation. No further relapses were assumed to occur beyond 5 years

from diagnosis and subsequent survival was estimated from life tables, adjusting for age and sex. OS beyond 4 years was predicted from the extrapolated DSF-estimates and observed survival after recurrence. QALYs, DFYs and LYs gained were calculated and discounted at 3% per annum. Utility estimates were obtained from literature.

3. Cost analysis

Lifetime costs of colon cancer-related healthcare resources were estimated from a US Medicare perspective, discounted to present values at a rate of 3% per annum. Costs were calculated from trial data, accounting for censoring. Costs for periods after relapse or 4 years were estimated using literature. 2003 cost data has been used.

4. Results and conclusion

See table 4.

Average standard cost of a recurrence was $61.200 for patients receiving adjuvant 5FU/LV as treatment and $58.800 for patients on adjuvant FOLFOX4.

5. Comments

- ICERs were also calculated for three alternative scenarios, resulting in modest variations in the outcomes.
- A probabilistic analysis was conducted using the bootstrap method to estimate the level of confidence in the cost-effectiveness results, given the sampling variability in the MOSAIC trial data. FOLFOX4 has a 91% to 96% probability of being cost-effective, assuming a willingness-to-pay of $50.000 to $100.000 per QALY gained.

Aballea and colleagues (2005). Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in the UK and Germany.

1. Overview

This meeting abstract outlines a cost-effectiveness analysis of oxaliplatin in combination with 5FU/LV. It uses patient level data from the MOSAIC trial, which compared oxaliplatin/5–FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Aballea et al. restricted their analysis to stage III colon cancer. They estimated the cost of adjuvant treatment with FOLFOX4 per QALY gained over a lifetime. A payer perspective was used.

2. Effectiveness analysis

DFS and OS were estimated up to 4 years from randomisation. A Weibull function was fitted to the DSF-curve and extrapolated to 5 years post-randomisation. No further relapses were assumed to occur beyond 5 years from diagnosis and subsequent survival was estimated from life tables, adjusting for age and gender. Lifetime OS was predicted using DSF and data on observed survival in relapsing patients.
Life-years accrued were assigned weights according to chemotherapy-related toxicities, recurrence and age, to estimate QALYs.
QALYs were discounted at 3.5% and 5% per annum for the UK and Germany respectively.

3. Cost analysis

Costs were estimated from trial data, accounting for censoring; while costs of relapse and subsequent management were estimated from literature. The cost analysis was performed from a payer perspective. Costs were discounted at 3.5% and 5% per annum for the UK and Germany respectively.

4. Results and conclusion

See table 4.

5. Comments

- If the willingness to pay for additional QALYs were £20.000 in the UK and €50.000 in Germany, FOLFOX4 would be cost-effective with probabilities of 95% and 96% in these countries respectively.
- Uncertainty was explored using a bootstrapping approach.
- No breakdown of the costs is given.
- The analysis is presented only in abstract form, hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

Aballea and colleagues (2005). Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in the U.S.

1. Overview

This ASCO (American Society of Clinical Oncology) Annual Meeting Abstract outlines a cost-effectiveness analysis of oxaliplatin in combination with 5FU/LV. It uses patient level data from the MOSAIC trial, which compared oxaliplatin/5–FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Aballea et al. restricted their analysis to stage III colon cancer. They estimated the cost of adjuvant treatment with FOLFOX4 per LYG over a lifetime. The perspective of the analysis was that of the US Medicare system.

2. Effectiveness analysis

The median follow-up of the used MOSAIC trial data was 44.2 months. DFS and OS were estimated up to 4 years from randomisation. A Weibull function was fitted to the DSF-curve and extrapolated to 5 years post-randomisation, with no further relapses assumed to occur beyond this time. A life table was used for survival of the US general population. OS beyond 4 years was predicted using the extrapolated DSF-estimates and data on observed survival in relapsing patients. Health benefits were discounted at 3%.

3. Cost analysis

Costs were calculated from trial data up to relapse, accounting for censoring. Costs for periods after relapse or 4 years were estimated using literature. The cost analysis was performed from a US Medicare perspective, with a discount rate of 3% applied to both costs and health benefits.

4. Results and conclusion

See table 4.

Expected cost of treatment following relapse was estimated at $54.000.

5. Comments

- Uncertainty was explored using a bootstrapping approach.
- No breakdown of the costs is given.
- The analysis is presented only in abstract form, hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

Muszbek and Odhiambo (2007). Cost-utility analysis of oxaliplatin in the adjuvant treatment of colon cancer in Hungary.

1. Overview

This meeting abstract outlines a cost-utility analysis of oxaliplatin in combination with 5FU/LV. It uses data from the MOSAIC trial, which compared oxaliplatin/5–FU/LV (FOLFOX4) to 5FU/LV alone in the adjuvant treatment of stage II and III colon cancer. Muszbek and Odhiambo restricted their analysis to stage III colon cancer. They estimated the incremental cost of adjuvant treatment with FOLFOX4 per QALY, DFY and LY saved over a lifetime. The analysis was accomplished from a Hungarian payer perspective.

2. Effectiveness analysis

The efficacy data of the MOSAIC trial was extrapolated for lifetime. Utilities values were incorporated from published sources. Age and gender specific general mortality rates and utilities were derived from epidemiology data of the Hungarian population and published utilities based on the EQ-5D questionnaire. Outcomes were discounted at 5%.

3. Cost analysis

The analysis was performed from a payer perspective thus, only direct medical costs were taken into account. Resource use was based on Hungarian treatment patterns and unit costs. Costs were discounted at 5%.

4. Results and conclusion

See table 4.

Expected cost of treatment following relapse was close to *21.000 in both arms.

5. Comments

- One-way sensitivity analysis was employed. The results were most sensitive to discount rate, general population data and the cost of chemotherapy.
- No breakdown of the costs is given.
- The analysis is presented only in abstract form, hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

Maniadadakis and colleagues (2009)(22). XELOX versus FOLFOX6 as an adjuvant treatment in colorectal cancer: an economic analysis.

1. Overview

In this economic analysis, XELOX (capecitabine/oxaliplatin) is compared to FOLFOX6 (5FU/LV/oxaliplatin) as adjuvant treatment for operated high risk stage B2 or stage C colorectal cancer patients in Greece. Interim data from a long-term, randomised, multi-centre, controlled, phase III, clinical trial were used. Treatment effectiveness was measured in terms of mean survival in each treatment group. Since survival rate was the same in the two arms, a cost-minimisation analysis was carried out. It was undertaken at a median trial follow-up of over a year, from the perspectives of the National Health Service (NHS), Social Insurance Funds (SIF) and patients in Greece.

2. Effectiveness analysis

Survival was calculated as the time from randomisation to death or loss to follow-up. The Kaplan-Meier method was used to analyse the survival data. The survival rate was 91.9% in the FOLFOX6 arm and 97.6% in the XELOX arm (p = 0.20) and the median survival for the follow up period time was 1.17 and 1.00 years respectively (p = 0.62). It was concluded that there was no difference in the survival rate and the mean survival for the follow up period in the two trial arms.

3. Cost analysis

Patient data were combined with 2008 unit prices to estimate the total cost of patient care, the patients' travelling expenditure and their productivity losses.

4. Results and conclusion

See table 4.

From a NHS as well as from a SIF perspective, mean chemotherapy costs are higher for XELOX than for FOLFOX6, while costs of administration and hospitalisations are higher for FOLFOX6 compared to XELOX. In result, total treatment costs were lower for XELOX compared to FOLFOX6, irrespective of the perspective of the analysis. From patients' perspective, XELOX resulted in a reduction of travelling expenditures and productivity losses.

5. Comments

- Raw data were bootstrapped 5000 times in order to allow statistical testing.
- Quality of life data were not considered.
- The analysis is presented in abstract form, hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

Cost-effectiveness oxaliplatin: comments

New cost-effectiveness information on adjuvant treatment with oxaliplatin published between 2005 and 2009 is limited. MOSAIC trial results were extrapolated and projected on various countries to estimate national cost-effectiveness of FOLFOX4 compared to 5FU/LV alone. Six of the eight articles included in this review were published by Aballea et al.. They were meeting abstracts published in 2005 and full text articles presenting results similar to the results of these 2005-meeting abstracts. The results of Aballea et al. are closely related to the estimates in the manufacturer's submission to the appraisal, already covered in Pandor et al. (2006). Since 2005, NSABP C-07 results have not been used to contribute to the reported MOSAIC-trial based estimates.

Table 4 - Results of the oxaliplatin cost-effectiveness review.

	Treatment	Comparator	Stage	Perspective	Effectiveness Treatment Comparator	Cost	Cost-effectiveness	Conclusion
Aballea et al. 2007	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	UK NHS	Number of LYs gained*: 11.739 10.971 LY difference: 0.768. Number of DFYs gained*: 11.153 9.906 DFY difference: 1.247. Number of QALYs gained*: 9.257 8.577 QALY difference: 0.680	Cost of relapses occurring in year 5 (treatment+follow-up)*: £205 £300 Costs of follow-up for patients relapsing during years 1-4*: £408 £547 Costs of follow-up for patients with no relapse*: £740 £644 Total*: £1352 £1491 Incremental costs*: -£140.	ICER: £4254 per LYG (dominant-dominated) £2620 per DFY gained (dominant-£8108) £4.805 per QALY gained (dominant-£45.658)	FOLFOX4 compares favourable with other accepted interventions in oncology.
Aballea et al. 2005	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	UK NHS	Extrapolated overall life-expectancy: 17.6 years 16.2 years Overall life-expectancy difference: 1.4 years (95% CI unknown). Lifetime extrapolated incremental DFS: 1.99 years (0.63-3.36). Number of QALYs gained: 9.26 8.58 QALY difference: 0.68 (0.08-1.31)	Total lifetime disease- related costs: £18.548 £15.281 Cost difference: £3.267.	ICER: £4.805 per QALY gained (dominant-£45.658)	FOLFOX4 compares favourable with other accepted interventions in oncology.
Aballea et al. 2005	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	German public health payer	Extrapolated overall life-expectancy: 17.51 years 16.18 years Overall life-expectancy difference: 1.3 years (-0.01-2.68). Lifetime extrapolated incremental DFS: 1.98 years (0.65-3.31).	Total lifetime disease- related costs: *23.129 *17.285 Cost difference: *5.844.	ICER: *9.328 per LYG	FOLFOX4 compares favourable with other accepted interventions in oncology.
Aballea et al. 2007	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	US Medicare	Number of LYs gained: 12.34 11.52 LY difference: 0.83.	Mean estimated costs: $56.300 $39.300 Cost difference: $17.000.	ICER: $20.603 per LYG (95% CI unknown)	FOLFOX4 compares favourable with other accepted interventions in oncology.

					Number of DFYs gained: 11.75 10.42 DFY difference: 1.32 Number of QALYs gained: 9.94 9.20 QALY difference: 0.75.		$12.873 per DFY gained (95% CI unknown) $22.804 per QALY gained (95% CI unknown)	
Aballea et al. 2005	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	Payer (UK and Germany)	QALY difference UK: 0.68 (0.08-1.31). QALY difference Germany: 0.57 (0.04-1.10).	Cost difference UK: £3267. Cost difference Germany: £5844.	ICER: UK: £4805 per QALY gained. Germany: €10.199 per QALY gained.	- FOLFOX4 compares favourable with other accepted interventions in oncology. - The difference between countries was largely attributable to the discount rates used rather than differences in organisation of health care.
Aballea et al. 2005	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	US Medicare	Extrapolated overall life-expectancy: 19.99 years 18.33 years Overall life-expectancy difference: 1.66 years (0.10-3.22). Lifetime extrapolated DFS: 2.31 years (0.72-3.89).	Total lifetime disease-related costs: $55.525 $38.093 Cost difference: $17.432.	ICER: $17.900 per LYG	FOLFOX4 compares favourable with other accepted interventions in oncology.
Muszbek and Odhiambo 2007	FOLFOX4 (oxaliplatin/ 5FU/LV)	5FU/LV	III	Payer (Hungary)	LY difference: 0.531. DFY difference: 0.958. QALY difference: 0.455.	Cost difference: HUF 1.310.064 (€5.240).	ICER: HUF 2.468.660 (€9.875) per LYG. HUF 1.367.712 (€5.471) per DFY gained. HUF 2.889.342 (€11.521) per QALY gained.	FOLFOX4 is a cost-effective strategy in Hungary for the postoperative adjuvant treatment of patients with stage III colon cancer compared to the De Gramont protocol.
Maniadakis et al. 2009 (22)	XELOX	FOLFOX6	High risk B2 and C	NHS, SIF and patients in Greece	Survival rate: 97.6% 91.9% (p=0.20) Median survival for the follow up period time: 1.17 years 1.00 years (p=0.62)	Total cost to the NHS: €12525 €17480 Cost savings: €4955 (95% CI €2423-€6524, p<0.001) Total cost to the SIF: €12617 €16240 Cost savings: €3623 (95% CI €1467-5439, p<0.001)	'Comparable' effectiveness, lower cost.	XELOX may be a cost-effective treatment approach for the management of colorectal cancer patients who had surgery in Greece.

FOLFOX4: 2-h infusion of 85 mg/m^2 oxaliplatin simultaneously with 200 mg/m^2 FA followed by a 400 mg/m^2 bolus of 5-FU day 1 followed by a 22-h protracted infusion of 600 mg/m^2 5-FU days 1-2, every 14 days for 12 cycles.
5FU/LV: 2-h infusion of 200 mg/m^2 FA followed by a 22-h protracted infusion of 600 mg/m^2 FU days 1-2, every 14 days for 12 cycles.
* Predicted beyond 4 years, discounted by 3.5% per annum.

References: systematic review of oxaliplatin

Aballea S, Frick M, Diel R, Rosenfeld S, Huppertz E, Sievert M, et al. Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in Germany. Ejc Supplements. 2005 Oct;3(2):182-3.

Aballea S, Chancellor J, Raikou M, Drummond M, Diel R, Frick M, et al. Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in the UK and Germany. Value in Health. 2005 Nov-Dec;8(6):A21-A.

Aballea S, Chancellor J, Raikou M, Drummond M, Weinstein M, Jourdan S, et al., editors. Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in the US; 2005 May 13-17; Orlando, FL. Amer Soc Clinical Oncology.

Aballea S, Chancellor JVM, Raikou M, Drummond MF, Jourdan S, Carita P, et al. Cost-effectiveness analysis of oxaliplatin/5FU/LV in adjuvant treatment of stage III colon cancer in the UK. Ejc Supplements. 2005 Oct;3(2):178-.

Aballea S, Chancellor JV, Raikou M, Drummond MF, Weinstein MC, Jourdan S, et al. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US. Cancer. 2007 Mar 15;109(6):1082-9.

Aballea S, Boler A, Craig A, Wasan H. An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the United Kingdom (UK). Eur J Cancer. 2007 Jul;43(11):1687-93.

Aballea S, Boler A, Craig A, Wasan H. An economic evaluation of oxaliplatin for the adjuvant treatment of colon cancer in the United Kingdom (UK). European Journal of Cancer. 2007 Jul;43(11):1687-93.

Aballea S, Chancellor JVM, Raikou M, Drummond MF, Weinstein MC, Jourdan S, et al. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US. Cancer. 2007 Mar 15;109(6):1082-9.

Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004 Jun 3;350(23):2343-51.

Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. J Clin Oncol. 2009 May 18.

De Gramont A, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years. Journal of Clinical Oncology. 2005;23(16S):3501.

De Gramont A, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with median follow-up of six years. Journal of Clinical Oncology. 2007;25(18S):4007.

De Gramont A, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. FOLFOX4 in adjuvant treatment of colon cancer: Survival results from the mosaic trial. Annals of Oncology. 2007;18:Vii23-Vii.

Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. Journal of Clinical Oncology. 2006 Sep 1;24(25):4085-91.

Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007 Jun 1;25(16):2198-204.

Maniadakis N, Fragoulakis V, Pectasides D, Fountzilas G. XELOX versus FOLFOX6 as an adjuvant treatment in colorectal cancer: an economic analysis. Current Medical Research and Opinion. 2009 Mar;25(3):797-805.

Muszbek N, Odhiambo R. Cost-utility analysis of oxaliplatin in the adjuvant treatment of colon cancer in Hungary. Value in Health. 2007 Nov-Dec;10(6):A337-A.
NICE. Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. 2006.

Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P. The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. Health Technol Assess. 2006 Nov;10(41):iii-iv, xi-xiv, 1-185.

Sargent DJ, Goldberg RM, Bleiberg H, De Gramont A, Tournigand C, Andre T, et al. A pooled safety and efficacy analysis of the FOLFOX4 regimen (bi-monthly oxaliplatin plus fluorouracil/leucovorin) in elderly compared to younger patients with colorectal cancer. Journal of Clinical Oncology. 2006 Jun 20;24(18):150s-s.

Sharif S, O'Connell MJ, Yothers G, Lopa S, Wolmark N. FOLFOX and FLOX regimens for the adjuvant treatment of resected stage II and III colon cancer. Cancer Invest. 2008 Nov;26(9):956-63.

Wolmark N, Wieand S, Kuebler J, Colangelo L, Smith R. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07. Journal of Clinical Oncology. 2005;23(16S).

Wolmark N, Wieand S, Kuebler P, Colangelo L, O'Connel M, Yothers G. A phase III trial comparing FULV to FULV+oxaliplatin in stage II or III carcinoma of the colon: Survival results of NSABP C-07. Journal of Clinical Oncology. [2008 ASCO Annual Meeting Proceedings]. 2008;26(15S).

Annex IV Summary of collected data

Data from the cancer registry

Demographics
- Patient identification number
- Date of birth
- Gender

Data source
- Hospital where patient was diagnosed

Diagnosis / tumor characteristics
- Date of diagnosis
- Location of the tumor
- Differentiation of the tumor
- Number of lymph nodes assessed/ positive
- Disease stage, metastasis stage

Treatment characteristics
- Surgery (yes/no)
- Chemotherapy (yes/no)
- Radiotherapy (yes/no)
- Hospital where patient was treated

Follow-up data
- Survival status
- Date of death or date last known to be alive

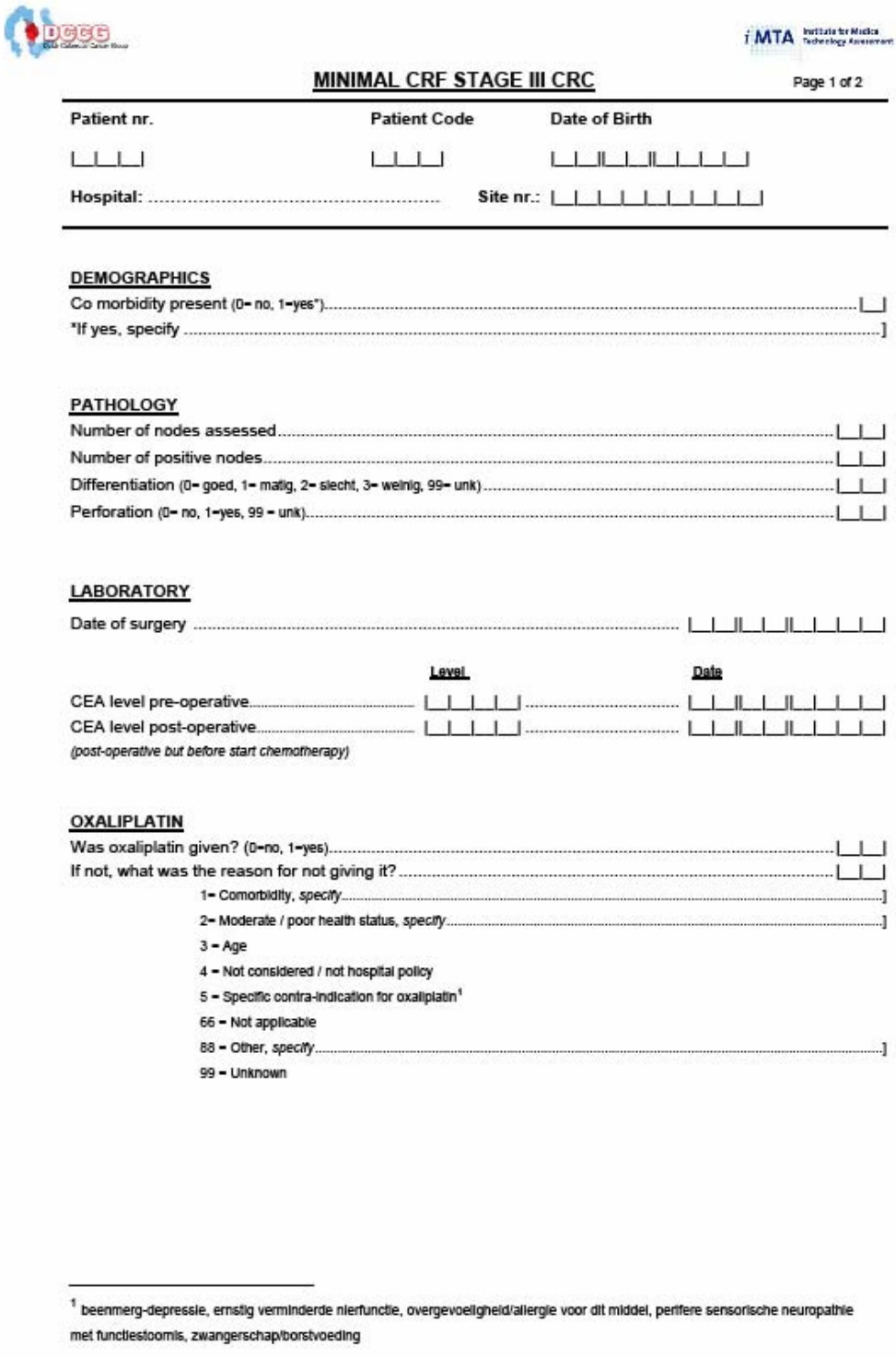
Additional data Minimal CRF

Patient characteristics
Co-morbidity
Tumor characteristics
Number of lymph nodes assessed
Differentiation of the tumor
Perforation of the intestine
Pre-operative carcinoembryonic antigen (CEA) level
Post-operative CEA level
Treatment characteristics
Date of adjuvant chemotherapy administration
Type of chemotherapy given
Reason for not giving oxaliplatin
Follow-up data
Survival status
Date last known to be alive or date of death
Disease status
In case of progression, date of progression
In case of death, main cause of death

Additional data Maximal CRF

Patient characteristics
Height
Weight at start every treatment cycle
Body Surface Area (BSA) at start every treatment cycle
WHO performance status at start every treatment cycle
Treatment characteristics
Prior radiotherapy
Type of chemotherapy given
Planned daily dose
Actual dose received
Dose reduction/ reason for dose reduction
Delay of treatment/ reasons for delay
Total number of cycles given
Major reason for discontinuation chemotherapy
Follow-up data
CEA level/ date of CEA laboratory test
Basis on which progression was diagnosed
Resource use
Number of visits to outpatient clinic
Hospital admissions
Laboratory tests
Radiology
Surgery
Radiotherapy
Other procedures
Concomitant medication

Annex V Summary of minimal CRF Stage III



DCCG

iMTA Institute for Medical Technology Assessment

MINIMAL CRF STAGE III CRC

Patient nr.	Patient Code	Date of Birth
___	___	__-__-____

Hospital: ..... Site nr.: _____

DEMOGRAPHICS

Co morbidity present (0= no, 1=yes*)..... __

*If yes, specify .....]

PATHOLOGY

Number of nodes assessed..... ___

Number of positive nodes..... ___

Differentiation (0= goed, 1= matig, 2= slecht, 3= weinig, 99= unk)..... ___

Perforation (0= no, 1=yes, 99 = unk)..... ___

LABORATORY

Date of surgery ..... __-__-____

	Level	Date
CEA level pre-operative.....	____	__-__-____
CEA level post-operative.....	____	__-__-____

(post-operative but before start chemotherapy)

OXALIPLATIN

Was oxaliplatin given? (0=no, 1=yes)..... ___

If not, what was the reason for not giving it? ..... ___

1= Comorbidity, *specify*.....]

2= Moderate / poor health status, *specify*.....]

3 = Age

4 = Not considered / not hospital policy

5 = Specific contra-indication for oxaliplatin[1]

66 = Not applicable

88 = Other, *specify*.....]

99 = Unknown

[1] beenmerg-depressie, ernstig verminderde nierfunctie, overgevoeligheid/allergie voor dit middel, perifere sensorische neuropathie met functiestoornis, zwangerschap/borstvoeding

MINIMAL CRF STAGE III CRC

Patient nr.	Patient Code	Date of Birth
___	____	__/__/____

ADMINISTRATION of TREATMENT

Date of start (dd,mm,yy)	Chemo (*)	Chemo (*)	Chemo (*)
__/__/__	__	+ __	+ __

Kind of chemotherapy given(*)
1 = 5 FU + Leucovorin
2 = Capecitabine
3 = Oxaliplatin
4 = Bevacizumab
66 = Not applicable
88 = Other, specify*
.....]

SURVIVAL

Date last known to be alive or date of death ..... __/__/____
Disease status (1=CRC free, 2=relapse) ..... __
Date of progression ..... __/__/____
Survival status (1=alive, 2=death) ..... __
In case of death: Main cause of death ..... __

1= Progression of disease
2= Toxicity, *specify*.....]
66= Not applicable
88= Other, *specify*".....]
99= Unknown

COMMENTS

.....
.....
.....
.....
.....
.....
.....
.....
.....

Annex VI Summary of maximal CRF Stage III

ON STUDY FORM STAGE III CRC (1)

Patient nr.	Patient Code	Date of Birth
___	____	_____

GENERAL PATIENT INFORMATION:

Gender (1=male, 2=female) ..... __

Height (cm) ..... ___

PRIOR TREATMENTS (related to this malignancy):

Radiotherapy (0=no, 1=yes) ..... __

If yes, specify site .....]

Specify reason .....]

Date radiotherapy started ..... _____

Date last radiotherapy dose given ..... _____

Total dose (Gy) ..... ___.__

TREATMENT FORM STAGE III CRC (2)

Patient nr.	Patient Code	Date of Birth
|_|_|_|	|_|_|_|	|_|_||_|_||_|_|_|_|

Cycle number .... |_\|_\|

Start date of this cycle .... |_\|_\|\|_\|_\|\|_\|_\|_\|_\|

PATIENT'S CHARACTERISTICS at start of this cycle:

Weight (kg).. |_\|_\|_\|.|_\|

Body surface area (m^2).. |_\|.|_\|_\|

Performance status (WHO).. |_\|

ADMINISTRATION of TREATMENT:

Chemo (*)	Planned total nr. of days	Planned daily dose (mg)	Actual nr. of days	Actual total dose (mg)	Reduction (**)	Reason (***)	Delay (****)	Reason (*****)
|__|	|_|_|	|_|_|_|_|	|_|_|	|_|_|_|_|_|	|_|	|__|	|_|	|__|
|__|	|_|_|	|_|_|_|_|	|_|_|	|_|_|_|_|_|	|_|	|__|	|_|	|__|
|__|	|_|_|	|_|_|_|_|	|_|_|	|_|_|_|_|_|	|_|	|__|	|_|	|__|
|__|	|_|_|	|_|_|_|_|	|_|_|	|_|_|_|_|_|	|_|	|__|	|_|	|__|
|__|	|_|_|	|_|_|_|_|	|_|_|	|_|_|_|_|_|	|_|	|__|	|_|	|__|

Kind of chemotherapy given(*)
1 = 5 FU bolus
2 = 5 FU infusion
3 = Leucoforin
4 = Capecitabine
5 = Oxaliplatin
6 = Irinotecan
7 = Bevacizumab
88 = Other, specify

....]

Dose reduction (**)
0 = No
1 = Yes, reduced >10%

Reason for dose reduction (***)
1 = Hematological toxicity
2 = Gastrointestinal toxicity
3 = Neurological toxicity
4 = Combination
66 = Not applicable
88= Other
Always specify.

....]

Delay of chemotherapy administration (****)
0 = No
1 = Yes, delayed >3 days
2 = Cycle skipped
3 = Stopped

Reason for delay (*****)
1 = Hematological toxicity
2 = Gastrointestinal toxicity
3 = Neurological toxicity
4 = Combination
66 = Not applicable
88 = Other
Always specify

....]

Only if applicable:

Cycle number(s) .... is/are exactly the same as above.

Start dates of these cycles are respectively; 2: |_\|_\|\|_\|_\|\|_\|_\|_\|_\| 6: |_\|_\|\|_\|_\|\|_\|_\|_\|_\|

3: |_\|_\|\|_\|_\|\|_\|_\|_\|_\| 7: |_\|_\|\|_\|_\|\|_\|_\|_\|_\|

4: |_\|_\|\|_\|_\|\|_\|_\|_\|_\| 8: |_\|_\|\|_\|_\|\|_\|_\|_\|_\|

5: |_\|_\|\|_\|_\|\|_\|_\|_\|_\|

END OF TREATMENT FORM STAGE III CRC (3)

Patient nr.	Patient Code	Date of Birth
|__|__|__|__|	|__|__|__|__|	|__|__||__|__||__|__|__|__|

Total number of 5FU/LV or Capecitabine cycles given .... |__|__|

Major reason for discontinuation 5FU/LV or Cap: .... |__|

1 = Ended according to protocol
2 = Progression of disease / relapse / death due to PD*
3 = Toxicity *(+ toxic death)*, ***specify***:..]
4 = Patient's refusal
5 = Intercurrent death (not due to malignant disease or toxicity)*
6 = Lost to follow-up
88 = Other, ***specify***:..]

Total number of Oxaliplatin or Irinotecan cycles given.. |__|__|

Major reason for discontinuation Oxaliplatin or Irinotecan: .... |__|

1 = Ended according to protocol
2 = Progression of disease / relapse / death due to PD*
3 = Toxicity *(+ toxic death)*, ***specify***:..]
4 = Patient's refusal
5 = Intercurrent death (not due to malignant disease or toxicity)*
6 = Lost to follow-up
88 = Other, ***specify***:..]

FOLLOW-UP

	Level	Date
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|
CEA	|__|__|__|__|	|__|__||__|__||__|__|__|__|

END OF TREATMENT FORM STAGE III CRC (3)

Patient nr.	Patient Code	Date of Birth
___	___	__/__/____

SURVIVAL

Date last known to be alive or date of death ..... __/__/____

Disease status (1=CRC free, 2=relapse) ..... __

Date of progression ..... __/__/____

Survival status (1=alive, 2=death) ..... __

In case of death: Main cause of death ..... __

1=Progression of disease

2=Toxicity, *specify* .....]

66=Not applicable

88=Other, *specify*" .....]

99=Unk

In case of progression: Progression diagnosed on the basis of ..... __

1 = Follow-up

2 = Symptoms

66 = Not applicable

88 = Other, specify .....]

COMMENTS

.....

.....

.....

.....

.....

.....

.....

.....

.....

RESOURCE USE FORM STAGE III CRC (4)

Patient nr.	Patient Code	Date of Birth
|_|_|_|	|_|_|_|	|_|_|-|_|_|-|_|_|_|_|

Hospital: ....]

Period (1= adjuvant chemo, 2 = follow-up, 3=post-relapse) ....|_\|

(In period 1 & 2: fill in all the below categories. In period 3: only fill in "visits to outpatient clinic" & "hospitalisations". Period 2 starts 30 days after the last day of chemotherapy. Period 3 starts on the first day of progression.)

Start date of this period .... |_\|_\|-\|_\|_\|-\|_\|_\|_\|_\|

End date of this period.... |_\|_\|-\|_\|_\|-\|_\|_\|_\|_\|

VISITS TO OUTPATIENT CLINIC (only those related to colorectal cancer)

Number of visits.... |_\|_\|

Number of telephone consults.... |_\|_\|

Number of day wards visits .... |_\|_\|

Number of emergency room visits.... |_\|_\|

RADIOTHERAPY

If yes, specify site(s) ....]

Total number of days.... |_\|_\|

Total dose (GY) .... |_\|_\|.|_\|

SURGERY

If yes, specify ....]

LABORATORY

Number during this line.... |_\|_\|

RADIOLOGY

X-ray, number during this line.... |_\|_\|

CT-scan, number during this line .... |_\|_\|

MRI, number during this line.... |_\|_\|

Radionucleide scan, number during this line.... |_\|_\|

PET scan, number during this line .... |_\|_\|

Echo / Ultrasound, number during this line .... |_\|_\|

Other, specify ....]

OTHER PROCEDURES

Colonoscopy, number during this line .... |_\|_\|

Insertion of a porth-a-cath (tunnelled central line), number during this line .... |_\|_\|

Other, specify ....]

RESOURCE USE FORM STAGE III CRC (4)

Patient nr.	Patient Code	Date of Birth
____	____	_____

Period (1= adjuvant chemo, 2 = follow-up, 3=post-relapse) ..... __

Start date of this period ..... _____

End date of this period ..... _____

HOSPITALISATIONS

Date of admission (dd,mm,yy)	Date of discharge (dd,mm,yy)	Days in Intensive Care Unit (*)	Department (**)	Major Reason (***)
_____	_____	____	____	____
_____	_____	____	____	____
_____	_____	____	____	____
_____	_____	____	____	____
_____	_____	____	____	____

Specify (if applicable).....

.....

(*) Days in ICU: If patient did not stay at all in ICU, indicate 0
(**) Department: If patient moved between different departments indicate the department where the patient stayed most of his time.

Days in ICU (*)
0 = none
99 = unknown

Department (**)
1 = oncology/general internal medicine ward
2 = surgery ward
3 = other
99 = unknown

Major reason for admission/visit (***)
1 = administration of chemotherapy
2 = surgery
3 = surgery complications
4 = toxicity
5 = progression of disease
6 = observation/routine follow-up
7 = social problems
8 = palliative care
88 = other, specify
99 = unknown

CONCOMITANT MEDICATION FORM STAGE III CRC (5)

Patient nr. |_|_|_| **Patient Code** |_|_|_| **Date of Birth** |_|_|-|_|_|-|_|_|_|_|

Period 1

Start date of this period.....|_|_|-|_|_|-|_|_|_|_|

End date of this period.....|_|_|-|_|_|-|_|_|_|_|

CONCOMITANT MEDICATION

Only drugs related to treatment of colorectal cancer

Generic drug name	Type (*)	Route (**)	Given (***)	Generic drug name	Type (*)	Route (**)	Given (***)
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|
.....]	|_|	|_|	|_|	.....]	|_|	|_|	|_|

*Type: 1= Analgesic, 2= Antibiotic, 3= Anti-emetic (except steroid), 4= Anti-diarrhea, 5= Laxative, 6= Diuretic, 7= Steroid, 8= Sedative, 9= Anti-coagulant, 10= anti-hypertensiva, 11= Anti-allergic, 12= Antacidum, 13= Growth factors, 14= Transfusion of ery's, 88= Other, specify:.....]
99 = unknown

**Route: 1= Per os, 2= Intravenous, 3= Subcutaneous, 4= Rectal, 5= Transdermal (patch), 6= Cutaneous, 7= Tracheal, 8= Intramuscular, 88=Other, 99= Unknown
Specify other:.....]

***Given 1= Temporary, 2= Ongoing, 3 = Routinely with every cycle, 88 = Other, 99= Unknown
Specify other: .....]

Annex VII Summary of minimal CRF Stage IV

DCCG iMTA Institute for Medical Technology Assessment

MINIMAL CRF IV

Patient seqnr. |__|__|__|__|__|__|__|__|__|__| Patient Code |__|__|__| Date of Birth |__|__|__|__|__|__|__|__|

Hospital: ………………………………

Complete resection of primary tumor (0=no, 1=yes, 9=unk) : |__|

Metastases in (0=no, 1=yes, 9=unk):

Lymph node	|__|	Bone	|__|
Lung	|__|	Ascitis	|__|
Liver	|__|	Pleural effusion	|__|
Skin	|__|	Other soft tissue	|__|
Other	|__| *If other, specify………………………………………………………		

LABORATORY (after surgery, before chemo)

Haematology: Date sample taken………………………………………………|__|__||__|__||__|__|__|__|

WBC / leukocyten (10^9/l)………………………………………………………|__|__|.|__|

Biochemistry: Date sample taken ………………………………………………|__|__||__|__||__|__|__|__|

LDH (U/l)…………………………………………………………………………|__|__|__|__|

Alkaline Phosphatase (U/l)………………………………………………………|__|__|__|

PERFORMANCE STATUS (WHO) (after surgery, before chemo)……………………………………|__|

(0=asymptomatic; 1=symptomatic fully ambulatory; 2=in bed <50%; 3=in bed>50%; 4=bedridden; 9= unknown)

CAIRO STUDY

Has the CAIRO study been considered? (0=no, 1=yes, 9=unknown) ……………………………|__|

Has the CAIRO study been discussed with the patient? (0=no, 1=yes, 9=unknown) ……………|__|

Why didn't the patient participate?………………………………………………………………|__|

1= doesn't fulfil the eligibility criteria, specify ……………………………………………

2= patient refusal, specify ……………………………………………………………

6= not applicable

8= other, specify……………………………………………………………

9= unknown

OXALIPLATIN

Was oxaliplatin given? (0=no, 1=yes) …………………………………………………………|__|

If not, what was the reason for not giving it?……………………………………………………|__|

1= comorbidity, specify ……………………………………………………………

2= moderate / poor health status, specify……………………………………………

3= age

4= not considered / not hospital policy

5= specific contra-indication for oxaliplatin [1]

6= not applicable

8= other, specify………………………………………………………………

9= unknown

[1] beenmerg-depressie, ernstig verminderde nierfunctie, overgevoeligheid/allergie voor dit middel, perifere sensorische neuropathie met functiestoornis, zwangerschap/borstvoeding

MINIMAL CRF IV

Patient seqnr.	Patient Code	Date of Birth
|__|__|__|__|__|__|__|__|__|	|__|__|__|	|__|__||__|__||__|__|__|__|

ADMINISTRATION of TREATMENT:

Line Number	Date of start (dd/mm/yy)	Chemo-1 (*)	Chemo-2 (*)	Chemo3 (*)
|__|	|__|__||__|__||__|__|	|__|	|__|	|__|
|__|	|__|__||__|__||__|__|	|__|	|__|	|__|
|__|	|__|__||__|__||__|__|	|__|	|__|	|__|
|__|	|__|__||__|__||__|__|	|__|	|__|	|__|
|__|	|__|__||__|__||__|__|	|__|	|__|	|__|

Kind of chemotherapy given (*)
1 = 5 FU
2= Leucovorin
3 = Capecitabine
4 = Oxaliplatin
5 = Irinotecan
6 = Bevacizumab
8 = Other, specify*
....]

If patient doesn't continue with next treatment line, reason... |__|

1 = No other treatment options
2 = Patient refusal
3 = No further benefit/poor PS
4 = Death
5 = Surgery
6 = Not applicable
8 = Other, specify*
9 = Unknown

SURVIVAL:

Date last known to be alive or date of death .... |__|__||__|__||__|__|__|__|

Survival status (1=alive, 2=death) .... |__|

In case of death: Main cause of death .... |__|

1= Progression of disease
2= Toxicity, *specify*..]
6 = Not applicable
8= Other, *specify** ....]
9= Unknown

COMMENTS:

....
....
....
....

Annex VIII Summary of maximal CRF Stage IV

DCCG / MTA Institute for Medical Technology Assessment

ON-STUDY FORM IV (1)

Patient seqnr. |__|__|__|__|__|__|__|__|__|__| Patient Code |__|__|__| Date of Birth |__|__|__|__|__|__|__|__|

GENERAL PATIENT INFORMATION

Gender (1=male, 2=female) ..... |__|

Weight (kg) (Wet, cycle 1) ..... |__|__|__|

Height (cm) ..... |__|__|__|

Medical history / Concomitant diseases (0=no, 1=yes) ..... |__|

If yes, specify: .....]

.....]

PRIOR TREATMENTS (related to this malignancy):

Resection of primary tumour (0=no, 1=yes) ..... |__|

If yes, date resection primary tumour ..... |__|__|__|__|__|__|__|__|

Prior resection of metastases (0=no, 1=yes) ..... |__|

Date prior resection metastases ..... |__|__|__|__|__|__|__|__|

Site of resection (1=liver, 2=lung, 8=other, specify .....) ..... |__|

Radiotherapy (0=no, 1=yes) ..... |__|

If yes, specify site .....]

Date radiotherapy started ..... |__|__|__|__|__|__|__|__|

Date last radiotherapy dose given ..... |__|__|__|__|__|__|__|__|

Total dose (Gy) ..... |__|__|.|__|

LABORATORY RESULTS (prior to chemotherapy)

Haematology:

Date sample taken ..... |__|__||__|__||__|__|__|__|

Neutrophils (10^9/l) ..... |__|__|.|__|

Platelets / Trombocyten (10^9/l) ..... |__|__|__|

Hemoglobin (mmol/l) ..... |__|__|.|__|

Biochemistry:

Date sample taken ..... |__|__||__|__||__|__|__|__|

CRP (mg/l) ..... |__|__|__|

Total bilirubin (µmol/l) ..... |__|__|

ASAT (SGOT) (U/l) ..... |__|__|__|

ALAT (SGPT) (U/l) ..... |__|__|__|

Creatinin (µmol/l) ..... |__|__|__|

Albumin (g/l) ..... |__|__|.|__|

CEA ..... |__|__|__|__|

TREATMENT FORM IV (2)

Patient seqnr. |__|__|__|__|__|__|__|__|__|__|

Patient Code |__|__|__|

Date of Birth |__|__|__|__|__|__|__|__|

Line number.....|__|

Cycle number.....|__|__|

First day of this cycle .....|__|__|__|__|__|__|__|__|

PATIENT'S CHARACTERISTICS at start of this cycle:

Weight (kg) ..... |__|__|__|

Body surface area (m^2).....|__|.|__|__|

Performance status (WHO) .....|__|

ADMINISTRATION of TREATMENT

Chemo (*)	Planned total nr. of days	Planned daily dose (mg)	Actual nr. of days	Actual total dose (mg)	Reduction (**)	Reason (***)	Delay (****)	Reason (*****)
|__| |__|__| |__|__|__|__|__| |__|__|__|__|__| |__|__| |__| |__| |__| |__|
|__| |__|__| |__|__|__|__|__| |__|__| |__|__|__|__|__| |__| |__| |__| |__|
|__| |__|__| |__|__|__|__|__| |__|__| |__|__|__|__|__| |__| |__| |__| |__|
|__| |__|__| |__|__|__|__|__| |__|__| |__|__|__|__|__| |__| |__| |__| |__|
|__| |__|__| |__|__|__|__|__| |__|__| |__|__|__|__|__| |__| |__| |__| |__|

Kind of chemotherapy given (*)
1 = 5 FU bolus
2 = 5 FU infusion
3 = Leucovorin
4 = Capecitabine
5 = Oxaliplatin
6 = Irinotecan
7 = Bevacizumab
8 = Other, specify
.....]

Reason for dose reduction (**)
1 = Hematological toxicity
2 = Gastrointestinal toxicity
3 = Neurological toxicity
4 = Combination
6 = Not applicable
8 = Other
Always specify.....]

Dose reduction (**)
0 = No
1 = Yes, reduced >10%

Delay of chemotherapy administration (***)
0 = No
1 = Yes, delayed >3 days
2 = Cycle skipped
3 = Stopped

Reason for delay (****)
1 = Hematological toxicity
2 = Gastrointestinal toxicity
3 = Neurological toxicity
4 = Combination
6 = Not applicable
8 = Other, specify
Always specify.....]

Toxicity

Diarrhoea (0=no, 1=yes) .....|__| Grade.....|__|

Febr. Neutropenia (0=no, 1=yes).....|__| Grade.....|__|

Only if applicable:

Cycle number(s) ..... from this line is/are exactly the same as above.

Start dates of these cycles are respectively; 2: |__|__|__|__|__|__|__|__| 6: |__|__|__|__|__|__|__|__|

3: |__|__|__|__|__|__|__|__| 7: |__|__|__|__|__|__|__|__|

4: |__|__|__|__|__|__|__|__| 8: |__|__|__|__|__|__|__|__|

5: |__|__|__|__|__|__|__|__| 9: |__|__|__|__|__|__|__|__|

END OF TREATMENT-LINE FORM IV (3)

Patient seqnr.	Patient Code	Date of Birth
|__|__|__|__|__|__|__|__|__|	|__|__|__|	|__|__|__|__|__|__|__|__|

Line number.....|__|

Total number of 5FU/LV or Capecitabine cycles given.....|__|__|

Major reason for discontinuation 5FU/LV or Cap:.....|__|

1 = Progression of disease / relapse / death due to PD*
2 = Toxicity (+ toxic death), specify:.....]
3 = Patient's refusal
4 = Intercurrent death (not due to malignant disease or toxicity)*
5 = Lost to follow-up
8 = Other, specify:.....]
9 = Unknown

Total number of Oxaliplatin or Irinotecan cycles given.....|__|__|

Major reason for discontinuation Oxaliplatin or Irinotecan:.....|__|

1 = Progression of disease / relapse / death due to PD*
2 = Toxicity (+ toxic death), specify:.....]
3 = Patient's refusal
4 = Intercurrent death (not due to malignant disease or toxicity)*
5 = Lost to follow-up
8 = Other, specify:.....]
9 = Unknown

Date of first documented progression, *if applicable*.....|__|__|__|__|__|__|__|__|

Date progression treatment line.....|__|__|__|__|__|__|__|__|

If patient doesn't continue with next treatment line, reason:.....|__|

1 = No other treatment options
2 = Patient refusal
3 = No further benefit/poor PS
4 = Death
5 = Surgery
6 = Not applicable
8 = Other, specify*.....]
9 = Unknown

LABORATORY before next treatment line

Haematology: Date sample taken.....|__|__|__|__|__|__|__|__|

WBC / leukocyten (10^9/l).....|__|__|.|__|

Biochemistry: Date sample taken.....|__|__||__|__||__|__|__|__|

LDH (U/l).....|__|__|__|__|

Alkaline Phosphatase (U/l).....|__|__|__|

SURVIVAL FORM IV (4)

Patient seqnr.	Patient Code	Date of Birth
|__|__|__|__|__|__|__|__|__|__|	|__|__|__|	|__|__|__|__|__|__|__|__|

SURVIVAL

Date last known to be alive or date of death ..... |__|__||__|__||__|__|__|__|

Survival status: (1=alive, 2=death) ..... |__|

In case of death: Main cause of death ..... |__|

1 = Progression of disease
2 = Toxicity, specify .....]
6 = Not applicable
8 = Other, specify .....]
9 = Unknown

COMMENTS

.....

.....

.....

.....

.....

.....

.....

.....

RESOURCE USE FORM (5)

Patient seqnr. |__|__|__|__|__|__|__|__|__|__| Patient Code |__|__|__| Date of Birth |__|__|__|__|__|__|__|__|

Hospital:.....]
Line number.....|__|__|
Start date of this line(=date progression from previous line) .....|__|__|__|__|__|__|__|__|
End date of this line(=day before progression from this line).....|__|__|__|__|__|__|__|__|

VISITS TO OUTPATIENT CLINIC (only those related to colorectal cancer)

Number of visits during this line.....|__|__|
Number of telephone consults during this line.....|__|__|
Number of daywards visits during this line.....|__|__|
Number of emergency room visits during this line.....|__|__|

RADIOTHERAPY

If yes, specify site(s) .....]
Total number of days.....|__|__|
Total dose (GY).....|__|__|.|__|

SURGERY

If yes, specify.....]

LABORATORY

Number during this line.....|__|__|

RADIOLOGY

X-ray, number during this line.....|__|__|
CT-scan, number during this line.....|__|__|
MRI, number during this line.....|__|__|
Radionucleide scan / nucleair scan, number during this line.....|__|__|
PET scan, number during this line.....|__|__|
Echo / Ultrasound, number during this line.....|__|__|
Other, specify.....]

OTHER PROCEDURES

Colonoscopy, number during this line.....|__|__|
Insertion of a porth-a-cath (tunnelled central line), number during this line .....|__|__|
Other, specify.....]

RESOURCE USE FORM (5)

Patient seqnr. |__|__|__|__|__|__|__|__|__|__| Patient Code |__|__|__| Date of Birth |__|__|__|__|__|__|__|__|

Line number ..... |__|__|

HOSPITALISATIONS

Date of admission (dd/mm/yy)	Date of discharge (dd/mm/yy)	Days in Intensive Care Unit (*)	Department (**)	Major Reason (***)
|__|__||__|__||__|__|	|__|__||__|__||__|__|	|__|__|	|__|__|	|__|__|
|__|__||__|__||__|__|	|__|__||__|__||__|__|	|__|__|	|__|__|	|__|__|
|__|__||__|__||__|__|	|__|__||__|__||__|__|	|__|__|	|__|__|	|__|__|
|__|__||__|__||__|__|	|__|__||__|__||__|__|	|__|__|	|__|__|	|__|__|
|__|__||__|__||__|__|	|__|__||__|__||__|__|	|__|__|	|__|__|	|__|__|

Specify (all reasons)..... .....

(*) Days in ICU: If patient did not stay at all in ICU, indicate 0
(**) Department: If patient moved between different departments indicate the department where the patients stayed most of his time.

Days in ICU (*)
0 = none
99 = unknown

Department (**)
1 = oncology/general internal medicine ward
2 = surgery ward
88 = other
99 = unknown

Major reason for admission/visit (***)
1 = administration of chemotherapy
2 = surgery
3 = surgery complications
4 = toxicity
5 = progression of disease
6 = observation/routine follow-up
7 = social problems
8 = palliative care
88 = other
99 = unknown

CONCOMITANT MEDICATION FORM STAGE IV CRC (6)

Patient nr.	Patient Code	Date of Birth
|__|__|__|	|__|__|__|	|__|__||__|__||__|__|__|__|

Line number……………………………|__|__|

Start date of this period…………………|__|__||__|__||__|__|__|__|

End date of this period…………………|__|__||__|__||__|__|__|__|

CONCOMITANT MEDICATION

Only drugs related to treatment of colorectal cancer

Generic drug name	Type (*)	Route (**)	Given (***)	Generic drug name	Type (*)	Route (**)	Given (***)
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|
……………………………………….]	|___|	|___|	|___|	……………………………………….]	|___|	|___|	|___|

*Type: 1= Analgesic, 2= Antibiotic, 3= Anti-emetic (except steroid), 4= Anti-diarrhea, 5= Laxative, 6= Diuretic, 7= Steroid, 8= Sedative, 9= Anti-coagulant, 10= anti-hypertensive, 11= Anti-allergic, 12= Antacidum, 13= Growth factors, 14= Transfusion of ery's, 88= Other, specify:……………………………….]
99 = unknown

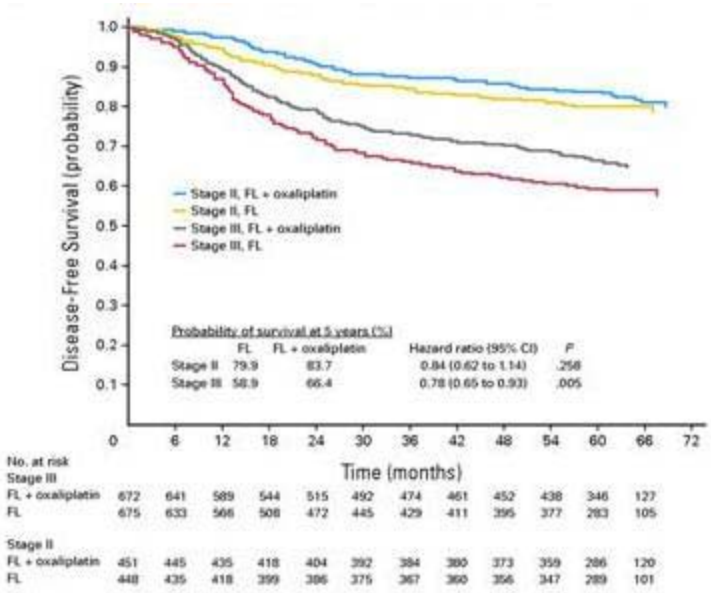
**Route: 1= Per os, 2= Intravenous, 3= Subcutaneous, 4= Rectal, 5= Transdermal (patch), 6= Cutaneous, 7= Tracheal, 8= Intramuscular, 88=Other, 99= Unknown
Specify other:……………………………….]

***Given 1= Temporary, 2= Ongoing, 3= Routinely with every cycle, 88 = Other, 99= Unknown
Specify other: ……………………………….]

Annex IX Kaplan Meier curves derived from MOSAIC trial and PILOT study

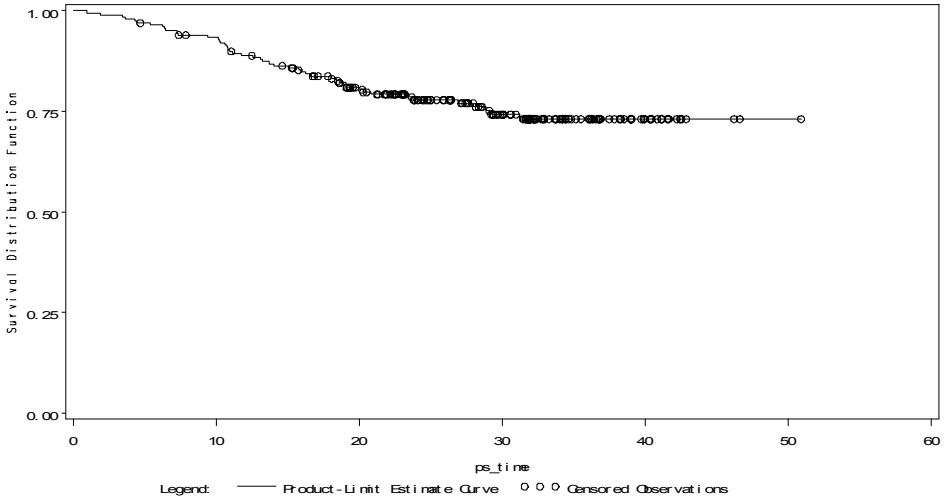
Kaplan Meier curves derived from MOSAIC trial.

Kaplan-Meier estimates of disease-free survival by treatment arm and by stage [2]



Kaplan Meier curves derived from PILOT study.

Kaplan-Meier estimates of disease-free survival of eligible oxaliplatin patients



Annex X Summary of the hospitals that participated

The following hospitals participated in the pilot study:

UMC St Radboud - Nijmegen
Erasmus MC - Rotterdam
LUMC - Leiden
Catharina ziekenhuis - Eindhoven
Mesos Medisch Centrum - Utrecht
Groene Hart ziekenhuis - Gouda
Diakonessenhuis - Utrecht
Gelderse Vallei - Ede
Martini ziekenhuis - Groningen
Reinier de Graaf Gasthuis - Delft
Medisch Centrum Alkmaar - Alkmaar
't Lange Land ziekenhuis - Zoetermeer
Ikazia ziekenhuis - Rotterdam
Nij Smellinghe - Drachten
Slotervaart ziekenhuis - Amsterdam
MC Haaglanden - Den Haag
Isala klinieken - Zwolle
Spaarne ziekenhuis - Hoofddorp
Jeroen Bosch -'s Hertogenbosch

Policy regulations for expensive medicines:

Methodological issues based on pilot outcomes research studies

M.G. Franken[1]

C.W.M. van Gils[1]

J. Gaultney[1]

P.C. Huijgens[2]

A. Steenhoek[1]

W. Redekop[1]

C.A. Uyl- de Groot[1]

[1] Institute for Medical Technology Assessment, Erasmus University, Rotterdam

[2] Department of Haematology, VU University Medical Center, Amsterdam

July 2010

Table of contents

Summary

Introduction

The Dutch policy regulations for expensive hospital medicines require evidence from outcomes research for the assessment of appropriate use and real-world cost-effectiveness of expensive medicines after three years of temporary additional funding. Outcomes research in this particular context is new in Dutch policy making and therefore experience in the application of outcomes research is lacking. The Dutch Health Care Insurance Board published the Guidance for Outcomes Research in collaboration with a working party of experts from relevant disciplines. This report is a practical addendum to this Guidance and provides empirical evidence about methodological issues related to outcomes research.

Method

We investigated methodological issues related to performing outcomes research. These issues can be classified into three categories: 1) study design and data collection; 2) appropriate use and dynamics in daily clinical practice; 3) ability to obtain valid and precise cost-effectiveness estimates. We explored recommendations from the Guidance for Outcomes Research and applied them in two pilot outcomes research studies. Both pilot studies investigated the appropriate use and cost-effectiveness of two expensive hospital drugs (i.e., oxaliplatin and bortezomib) in real-world clinical practice in the Netherlands. Despite the strong recommendations in the Guidance to use a prospective research design, both pilot studies adopted a retrospective study design because they needed to be completed within a short time period.

Results

In both pilot studies, it was possible to collect data on the diffusion of the drug, baseline patient characteristics, application of treatment regimes, dose modifications, treatment related toxicities and direct medical costs. The feasibility of collecting data in an efficient way was challenged by our retrospective research design and by the fact that detailed data were retrieved from hospital medical records. We were able to obtain information on appropriate use of drugs and dynamics of treatment in daily practice. A high degree of treatment variation was revealed in the bortezomib pilot study, whereas the oxaliplatin pilot study (in both stage III colon cancer and metastatic colorectal cancer) showed that

patients were treated in a way that was reasonably similar to the treatment of patients in clinical studies. Subsequently, evidence synthesis using modelling techniques of evidence from outcomes research and evidence from the literature enabled the estimation of a valid and precise incremental outcome measure in the oxaliplatin pilot study for stage III colon cancer. Evidence synthesis was not performed in the oxaliplatin pilot study for metastatic colorectal cancer, but we concluded that synthesis would not result in an important change in the incremental cost-effectiveness ratio. Although evidence synthesis was not performed in the bortezomib study, it is debatable as to whether any synthesis would have led to a valid and precise estimate of the incremental cost-effectiveness of bortezomib versus other treatments.

Discussion

Taking into account the recommendations from the Guidance for Outcomes Research, our pilot studies had some limitations. Use of the retrospective study design resulted in three consequences: no data could be collected on Health Related Quality of Life, only direct healthcare costs were studied, and treatment randomisation was not possible. However, we believe that the retrospective design did not significantly affect the conclusions about the cost-effectiveness of oxaliplatin and bortezomib. In observational studies, irrespective of whether data are prospectively or retrospectively collected, patients are not randomly allocated to different therapies and there is no guarantee that patient groups are comparable. Although disease specific registries cannot resolve all of the drawbacks of data collection, they can help to obtain sufficient numbers of similarly treated patients, enable uniform response criteria, support data collection and thereby facilitate outcomes research. Based on the pilot studies, we conclude that it is feasible for an outcomes research study to provide relevant information about appropriate drug use (who gets it, and what do they receive) as well as the diffusion of the drug and the dynamics of treatment in daily practice. Furthermore, where appropriate, cost-effectiveness estimates should be based on a synthesis of real-world data and other available evidence.

We believe that the findings from the pilot studies are reasonably generalisable to the situation with other drugs on the expensive drug list. However, if outcomes research is going to be used in an optimal way for different types of diseases and treatments, it is necessary to accept flexibility in study characteristics, including the evidence development time frame and the questions that outcomes research should answer.

KEY MESSAGES

Critical success factors

- Appropriate research design available at T=0
- Clearly defined research question
- Research question aims to reveal and/or reduce uncertainty at reappraisal
- Collaboration between regulatory agency, medical field and HTA agencies
- Flexibility and customisation

Drawbacks

- Outcomes research requires financial and time investments
- Observational studies have important bias and confounding issues
- Existing data sources do not provide sufficient data for outcome research requiring additional data collection
- Medical records have important missing values on prognostic factors and outcome measures
- Dynamics in daily practice can compromise the comparability with the clinical registration trial and hinder the ability to estimate a valid and precise cost-effectiveness ratio

Recommendations

- Choice of research design should depend on type of disease, type of drug and expected dynamics in daily practice
- Appropriate time frame depends on type of disease and drug
- Disease specific registries can help to obtain sufficient numbers of similarly treated patients and enable uniform response criteria
- Real-world evidence development on appropriate use should reveal who receives the drugs and how the drug is given in daily practice
- Insight into who receives the drug requires a minimal real-world dataset
- Insight into how the drug is given requires a detailed real-world dataset
- Flexibility is needed regarding the objectives and subsequent requirements of outcomes research
- Where appropriate, cost-effectiveness estimates should be based on a synthesis of real-world data and other evidence

1. Introduction

Since 2006, Dutch policy regulations for expensive hospital drugs require outcomes research. Outcomes research *("uitkomstenonderzoek"*) in this particular context is defined as the collection of data from daily clinical practice in order to assess appropriate use (*"doeltreffende toepassing"*) and real-world cost-effectiveness (*"doelmatigheid"*) of a drug. According to this policy regulation, hospitals are entitled to receive additional funding for enlisted expensive hospital or orphan drugs after regulatory approval for a limited period of time. After three years, a re-appraisal is conducted regarding the real-world therapeutic added value, actual budget impact, appropriate use and cost-effectiveness in daily practice. The decision whether or not to continue financial compensation for hospitals is based on the results of outcomes research.

The outcomes research requirement in this context is new in Dutch policy making; therefore, experience in the application of outcomes research is lacking. Important questions arising in this particular context of outcomes research are: 1) which study design and outcome parameters should be used; 2) what kind of data can be collected; 3) which data sources are available and appropriate; 4) how should dynamics in daily clinical practice be dealt with; 5) in what way can outcomes research lead to valid, precise and generalisable results; 6) what is the impact of the decision to use a three-year time frame; and 7) how to set up outcomes research studies in an efficient and pragmatic way?

The Health Care Insurance Board (CVZ) initiated several research activities to investigate how outcomes research should be conducted. In 2007, the institute for Medical Technology Assessment performed a literature search and, in parallel, experts from relevant disciplines cooperated in a working party with the aim to identify, elaborate and draw up relevant methodological issues. This resulted in the Guidance for Outcomes Research (*"Leidraad voor uitkomstenonderzoek"*) published in December 2008 by the Dutch Health Care Insurance Board (Delwel 2008). To evaluate this Guidance, the institute for Medical Technology Assessment conducted two outcomes research pilot studies. Two different existing databases for identifying eligible pilot patients and two different types of diseases were intentionally selected in order to assess methodological issues related to outcomes research from a broad perspective. The Guidance for Outcomes Research provides recommendations how to perform outcomes research based on literature and expert opinion, whereas the pilot studies present primary information on empirical findings of performing outcomes research while taking into account this Guidance.

The main objectives of this study were 1) to obtain experience with designing and executing outcomes research; 2) to generate knowledge with respect to methodological issues associated with dynamics in daily clinical practice; and 3) to examine the feasibility to obtain valid and precise incremental cost-effectiveness estimates. These objectives address the previously described seven questions that arise in the application of outcomes research in the context of the policy regulations for expensive hospital drugs. This report presents the findings regarding the methodological issues based on the pilot studies; the results of the pilot studies are described in separate reports. These empirical findings are a practical addendum to the Guidance for Outcomes Research.

2. Methods

We investigated methodological issues related to performing outcomes research as required by Dutch policy regulations for expensive hospital medicines. Two pilot outcomes research studies were the core of this research. We choose a pragmatic research design for both pilot studies. Considering the research questions, methodological issues were investigated according to the following three categories: 1) study design and data collection; 2) appropriate use and dynamics in daily clinical practice; and 3) ability to obtain valid and precise cost-effectiveness estimates. For all three categories, we explored the recommendations from the Guidance for Outcomes Research and applied them in the two pilot outcomes research studies.

The pilot studies investigated the appropriate use and cost-effectiveness of two expensive hospital drugs (i.e., bortezomib and oxaliplatin) in real-world clinical practice in the Netherlands. Two different data sources for identifying eligible pilot patients and two different types of drugs were intentionally selected in order to assess methodological issues of outcomes research from a broad perspective. The selection for bortezomib and oxaliplatin was based on factors such as type of drug, disease population (i.e., small versus large), indication, expectations regarding shift in indication, relevant outcome measures (i.e., intermediate endpoints versus final endpoints), expected way of treatment (i.e., trial based versus daily practice) and availability of data sources to identify eligible patients (i.e., trial database versus population based registry).

The bortezomib pilot study examined the appropriate use and cost-effectiveness of bortezomib by exploring how bortezomib was used in Dutch daily practice of relapsed or refractory multiple myeloma and by investigating real-world treatment effects and costs of bortezomib treatment. Pilot patients were selected from patients who relapsed from treatment protocol of a clinical trial (HOVON50) for upfront therapy of multiple myeloma. First, a minimal Case Report Form was obtained from the HOVON50 database in order to identify eligible patients. Second, detailed case reports were retrospectively completed using hospital medical records available from the time of first relapsed or refractory disease until end of follow-up. We investigated the diffusion of bortezomib, application of treatment regimes, dose modifications and treatment-related toxicities. Different adjustment techniques were compared in order to analyse the effect of bortezomib treatment on overall survival. Treatment costs were computed from a healthcare

perspective and costs for individual patients were determined by applying unit costs to individual resource use.

The oxaliplatin pilot study examined the appropriate use and cost-effectiveness of oxaliplatin by exploring how oxaliplatin was used in Dutch daily practice for a) the treatment of stage III colon cancer; and b) the treatment of metastatic colorectal cancer. Real-world effects and costs of oxaliplatin treatment were investigated. The pilot population was identified via the database of the Comprehensive Cancer Centres in the Netherlands and comprised patients diagnosed with stage III colon or stage IV colorectal cancer. First, minimal Case Report Forms were retrospectively completed using hospital medical records. Second, maximal Case Report Forms were used to collect further detailed data for a representative sub-group. We investigated how oxaliplatin was used in daily practice and analysed application of treatment regimes, dose modifications and treatment-related toxicities. Cox multivariate regression techniques were used to analyse the effect of oxaliplatin on disease-free survival (stage III) and overall survival (stage IV). Treatment costs were calculated using the hospital perspective and resource use was assessed per individual patient by means of micro-costing estimates. Additionally, the incremental cost-effectiveness of oxaliplatin in stage III colon cancer was determined using a probabilistic Markov model, synthesising evidence from the pilot study and the pivotal clinical registration trial (MOSAIC).

3. Results

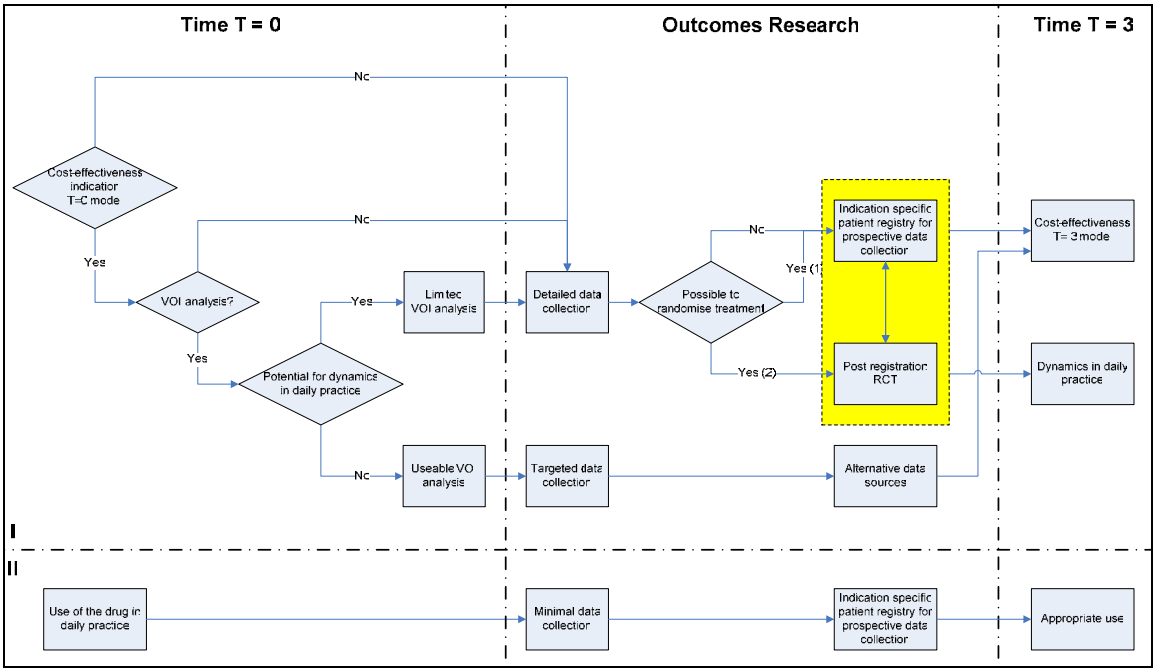
The empirical findings from the two pilot outcomes research studies are presented in three categories: experiences regarding study design and data collection; appropriate use and dynamics in daily clinical practice; and ability to obtain valid and precise of cost-effectiveness estimates.

3.1 Study design and data collection

Study design

The Guidance for Outcomes Research provides a flowchart describing how to set up a pragmatic outcomes research design (Figure 3.1). At time T=0 (i.e., time of the initial assessment), the availability of a T=0 model, Value of Information (VOI) analysis and the expectation for potential dynamics in daily practice determine what data needs to be collected (i.e., detailed data versus target specific data). The Guidance describes several potential data sources for outcomes research, such as ongoing clinical trials, existing patient registries, hospital medical records, and prospective observational patient registries (Delwel 2008). CVZ strongly recommends to use disease or indication specific patient registries in order to prospectively collect data useful for the assessment of both appropriate use and (incremental) cost-effectiveness of an expensive drug at time T=3 (i.e., time for reappraisal after three years) in daily practice. For more detailed information on this flowchart and on pragmatic outcomes research designs, we refer to the Guidance for Outcomes Research (Delwel 2008).

Figure 3.1: Flowchart for a pragmatic research design for outcomes research



Source: Delwel 2008

The pilot studies conducted outcomes research of two expensive hospital drugs (i.e., bortezomib and oxaliplatin). For both studies, an initial cost-effectiveness indication and a T=0 model were not available for the reimbursement decision body due to the year of registration. For the bortezomib pilot study, we anticipated high variation in daily practice and the expected use of a VOI analysis, in order to establish which specific data should be collected, would have had limitations. In contrast, a VOI analysis might have been relevant for the oxaliplatin pilot study. Nevertheless, in both pilot studies a VOI analysis was not performed, but detailed data were collected for the assessment at time T=3 of outcomes research regarding the dynamics in daily practice, appropriate use and cost-effectiveness. In contrast to a prospective study design as recommended by the Guidance, both pilot studies applied a retrospective study design for pragmatic reasons (i.e., time restrictions due to the fact that the empirical evidence as addendum to the Guidance needed to be obtained within a short time period).

In both pilot studies, an existing patient registry was used to identify eligible patients. First, the bortezomib pilot study obtained a minimal dataset from the HOVON50 database in order to identify eligible patients. This is a database of a clinical trial performed in patients younger than 65 years for upfront therapy in multiple myeloma. It contains information on 543 Dutch patients and is a representative sample for younger multiple

myeloma patients in the Netherlands. Data from this database for all 543 Dutch patients could be retrieved immediately after granted permission from the principal investigator. The database provided sufficient information to identify eligible pilot patients. In addition, this database provided information such as the hospital where the patient was treated, age, gender, date of diagnosis, disease stage, treatments, response to treatment, adverse events, time to first progression and survival status. The database often lacked the previous year's follow-up. Therefore, this data source not only restricted our pilot population to younger patients but also the available follow-up limited the ability to identify patients who were treated for relapsed or refractory disease in the last one to two years. Consequently, we were forced to apply lenient inclusion criteria in order to be able to include a sufficient number of patients. Detailed data for 139 pilot patients were retrospectively collected from hospital medical records. Since access to these records required consent from clinicians in each participating hospital, a short time delay (i.e., one to six weeks) before data collection could take place.

Second, the oxaliplatin pilot study used the database of the population based registry of the Comprehensive Cancer Centres in the Netherlands to identify pilot patients. After the request for data was submitted, it took two months to obtain data approval and another six months to receive the data from this registry on 4031 patients diagnosed with stage III colon cancer and 4201 patients diagnosed with stage IV colorectal cancer. The merging process of regional databases into one national database might have prolonged this process. Subsequently, granted permission of physicians was necessary before data could be collected from hospital medical records. The data from this registry offered sufficient information to identify eligible pilot patients and provided information such as hospital where patient was diagnosed, age, gender, date of diagnosis, disease stage, tumour location, degree of malignancy, initial treatment data and survival. This information is in itself not sufficient for outcomes research and extra information was needed for further patient selection, such as type of chemotherapy received. Detailed data (e.g. treatment, effects and costs) were completed using hospital medical records. The required hospital consent did not cause any time delay because we could make use of the network of our close collaboration partners (Dutch Colorectal Cancer Group Nijmegen) which resulted in immediate granted permission in 40 hospitals.

Detailed data collection

In the Guidance for Outcomes Research, it is stated that a pragmatic approach for detailed data collection implies that all relevant data should be collected, such as data on costs, clinical outcomes, patient characteristics, patient reported outcomes and data on comparative treatments (Delwel 2008). The (re-)assessment of the therapeutic value of medicines is based on efficacy, effectiveness, side effects, experience, applicability and user-conveniences (Kuijpers and Toenders 2006). Therefore, relevant outcome measures in outcomes research of cancer treatments are amongst others life-years, quality adjusted life years (QALY), progression-free survival and disease-free survival. The assessment of appropriate use requires data on who receives the drug, how patients are treated and dynamics in daily practice. Real-world cost effectiveness estimations involve data on comparative treatments and the costs of resource use. Although a cost-utility analysis is preferred since quality of life is a relevant outcome measure, a cost-effectiveness analysis may provide essential additional decision making information (Drummond et al. 2005; CVZ 2006; Delwel 2008). Reimbursement decisions are made for the entire population and therefore outcomes research should be conducted from a societal perspective (CVZ 2006; Delwel 2008).

Both pilot studies retrospectively collected detailed data from hospital medical records. The bortezomib study obtained detailed data on baseline patient characteristics, treatment application, treatment effects and resource use for all 139 included patients. Based on the information from the registry of the Comprehensive Cancer Centres on 463 patients (in 19 hospitals) and 433 patients (in 29 hospitals) with stage III colon and metastatic colorectal cancer respectively, the oxaliplatin pilot study retrieved a minimal data set from hospital medical records for 391 and 312 patients respectively. This minimal dataset contained information on baseline characteristics, diffusion of oxaliplatin, considerations for choosing a treatment regime and clinical effects. Additionally, detailed data on dosage schemes, side effects and resource use was obtained for a representative subgroup of 206 and 130 patients with stage III colon and metastatic colorectal cancer respectively.

It was possible to collect data on baseline patient characteristics. For patients treated for stage III colon cancer, we could obtain information on physicians' motivation regarding the choice not to prescribe oxaliplatin in 77% of the patients. For example, age and co-morbidity were identified as independent predictors of non-prescription of oxaliplatin. Nevertheless, information on performance scores, which is thought to influence

both physician choice and prognosis, was missing in nearly half of the patients in both stage III colon and metastatic colorectal cancer. In the bortezomib pilot study, it was hardly ever possible to find information on physicians' motivations regarding treatment choices for relapsed or refractory multiple myeloma disease. Besides that, essential information on prognostic factors was frequently missing. For both pilot studies, information on treatment details, such as received treatments and applied dosages, was usually reported in detailed chemotherapy lists.

Regarding treatment outcomes, the availability of information on intermediate and final endpoints varied per pilot study. In the oxaliplatin study, progression free survival and overall survival were well described for stage III colon and metastatic colorectal cancer respectively. The median follow-up time in the oxaliplatin pilot study was approximately two years. In the bortezomib pilot study, treatment responses were often not reported according to universal standards and the reasons for starting a new treatment regime were not always transparent (i.e., progression, refractory or toxicity). However, effectiveness in life years could be estimated since the median follow-up available was approximately four years due to the fact that data were retrospectively collected for a drug already on the market before it was admitted on the policy list for expensive drugs. Information on treatment related toxicity was only moderate available for both pilot studies. Firstly, toxicities were hardly ever objectively recorded according to a standardised grading system. Secondly, it was not only time consuming to find data on toxicity in both pilot studies, but also difficult to find sufficient information on concomitant medication.

Although treatment costs should be calculated from a societal perspective according to the Guidance for Outcomes Research and Guidelines for Pharmacoeconomic Research, both pilot studies only computed direct medical costs and thus used a healthcare perspective. A retrospective study design limits the feasibility and validity of using costs from a societal perspective. Data on individual resource use was available in patient medical records or in electronic databases. Unit costs (e.g. inpatient hospital days) were based on detailed micro-costing studies including full hospital costs (including overhead costs). It was possible to conduct these micro-costing studies by means of questionnaires for oncologists, haematologist and nurses involved in colon and colorectal cancer and multiple myeloma treatment. The costs of radiotherapy, surgical procedures and medical imaging were available by using tariffs issued by the Dutch Healthcare Authority. Finally, costs for medicines could be obtained from the Pharmaceutical Guideline of the Pharmaceutical Advisory Committee *("Farmacotherapeutisch Kompas"*).

Feasibility of the study design and data collection

Two different patient registries for recruiting pilot patients and two different types of diseases were used to assess methodological issues of outcomes research from a broad perspective. Table 3.1 presents the findings regarding study design and data collection for the bortezomib and oxaliplatin pilot studies in a summarised format. The study design and data collection were feasible for both pilot outcomes research studies. Both pilot studies applied a pragmatic research design set up with the aim to collect data in order to reduce uncertainty at the initial coverage decision and to evaluate appropriate use and real-world cost-effectiveness in Dutch daily practice. The oxaliplatin pilot study was able to examine two years of follow-up within the three year time frame of outcomes research for both stage III colon and metastatic colorectal cancer. The bortezomib pilot study was able to obtain approximately four years of follow-up due to a retrospective study design which assessed overall survival from start of diagnosis and included patients treated for multiple myeloma disease before bortezomib was added to the expensive drug list.

However, the feasibility to collect data in an efficient way was challenged by several reasons. First, our retrospective study design made it impossible to use Health Related Quality of Life (HRQOL) as an outcome measure. We did not collect real-world HRQOL data of pilot patients. Second, our retrospective study design resulted in missing values, such as important prognostic factors and intermediate outcome measures, since they were not always reported in medical records. Third, the existing data sources (HOVON50 database and the population based registry of the Comprehensive Cancer Centres) provided sufficient data to identify eligible pilot patients. However, it was necessary to collect additional data using hospital medical records. Data collection on treatment details and resource use was time consuming for both pilot studies. For example, the required time (up to four hours per patient) for obtaining information on concomitant medication in the bortezomib pilot study forced us to base concomitant medication resource use on detailed data of eighteen patients. For the remaining 121 patients, data was collected in categories of concomitant medication use in set time periods and resource use costs involved were computed on costs per day treated. The oxaliplatin pilot study obtained minimal case report forms for 391 patients with stage III colon cancer in 19 hospitals, and for 312 patients with metastatic colorectal cancer in 29 hospitals. It required one full day of work to collect minimal case reports forms for approximately 25 patients. Additionally, it was possible to retrieve approximately 6 and 4 maximal case reports forms per day for a subsample of 206 patients with stage III colon

and 130 patients with metastatic colorectal cancer respectively. Fourth, many multiple myeloma patients (49%) were treated in more than one hospital. Consequently, over 1700 hours were needed for data collection for the bortezomib pilot in 42 different hospitals in order to collect detailed data for a total of 139 patients.

All data were collected by the principal investigators and medical students under the guidance of these investigators between April 2008 and May 2009. The retrospective study design enabled a relatively short time-period required for data collection. It is important to realise that the time frame to perform outcomes research not only includes the time needed for data collection, but also the time needed to design and implement the study and/or disease registry (including administrative steps such as approval by medical ethics committees) and the time needed for data analysis and reporting. Based on our experiences, we estimate that the study design and implementation phase would involve an average of three to six months (which could in theory be completed before time T=0), whereas the data analysis and reporting phase could require three to six months.

Table 3.1: Experiences regarding study design and data collection

	Pilot bortezomib in MM	**Pilot oxaliplatin in stage III CC**	**Pilot oxaliplatin in metastatic CRC**
Was it possible to collect population-based data?	No, HOVON50 database does not cover the entire Dutch population.	Yes, registry of cancer centres is population based. Random subset was used.	Yes, registry of cancer centres is population based. Random subset was used.
Was it possible to use existing data sources:			
To identify patients	Yes, HOVON50 database.	Yes, registry of cancer centres.	Yes, registry of cancer centres.
For additional data	No, patient-level data was required from hospital medical records.	No, patient-level data was required from hospital medical records.	No, patient-level data was required from hospital medical records.
How long did it take before the data collection could start?	Immediately after granted permission.	8 months	8 months
Study design data collection	Retrospective	Retrospective	Retrospective
Was it possible to collect data regarding:			
Patient baseline characteristics	Yes, but limited availability of performance scores and some other prognostic factors.	Yes, but limited availability of performance scores.	Yes, but limited availability of performance scores and some other prognostic values.
Motivation regarding treatment choice	No, not reported in hospital medical records.	Yes	Yes
Treatment regimes	Yes	Yes	Yes
Treatment dosages and dose modifications	Yes	Yes	Yes
Efficacy (intermediate endpoint)	Moderate: progression not always transparent, treatment response rarely.	Yes, progression free survival.	Yes, overall survival.
Effectiveness (Life years)	Yes, due to retrospective study design.	Limited: due to follow-up.	Yes, sufficient follow-up.
Quality of Life	Not possible given retrospective study design.	Not possible given retrospective study design.	Not possible given retrospective study design.
Adverse events	Somewhat, no standardised grading system.	Yes, but no standardised grading system.	Yes, but no standardised grading system.
Direct medical costs	Yes	Yes	Yes
Indirect cost data	N/A	N/A	N/A
How much follow-up could be obtained within the three-year time frame?	Approximately 4 years, due to retrospective study design and restricted use of appropriate outcome measures.	2 years	2 years
Was is feasible to collect data in an efficient way?			
Minimal data set	Yes, 15-25 per day.	Yes, 25 per day.	Yes, 25 per day.
Maximal data set	No, treatment details and resource use time consuming, required over 1700 hours.	No, 6 per day, treatment details and resource time consuming.	No, 4 per day, treatment details and resource time consuming.
Number of hospitals visited	42 hospitals for 139 patients	19 hospitals for 391 patients	29 hospitals for 312 patients

3.2 Appropriate use and dynamics in daily practice

Appropriate use has two different aspects, namely who receives the drug and how the drug is used in daily practice. The Guidance advises collection of a minimal data set for investigating appropriate use and detailed data for examining dynamics in daily practice, both by means of an indication specific registry that prospectively follows patients (see Figure 3.1). The Guidance for Outcomes Research describes 'dynamics in daily practice' in terms of potential differences in a drug's usage according to the registered indication and the actual application of this drug in daily practice. When assessing the potential for such difference, relevant aspects to be considered include the representativeness of the patient population, diffusion of drugs, patient compliance, shift in indication, off-label use, safety information and under-usage because of high costs (Delwel 2008). It is important that outcomes research reveals these dynamics in daily practice, not only by studying the appropriate use of a drug, but also by investigating treatment patterns, comparative treatments, treatment toxicities, diffusion of the drug and shifts in indication.

As mentioned before, both pilot studies retrospectively collected detailed data from hospital medical records on diffusion of both new drugs, application of treatment regimes, dose modifications, and treatment-related toxicities, effects and costs. It should be noted that the oxaliplatin pilot study only collected detailed data for a representative subgroup of patients regarding treatment details and resource use. Dynamics in daily practice could only be revealed from our detailed datasets. Appropriate use regarding the patient group who receive the drug could be retrieved from our minimal datasets, whereas appropriate use regarding the application of the drug could only be revealed from our detailed datasets. The findings on appropriate use and dynamics in daily practice are presented in two categories: diffusion of oxaliplatin and bortezomib and actual treatment in daily practice. Table 3.2 provides a summary of these results. Experiences regarding the estimation of a valid and precise incremental effectiveness, which is according to the Guidance for Outcomes Research also part of establishing appropriate use, are reported in section 3.3.

Diffusion of oxaliplatin and bortezomib

The degree of diffusion of new innovative hospital medicines can amongst others be influenced by professional guidelines or enlisting the drug under the policy regulations for expensive drugs. Bortezomib was initially recommended as third line therapy, but was

subsequently shifted to use in second line. It was possible to reveal this shift in indication, the majority of patients receiving bortezomib after the indication shift in 2007, received it in second line (56%). It was possible to show the diffusion of bortezomib with the minimal dataset retrieved from the HOVON50 database. Although additional data obtained from the national DBC registration system (DIS) was incomplete, it illustrated an increased usage over the years and showed that all different types of hospitals used bortezomib treatment. It was possible to reveal that physicians needed several years before bortezomib was common practice by means of exploring the diffusion of bortezomib in multiple myeloma patients in the Netherlands with national sales data provided by the manufacturer.

In stage III colon cancer, it was not possible to show a shift in indication towards high risk stage II patients, because we did not collect data for this population. Both pilot studies were not designed to retrieve data on off-label use. Subsequent to the inclusion of oxaliplatin in national guidelines, we observed rapid diffusion of oxaliplatin in stage III disease. Our data showed that oxaliplatin was already completely diffused to all involved hospitals of the metastatic colorectal cancer pilot study.

Treatment in daily practice

Generally, the patient population included in a clinical trial is a homogeneous group and may not be representative for a more heterogeneous patient group receiving the drug in daily practice. This potentially has an impact on the effectiveness and safety of the drug. Therefore, the oxaliplatin stage III colon cancer study compared the baseline characteristics of the pilot patients to the inclusion criteria of the pivotal clinical registration trial (MOSAIC trial). It could be concluded that the majority of patients (82%) receiving oxaliplatin fulfilled these inclusion criteria. Similarly, 71% of the patients included in the metastatic colorectal cancer pilot would have been eligible for the CAIRO-1 study and baseline patient characteristics of these patients were thus comparable. The bortezomib study found some small differences (e.g. age, previous treatment combinations) between the baseline characteristics of pilot patients and patients of the pivotal clinical registration trial (APEX trial). However, although only slight differences were observed in prognostic biomarkers, valid comparisons were difficult as a result of large missing values in the pilot study.

Treatment effectiveness can also differ from the efficacy shown in a clinical trial because drugs can be used differently in daily practice. Therefore, it is important to collect

data on comparative treatments, treatment regimes, dosages schemes, dose modifications and treatment related toxicities. In the stage III oxaliplatin pilot, our data revealed that pilot patients were treated according to professional guidelines. Furthermore pilot patients and MOSAIC study patients showed similar patterns of dose reductions resulting in comparable total cumulative dosages received. We could reveal that haematological- and neurotoxicity were the most frequent reasons for dose modifications or treatment interruptions; however, reasons for lowering a dose or discontinue treatment were not always transparent from medical records.

On the contrary, in the bortezomib pilot there was a high degree of treatment variation and thus the treatment in the comparator arm differed significantly from the clinical registration trial. The majority of multiple myeloma patients received similar bortezomib regimes. However, daily practice patients received on average lower bortezomib dosages (87%) and fewer treatment cycles (4 versus 6) compared to the clinical registration trial. In total, 53% of all bortezomib regimes required a dose modification. We could identify the most common reported toxicity which required a dose modification (i.e., neurotoxicity). However, the reasons for lowering a dose or discontinue treatment were not always transparent in medical records. It could indicate that pilot patients had lower tolerance or more frequently experienced side-effects. On the other hand, it can also mean that physicians are more reluctant to new novel pharmaceuticals.

Both pilot studies concerned hospital drugs administered intravenously in ambulatory care. Therefore, compliance is not expected to be a major issue. Nevertheless, the burden of repetitive treatment boluses requiring ambulatory care could possibly have an impact on the treatment choice both by physician and patient.

Table 3.2: Experiences regarding appropriate use and dynamics in daily practice

	Pilot bortezomib in MM	**Pilot oxaliplatin in stage III CC**	**Pilot oxaliplatin in metastatic CRC**
Diffusion			
Was it possible to reveal the diffusion?	Yes	Yes	N/A (full diffusion at T=0)
Was there an impact of the diffusion rate?	Yes, physicians selected prognostically favourable patients, resulting in incomparable patient groups.	Yes, resulted in incomparable patient groups.	N/A
Shift in indication			
Was it possible to reveal shifts in indication?	Yes, shift from third to second treatment line.	No, no data collected on possible shift towards high risk stage II patients.	N/A
Did indication shifts occur during study period?	Yes	Possibly	No
Was it possible to reveal off-label use?	No, study not designed to collect this data.	No, study not designed to collect this data.	N/A
Pilot population			
Does the treated population in daily practice differ from the population in clinical trials?	No, eligibles: reasonably comparable; all pilot patients: younger and slightly less favourable prognostic laboratory levels.	No: eligibles: comparable.	No, eligibles comparable.
Treatment comparator			
Is treatment comparator in daily practice similar to comparator in clinical trials?	No, high degree of variation in daily practice.	Yes, reasonably similar.	Yes, reasonably similar.
Treatment dosages			
Are professional guidelines similar to dosages prescribed in clinical trials?	Yes	Yes	Yes
Were dosages given according to guidelines?	Yes	Yes	Yes
Are dosages in daily practice similar to dosages in clinical trials?	Slightly lower (13%).	Yes, fewer cycles but higher dosages, similar total cumulative dosage.	Yes, reasonably similar.
Do physicians in daily practice use similar "stopping rules" as suggested in guidelines/ observed in clinical trials?	No, physicians were more likely to discontinue or reduce the dose, reasons not always transparent.	Yes, although physicians were more likely to discontinue or reduce the CAPOX dose, reasons not always transparent.	Not examined.
Appropriate use			
Was it possible to reveal which patients received the treatment?	Yes, required minimal dataset.	Yes, required minimal dataset.	Yes, required minimal dataset.
Was it possible to reveal how the drug is used in daily practice?	Yes, required detailed dataset.	Yes, required detailed dataset.	Yes, required detailed dataset.

3.3 Ability to obtain valid and precise cost-effectiveness estimates

The decision to enlist bortezomib and oxaliplatin on the expensive drug list was based on data obtained in randomised controlled trials. Generally, randomised experiments are considered the gold standard for demonstrating clinical efficacy (Garrison et al. 2007). To demonstrate clinical efficacy, these trials are designed to be internally valid and to result in precise effect measures. Internal validity is the degree to which extent the effect measures represent the actual treatment effect in a comparable group of patients. The main threats to internal validity include confounding, selection bias and information bias. Furthermore, precision of the estimated effects are ensured by large sample sizes of homogeneous patient groups. Despite the fact that a randomised controlled trial provides results on the efficacy of a treatment obtained under ideal experimental conditions, the applicability of these results to the actual effectiveness in a real-world setting can be limited (Drummond et al. 2005). Although real-world observational studies can be subject to biases that threaten internal validity, the degree of heterogeneity in the study population is more representative to the patient population found in daily clinical practice. Consequently, real-world data obtained from outcomes research can lead to a greater degree of external validity and the results are thus more generisable to daily practice compared to clinical trial results. This section describes experiences from the pilot studies regarding evidence obtained within the three-year time frame of outcomes research and elaborates on the precision, internal and external validity and generisability of our pilot outcome measures.

Evidence at Time T=3 from outcomes research and literature

During the three-year time frame of outcomes research (i.e., time T=3 is time for reappraisal after three years), new evidence is generated by outcomes research and by new evidence from literature. In the stage III colon cancer pilot study, we could obtain a median follow-up time of two years for 391 patients. All relevant data could be obtained in the three-year time frame of outcomes research, therefore, we did not experience any time restrictions. Information on essential parameters was available, however, the fast diffusion rate resulted in incomparable patient groups treated and not treated with oxaliplatin and insufficient possibilities to correct for confounding. As a consequence, our pilot study sample size (N=391) was not sufficient to obtain precise results as illustrated by large confidence intervals. In metastatic colorectal cancer, all relevant data could be obtained within the three-year time frame of outcomes research due to the shorter life expectancy of

this patient group. However, there was a large degree of missing data on essential parameters which limited the possibility to fully correct for confounding. On the other hand, considering trial eligible patients only, the oxaliplatin treatment arm and comparator arm seemed comparable regarding baseline patient characteristics, limiting the need for advanced adjustment methods.

In the three year time frame for outcomes research more evidence became available in the literature. For stage III colon cancer, the pivotal clinical registration trial (MOSAIC) had a three years follow-up and provided intermediate endpoints; however, six years extended follow-up data provided information on disease free survival and overall survival estimates. The registration trial did not report on quality of life and only limited information regarding quality of life was published for stage III colon cancer. One study reported utility values for various colorectal cancer disease stages (Ness et al. 1999). In metastatic colorectal cancer, the post registration CAIRO study measured disease specific quality of life by means of the EORTC QLQ-C30 questionnaire. A model to convert these QLC-C30 values into utilities in haematological cancer has recently been developed (Versteegh et al. 2010). The influence of disease type is expected to be small, the validation to colorectal cancer is currently under investigation by the institute for Medical Technology Assessment. Furthermore, some new data regarding costs of oxaliplatin treatment were published. However, these studies only provided cost data of clinical trials and were not based on a Dutch setting.

In the bortezomib pilot study, we did experience time restrictions related to the three-year outcomes research time frame. In the last few years, there were many advances in treatment for multiple myeloma resulting in changes to the professional guidelines, which is reflected by the heterogeneity in our data. Consequently, comparisons that were relevant at time T=0 were less relevant at time T=3 in outcomes research. Overall survival depended on upfront therapy and on the line in which bortezomib was administered, resulting in small sample sizes. Furthermore, essential data on prognostic factors and treatment responses were often missing in medical records. Patient not treated with bortezomib differed in baseline characteristics compared to patients treated with bortezomib. Additionally, a high degree of treatment variation was observed, which made it impossible to identify a treatment comparator. Small patient numbers limited the ability to correct for confounding, and we presumed residual confounding to be present. Consequently, our pilot sample size (N=139) was not sufficient to estimate internally valid and precise outcome measures.

In the three year time frame for outcomes research more evidence became available in the literature. Extended follow-up from the clinical registration trial and from various ongoing studies provided new evidence on efficacy and effectiveness outcomes. Several publications reported more detailed data on toxicity of bortezomib. In contrast, no new information became available on costs of bortezomib treatment as well as no new information regarding treatment related quality of life.

Modelling and evidence synthesis

Randomised controlled trials and observational studies are important sources for economic evaluations. However, it is almost inevitable to synthesise evidence by means of modelling techniques (Buxton et al. 1998; Brennan and Akehurst 2000). The incremental cost-effectiveness of a drug depends amongst others on dosage schemes, indication, patient characteristics and the selected comparator. The Guidance for Outcomes Research suggests to base the real-world incremental cost-effectiveness measure on a reanalysis of the valid and if necessary adapted T=0 model (Delwel 2008).

We developed a probabilistic Markov model for stage III colon cancer by using a NICE model which we adapted and validated for the Dutch setting. Both the clinical registration trial (MOSAIC) and the pilot study assessed disease free survival as primary endpoint. We could use the overall survival from the extended follow-up data of the registration trial to extrapolate intermediate endpoints to life years gained. Furthermore, it was necessary to use the comparator arm of the registration trial in our model since pilot patients not treated with oxaliplatin were not comparable to pilot patients receiving oxaliplatin. The latter group, especially patients eligible for the registration trial, had similar baseline patient characteristics as patients from the registration trial. Evidence synthesis was not performed in the metastatic colon cancer pilot study; we concluded that synthesis would not result in an important change in the incremental cost-effectiveness ratio.

We did not develop a model for the bortezomib pilot study to estimate an incremental cost-effectiveness measure. We only compared the results of the pilot study to the clinical registration trial. We assume that it would have been possible to develop a model, requiring evidence synthesis. Nevertheless, it is debatable as to whether any synthesis would have led to a valid and precise estimate of the incremental cost-effectiveness of bortezomib versus other treatments.

Internal validity and precision of cost-effectiveness estimates

As mentioned before, randomised clinical trials generally provide internally valid and precise outcome measures (such as clinical effectiveness), whereas heterogeneity in outcomes research (such as practice variation and rapid diffusion) can lead to biases that threaten internal validity and precision. We developed a model for stage III colon cancer which made it possible to extrapolate intermediate outcome measures and synthesise evidence from various sources. Therefore, we concluded that it was possible to obtain an internally valid incremental cost-effectiveness ratio of oxaliplatin in stage III disease. Our relatively small confidence intervals showed that we were able to estimate a precise estimate. As mentioned before, evidence synthesis was not performed in the oxaliplatin pilot study for metastatic colon cancer. The pilot patient population was similar to the trial patient population; we could therefore conclude that evidence synthesis would not result in an important change in the incremental cost-effectiveness ratio of oxaliplatin in metastatic colorectal cancer.

In contrast, in the bortezomib pilot study, patients treated with bortezomib were not comparable with patients not treated with bortezomib. Unfortunately, we were not able to correct for confounding and other biases, partly due to small sample sizes. The registration trial compared bortezomib with dexamethasone and many treatment crossovers occurred during the trial. A great deal of treatment variation was seen in our pilot study, and the different treatment combinations and thus the treatment comparator was not similar to the comparators used in the pivotal clinical registration trial or any other clinical trial. Consequently, we could not establish an internally valid and precise incremental cost-effectiveness ratio for bortezomib, let alone produce an estimate that could be compared with a cost-effectiveness ratio based on the pivotal clinical trial results. Although we did not develop a model for this pilot, we suspect that a model would not guarantee the ability to establish a valid and precise estimate of the incremental cost-effectiveness of bortezomib versus other treatments. In future research, we aim to perform evidence synthesis and investigate the feasibility to establish an internally valid outcome measure.

External validity and generisability of cost-effectiveness estimates

In contrast to homogeneous patient groups included in randomised clinical trials, data from outcomes research better represents the heterogeneity found in daily clinical practice and can thus lead to a greater degree of external validity and generisability of the results to the disease population in daily practice. In stage III colon cancer, we could conclude that it

was possible to estimate an externally valid incremental cost-effectiveness ratio based on our representative population-based sample. It should be noted that we did not collect data on stage II disease and thus cannot guarantee an externally valid estimate of oxaliplatin if its usage is shifted to high risk stage II patients since this might affect the incremental cost-effectiveness estimate of oxaliplatin. Furthermore, we were able to estimate an externally valid incremental cost-effectiveness ratio of oxaliplatin in metastatic colorectal cancer since also this pilot population was a representative sample. It is worth to mention that we only included stage IV patients and did not collect data on patients metastasising from stage I, II or III disease. However, we are confident that our study results are generalisable to the entire metastatic colorectal cancer population in the Netherlands based on published literature showing these groups generally to be comparable.

In the bortezomib pilot study, we concluded that our cost-effectiveness estimates expressed in cost per month of survival are highly likely to be externally valid for younger multiple myeloma patients since the heterogeneity found in the pilot data is representative of that found in actual clinical practice of treatment for multiple myeloma. However, due to small sample sizes, incomparability of pilot patients and practice variation we could not estimate an incremental cost-effectiveness ratio of bortezomib compared to other treatments using the patient population included in this study and were therefore unable to estimate an externally valid incremental cost-effectiveness ratio of bortezomib.

Table 3.3. Experiences regarding the ability to obtain valid and precise cost-effectiveness estimates

	Pilot bortezomib in MM	**Pilot oxaliplatin in stage III CC**	**Pilot oxaliplatin metastatic CRC**
Knowledge at time T=3			
Data from outcomes research			
Were missing values on essential parameters present?	Yes, performance status and some other prognostic factors, treatment response and duration.	Yes, performance status.	Yes, performance status and some prognostic laboratory values.
Were treatment and comparator arms comparable regarding baseline characteristics?	No	No	Yes, reasonable.
Was the sample population sufficient to obtain statistical power?	No	No, large confidence intervals.	Yes, reasonable.
Was it possible to correct for confounding?	No	No, due to fast diffusion rate and limited power.	Limited confounding, but too many missing values to fully correct for confounding.
Data from literature			
Was it possible to obtain relevant additional data regarding:			
(incremental) efficacy?	Yes, extended follow-up and various new (ongoing) studies.	Yes, extended follow-up and various new (ongoing) studies.	Yes, CAIRO study simultaneously in similar population.
(incremental) effectiveness?	Yes	Yes	Yes
(incremental) Quality Adjusted Life Years?	No	Moderate, maybe not representative, utility values available.	Yes, indirect utilities (QLC-C30).
toxicity?	Yes	Yes	Yes
(incremental) costs?	No	No	No
Did the three-year time frame of outcomes research lead to serious restrictions?	Yes, rapid advances in treatments.	No	No
Modelling and data synthesis			
Was it necessary to develop a model?	Yes, but not conducted.	Yes, extrapolation from intermediate endpoints.	No
Was it possible to develop a model?	Yes, would require data synthesis, would not guarantee sufficiently valid and precise estimates.	Yes, adapted version of NICE model.	Yes, but not conducted.
Was it necessary to combine data sources?	Yes, but not conducted.	Yes, because of incomparable comparators.	No
Was it possible to combine data sources?	Not examined.	Yes	Yes, but not conducted.
Internal and external validity			
Was it possible to obtain an internally valid incremental cost-effectiveness measure?	Most likely No, but not examined.	Yes	Most likely Yes, but not examined.
Was it possible to obtain a precise incremental cost-effectiveness measure?	Most likely No, but not examined.	Yes	Most likely Yes, but not examined.
Was it possible to obtain an externally valid incremental cost-effectiveness measure?	Most likely No, but not examined.	Yes	Most likely Yes, but not examined.

4. Discussion

Although an early assessment of innovative drugs ensures access to promising drugs, it implies that policymakers face uncertainty when deciding on value for money. In the initial assessment phase, uncertainty may exist on actual clinical therapeutic value, real-world cost-effectiveness, and budget-impact. The Dutch policy regulation aims to reduce the uncertainties about promising but expensive hospital medicines but also ensures undelayed access by evaluating these medicines after a certain number of years of initial coverage. Initially, these policy regulations focused on a three-year time period before a reassessment would take place, but this has been changed to four years. The decision in the re-appraisal phase about whether or not to continue financial compensation for hospitals is based on the results of outcomes research regarding appropriate use and real-world cost-effectiveness. Outcomes research in this particular context is new in Dutch policy making. Therefore, experience in the application of outcomes research is lacking. The Dutch Health Care Insurance Board published the Guidance for Outcomes Research in collaboration with a working party of experts from relevant disciplines. This report is a practical addendum to this Guidance and provides empirical evidence about methodological issues related to outcomes research. We investigated these methodological issues addressing three research categories: 1) study design and data collection; 2) appropriate use and dynamics in daily practice; 3) ability to obtain valid and precise cost-effectiveness estimates. Two pilot outcomes research studies formed the core of this research. These studies investigated the appropriate use and cost-effectiveness of two expensive hospital drugs (i.e., bortezomib and oxaliplatin) in real-world clinical practice in the Netherlands.

Experiences from the pilot studies

Two different data sources for recruiting pilot patients (i.e., trial database versus population based registry) and two different types of diseases (i.e., multiple myeloma and colon and colorectal cancer) were intentionally selected in order to assess methodological issues from a broad perspective. Despite the strong recommendations in the Guidance for Outcomes Research to use a prospective research design, both pilot studies adopted a retrospective study design because they needed to be completed within a short time period to obtain empirical evidence as addendum to the Guidance for Outcomes Research.

Both pilot studies retrospectively collected detailed data from hospital medical records. The studies were able to examine diffusion of the drugs, baseline patient characteristics, application of treatment regimes, dose modifications, treatment related toxicities and direct healthcare costs. A high degree of treatment variation was revealed in the bortezomib pilot study, whereas the oxaliplatin pilot study showed that patients were treated reasonably similar compared to clinical studies. In the oxaliplatin pilot study for stage III colon cancer, evidence synthesis using modelling techniques, evidence from outcomes research and evidence from the literature enabled the estimation of a valid and precise incremental cost-effectiveness ratio. Although evidence synthesis was not performed in the bortezomib study, it is questionable as to whether any synthesis would have led to a valid and precise estimate of the incremental cost-effectiveness of bortezomib versus other treatments due to small samples sizes, incomparability of patients, practice variation and frequent missing values.

Limitations of the pilot studies and implications for outcomes research

Taking into account the flowchart for a pragmatic research design and the recommendations from the Guidance for Outcomes Research, both pilot study designs have their limitations. To begin with, both pilot studies had to apply a retrospective study design because these studies had to be completed within a short time period. The use of a retrospective design meant that some of the techniques and strategies normally available in outcomes research were simply impossible to apply. First, we were unable to collect data on Health Related Quality of Life (HRQOL) since this is inherently impossible in a retrospective study design. Therefore, we cannot provide empirical conclusions about HRQOL data collection in outcomes research. Generally, quality of life is viewed by policymakers as an important factor in health outcomes and its use is also strongly recommended by the Guidance for Outcomes Research. Although we could not collect HRQOL data on Dutch stage III colon cancer patients, we were able to integrate utility data from the literature in our analyses and found that this did not change the conclusions about the cost-effectiveness of oxaliplatin use. Regarding oxaliplatin use for metastatic colorectal cancer, the post registration CAIRO study provided disease specific quality of life data (QLQ-C30) on Dutch patients, which meant that there was little need to collect real-world quality of life data. The situation with HRQOL in relapsed/refractory multiple myeloma patients was different: there is currently no evidence in the literature of any differences in HRQOL between treatment strategies. Evidence synthesis to produce a valid and precise

estimate of the incremental cost-effectiveness of a drug is only as good as the available data. Given the lack of good HRQOL data on multiple myeloma patients, it would have been valuable to have collected real-world HRQOL data to facilitate the assessment of bortezomib.

The Guidance for Outcomes Research includes the recommendation to use a societal perspective in the cost-effectiveness analysis. However, a retrospective study design limits the feasibility of collecting data on all costs, and this limitation may endanger the validity of the cost-effectiveness estimates of a drug. Since both pilot studies adopted a retrospective design, we cannot report any findings regarding the application of a societal perspective in outcomes research. A prospective study design would have made it possible to use health and labour questionnaires to assess costs of absence from work and productivity losses of paid and unpaid work. However, we expect that the inclusion of productivity costs would have had limited impact on the results of our pilot studies because multiple myeloma, colon and metastatic colorectal cancer most often occur in the elderly population. Although the bortezomib pilot study only included younger multiple myeloma patients, the majority of multiple myeloma patients do not work due to the disease severity and they will not return to work after treatment. We did not collect data on direct non-medical costs (such as travel costs), even though this might have been possible by using postal codes. Although we realise that the exclusion of indirect healthcare costs and (in)direct non-medical costs might have affected our results somewhat, we believe that their exclusion did not significantly influence the conclusions about the cost-effectiveness of oxaliplatin and bortezomib.

Another consequence of a retrospective study design is the inability to randomly allocate patients to receive a specific treatment. This meant that even though the flowchart in the Guidance for Outcomes Research refers to an option for a post registration RCT, this option was simply not possible in our pilot studies. Therefore, we can only speculate about its potential added value. If a prospective study design had been applied in the bortezomib study, it could have been theoretically possible to randomise multiple myeloma patients in daily practice to receive either bortezomib or lenalidomide (i.e., another expensive (orphan) drug for the same indication). We believe that RCTs should be seriously considered when there are new indications of a drug (e.g. the CAIRO post-registration study for oxaliplatin in metastatic colorectal cancer).

A retrospective design can result in greater problems with bias and confounding compared to a prospective design. However, selection bias was minimised by our use of

representative samples of the Dutch patient population (i.e., HOVON50 database and Comprehensive Cancer Centres registry) and information bias was addressed by additionally collecting detailed data from hospital medical records. Consequently, we believe that the retrospective research design did not significantly affect our conclusions about the real-world cost-effectiveness of oxaliplatin and bortezomib.

Although a retrospective design has its shortcomings, it also has its advantages. It requires less time to retrospectively collect data because data can be retrieved at one time instead of many points in time. In addition, the time required to set up the outcomes research study (e.g. research design, permission from medical ethics committees, collaboration physicians) does not reduce the amount of time that is available for data collection. Both pilot studies revealed that a retrospective design already requires a significant amount of time for data collection. Additionally, the bortezomib study showed that if data is retrospectively collected, retrieved follow-up of patients can be extended beyond the three-year time frame. Although a prospective research design offers greater control over data collection, all observational designs rely on information that is provided by others (e.g. physicians). For example, the Population HAematological Registry for Observational Studies (PHAROS) is an observational population based registry for haematological diseases that was created to facilitate outcomes research. This registry aims to monitor dynamics in daily practice, treatment regimes and survival. Although the PHAROS registry prospectively collects patient level data, we expect that missing values (e.g. regarding essential prognostic factors, universal response criteria) are still present since data are collected from medical records by staff at the Comprehensive Cancer Centres. Consequently, it is not only necessary to set up an appropriate prospective registry collecting essential data but also to involve physicians who treat the patients and report in medical records. Nevertheless, registries may help to obtain information on a sufficient number of patients and ensure the usage of uniform response criteria and standardised toxicity grading systems.

One other limitation about the pilot studies is that a value of information (VOI) analysis was not performed. A VOI analysis provides information on the costs forgone due to incorrect decision-making under uncertainty (Claxton et al. 2004). It was expected that dynamics in daily practice of multiple myeloma would have limited the use of a VOI analysis in the bortezomib pilot study. However, it is possible that a VOI analysis could have been relevant for the oxaliplatin pilot study, particularly in stage III disease. We are therefore currently investigating in another study if a VOI analysis in the stage III colon

cancer pilot study could have resulted in targeted data collection and thereby improved the efficiency of the cost-effectiveness analysis study.

Other considerations regarding outcomes research

It is generally acknowledged that an appropriate research design to reduce the uncertainty at the initial coverage decision should clearly define the specific aim of evidence development (Tunis and Pearson 2006; Carbonneil, Quentin, and Lee-Robin 2009; Towse and Garrison 2010; Menon et al. 2010; McCabe et al. 2010; MacLeod and Mitton 2010; Trueman, Grainger, and Downs 2010). Carbonneil et al. (2009) identified four critical success factors for access with evidence generation: coordination between decision-makers, medical and HTA agencies; methodological guidance; funding; and an implemented regulatory framework. Our pilot studies provide empirical findings to strengthen the methodological guidance. Since we only conducted pilot studies for two expensive drugs, we can only base our conclusions on these two studies. There is no consensus in the literature on the time frame required for evidence collection (Hutton, Trueman, and Henshall 2007; Tunis and Chalkidou 2007; Drummond, Manca, and Sculpher 2005). The oxaliplatin pilot study showed that a three year frame was sufficient if extended follow-up from the pivotal registration trial was used in addition to our real-world pilot data. In contrast, the bortezomib pilot revealed that advances in treatment and shifts in indication limited the relevance of the uncertainty at T=0 for the decision to be made at T=3. As result, the degree of uncertainty about oxaliplatin at time T=0 was reduced by time T=3, whereas the degree of uncertainty about bortezomib possibly increased between T=0 and T=3. This implies that both an appropriate research design for outcomes research and an appropriate time-frame can depend on the type of disease and the treatment under investigation. If this is the case, then the regulatory reimbursement agency will need to be more flexible regarding the quality of outcomes research study plans. It is important to realise that the time frame to perform outcomes research not only includes the time needed for data collection, but also the time needed to design and implement the study and/or disease registry (including administrative steps such as approval by medical ethics committees) and the time needed for data analysis and reporting. Based on our experiences, we estimate that the study design and implementation phase would involve an average of three to six months (which could in theory be completed before time T=0), whereas the data analysis and reporting phase could require three to six months.

Generalisability to other expensive hospital medicines

We investigated methodological issues related to the outcomes research requirement of the policy regulations for expensive medicines addressing three research categories: 1) study design and data collection; 2) appropriate use and dynamics in daily practice; 3) ability to obtain valid and precise cost-effectiveness estimates. Although we only conducted pilot studies for two expensive drugs, we assume that our findings are most likely generalisable to other (orphan) drugs enlisted on the policy regulation for expensive hospital medicines. This is due to the fact that we intentionally selected two different types of diseases to assess these methodological issues from a broad perspective. Many of the enlisted expensive medicines are to be used for different types of cancer, but there are also other drugs on the list which are indicated for other diseases such as rheumatoid arthritis, macular degeneration, multiple sclerosis, severe asthma and multiple organ failure sepsis. We expect that the limitations of a retrospective research design can have a different impact on different diseases. In our pilot studies we believe that our retrospective research design did not significantly affect our research outcomes. However, survival is an essential outcome in haematological and colorectal cancer patients, whereas quality of life is a more appropriate primary outcome measure for other diseases such as rheumatoid arthritis. Consequently, appropriate outcome measures (e.g. intermediate versus final endpoints) are important decision factors for the study design (retrospective versus prospective). Additionally, we concluded that the use of a healthcare sector perspective did not significantly affect our results about the cost-effectiveness of oxaliplatin or bortezomib since we expected that treatment with these drugs would not have an important impact on indirect health care costs and (in)direct non-medical costs. However, it is possible that treatment with expensive hospital medicines could have an impact on indirect health care costs and (in)direct non-medical costs in other disease types (e.g. rheumatoid arthritis, multiple sclerosis). Therefore, it is important to have a comprehensive understanding of the disease and the treatment effect in order to design an appropriate outcomes research study. We believe that it is possible to collect real-world data that provides evidence on appropriate use and dynamics in daily practice for any of the listed drugs. However, the data needed for this type of evidence may include detailed data that need to be retrieved from hospital medical records. Regarding orphan drugs, it might be necessary to set up an international registry in order to obtain a sufficient amount of real-world data. One example of such a registry is the Pompe Registry to track the natural course of Pompe disease. As mentioned before, we suggest that the most appropriate

time frame for evidence development will depend on the treatment and the treatment indication. Furthermore, it is essential to realise that it might not be feasible to estimate a valid and precise incremental cost-effectiveness ratio for some indications, even if data are combined from various sources. This necessitates flexibility from the regulatory decision authority when assessing the quality of outcomes research proposals.

Recommendations

In the context of Dutch policy regulations for expensive medicines, the aim of outcomes research is to reduce the uncertainty about the cost-effectiveness of a drug, which exists at the time of the initial coverage decision (i.e., T=0). Based on our findings in both pilot studies, we recommend that the study plan should include a clear statement of how the data collection will reduce uncertainty for decision makers at the reappraisal time. Comprehensive knowledge of the disease and the treatment, early modelling and/or VOI can assist in the identification of important knowledge gaps. This implies that policy regulations in outcomes research require flexibility. As both of our pilot studies revealed, there is not just one formula for evidence building when it comes to drugs for different diseases and indications; customisation is necessary. Furthermore, we recommend that the Guidance for Outcomes Research should further refine the definition of appropriate use. Establishing evidence on appropriate use should address two research questions: who receives the drug and how is the drug used in daily practice? It is important to realise that the first question ("the who") can require a minimal data set whereas the second one ("the how") will require detailed data. Although appropriate use of a drug influences the degree of effectiveness of that drug in daily practice, we suggest that an incremental cost-effectiveness measure should be based on a synthesis of the evidence drawn from different sources, including real-world experiences with the drug, extended follow-up results from the pivotal clinical registration trial and other evidence available from the literature. Outcomes research studies provide valuable information about the application of the drug in daily practice and thereby enable assessments of appropriate use and dynamics in daily practice. However, in order to obtain a valid and precise incremental cost-effectiveness measure, real-world evidence should be synthesised with evidence from randomised controlled trials by using modelling and statistical techniques. It is essential to realise that some indications might have many treatment advances during the first three years that a drug can be used for a particular indication, and these advances will result in a high degree of dynamics (i.e., rapid changes in treatment) and practice

variation. We therefore suggest that it might be impossible to establish sufficiently valid and precise estimates of the incremental effectiveness and cost-effectiveness of a drug for some indications. As a consequence, we recommend that a more customised outcomes research design is required if a high level of dynamics in daily practice is expected in the first three years after a drug has been added to the expensive medicines list.

Finally, active physician participation and patient registries can help to obtain sufficient numbers of similarly treated patients, enable uniform response criteria, support data collection and thereby facility outcomes research. Some registries may even contain patient-related outcomes such as HRQOL. However, while disease or indication specific registries can facilitate the collection of relevant data, they cannot resolve all of the drawbacks of data collection from medical records. This is another reason why the most appropriate outcomes research study plan for a particular drug requires a good understanding of the merits and shortcomings of the different data sources.

References

Brennan, A., and R. Akehurst. 2000. Modelling in health economic evaluation. *PharmacoEconomics* 17, (5): 445-59.

Buxton, M. J., M. F. Drummond, B. A. Van Hout, R. L. Prince, T. A. Sheldon, T. Szucs, and M. Vray. 1998. Modelling in ecomomic evaluation: An unavoidable fact of life. *Health Economics* 6, (3): 217-27.

Carbonneil, C., F. Quentin, and S. H. Lee-Robin. 2009. A common policy framework for evidence generation on promising health technologies. *International Journal of Technology Assessment in Health Care* 25, (S2): 56-67.

Claxton, K., L. Ginnelly, M. Sculpher, Z. Philips, and S. Palmer. 2004. A pilot study on the use of decision theory and value of information analysis as part of the NHS health technology assessment programme. *Health Technol Assess* 8, (31): 1-103.

CVZ. 2006. *Richtlijnen voor farmaco-economisch onderzoek, geactualiseerde versie.* Diemen: College voor zorgverzekeringen, 25001605.

Delwel, G. O. 2008. *Leidraad voor uitkomstenonderzoek.* Diemen: College voor Zorgverzekeringen, 270.

Drummond, M., A. Manca, and M. Sculpher. 2005. Increasing the generalizability of economic evaluations: Recommendations for the design, analysis, and reporting of studies. *International Journal of Technology Assessment in Health Care* 21, (02): 165-71.

Drummond, M. F., M. J. Sculpher, G. W. Torrance, B. J. O'Brien, and G. L. Stoddart. 2005. *Methods for the economic evaluation of health care programmes*Oxford University Press, USA.

Garrison, L. P., P. J. Neumann, P. Erickson, D. Marshall, and C. D. Mullins. 2007. Using real-world data for coverage and payment decisions: The ISPOR real-world data task force report. *Value in Health* 10, (5): 326.

Hutton, J., P. Trueman, and C. Henshall. 2007. Coverage with evidence development: An examination of conceptual and policy issues. *International Journal of Technology Assessment in Health Care* 23, (04): 425-32.

Kuijpers, M. R., and W. G. M. Toenders. 2006. *Procedure beoordeling intramurale geneesmiddelen.* Diemen: College voor Zorgverzekeringen, 241.

MacLeod, S., and C. Mitton. 2010. We know accurately only when we know little. *PharmacoEconomics* 28, (2): 105-7.

McCabe, C. J., T. Stafinski, R. Edlin, and D. Menon. 2010. Access with evidence development schemes: A framework for description and evaluation. *PharmacoEconomics* 28, (2): 143-52.

Menon, D., C. J. McCabe, T. Stafinski, and R. Edlin. 2010. Principles of design of access with evidence development approaches. *PharmacoEconomics* 28, (2): 109-11.

Ness, R. M., A. M. Holmes, R. Klein, and R. Dittus. 1999. Utility valuations for outcome states of colorectal cancer. *The American Journal of Gastroenterology* 94, (6): 1650-7.

Towse, A., and L. P. Garrison. 2010. Cant get no satisfaction? will pay for performance help?: Toward an economic framework for understanding performance-based risk-sharing agreements for innovative medical products. *PharmacoEconomics* 28, (2): 93-102.

Trueman, P., D. L. Grainger, and K. E. Downs. 2010. Coverage with evidence development: Applications and issues. *International Journal of Technology Assessment in Health Care* 26, (01): 79-85.

Tunis, S. R., and K. Chalkidou. 2007. Coverage with evidence development: A very good beginning, but much to be done. commentary to hutton et al. *International Journal of Technology Assessment in Health Care* 23, (04): 432-5.

Tunis, S. R., and S. D. Pearson. 2006. Coverage options for promising technologies: Medicare's' coverage with evidence development'. *Health Affairs* 25, (5): 1218.

Versteegh, M. M., A. Leunis, J. J. Luime, M. Boggild, C. Uyl-de Groot, and E. A. Stolk. 2010. Mapping QLQ-C30, HAQ and MSIS-29 on EQ-5D: Influence of overlap in dimensions. *Submitted*.