The cost-effectiveness of pomalidomide for treating patients with relapsed multiple myeloma refractory to both lenalidomide and bortezomib

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Abbreviations

ASCT	**Autologous stem cell therapy**
AE	**Adverse event**
BNF	**British National Formulary**
BOR	**Bortezomib**
CEA	**Cost-effectiveness analysis**
CEAC	**Cost-effectiveness acceptability curve**
C.I.	**Confidence interval**
DEX	**Dexamethasone**
DCEP	**Dexamethasone, cyclophosphamide, etoposide and cisplatin**
ICER	**Incremental cost-effectiveness ratio**
HCHS	**Hospital & community health services**
HR	**Hazard ratio**
iMID	**Immunomodulatory drug**
KM	**Kaplan-Meier**
LEN	**Lenalidomide**
LYG	**Life years gained**
MM	**Multiple myeloma**
MGUS	**Monoclonal gammopathy of undetermined significance**
MLE	**Maximum likelihood estimation**
NHS	**National Health Services**
NICE	**National institute for clinical excellence**
OS	**Overall survival**
OSA	**One-way sensitivity analysis**
PFS	**Progression-free survival**
PPS	**Post-progression survival**
POM	**Pomalidomide**
PSA	**Probabilistic sensitivity analysis**
QALY	**Quality-adjusted life year**
QoL	**Quality of life**
rrMM	**Relapsed refractory multiple myeloma**
SMM	**Smoldering multiple myeloma**
U	**Utility**
UK	**United Kingdom**
VAT	**Value added tax**
WTP	**Willingness-to-pay**

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Summary

Background

Multiple myeloma (MM) is a neoplastic disease of plasma and the second most common hematological cancer. The malignancy is incurable, but the introduction of both lenalidomide and bortezomib has improved survival outcomes for patients with MM. Now there is a need for a treatment for patients who become refractory to lenalidomide and bortezomib. Pomalidomide has shown efficacy and acceptable safety, but since health care resource are scarce, it is important to know if pomalidomide is 'good value for money' using common benchmarks for cost-effectiveness of the National Health Service (NHS) in the United Kingdom (UK), which is £30,000 per QALY gained. Because information about the effectiveness of pomalidomide is scarce, information about the patient population that most resembles the population that will receive pomalidomide is determined.

Methods

A Markov model was built to assess the cost-effectiveness of pomalidomide plus low-dose dexamethasone compared to high-dose dexamethasone. The usefulness of information on lenalidomide and bortezomib for the model on pomalidomide was tested by patient similarity through a survival analysis. Kaplan-Meier survival curves of lenalidomide and bortezomib were reconstructed and parameters for the Weibull equation were estimated through maximum likelihood estimation in order to reconstruct the survival. Results from the survival analysis show that only the information of trials on lenalidomide seem reliable to use in the model for pomalidomide. Data on survival from pomalidomide plus low-dose dexamethasone and from high-dose dexamethasone was obtained from the MM-003 trial. The model has a 10 years' time horizon. The model is based on the different health states the patient can experience: progression-free state, progressed state, and death. In each cycle, a patient can transfer to another stay or remains in the same state. All states include costs and a determined quality of life. The Markov model calculates the total costs, life years, and QALYs gained over the full time horizon.

Results

The incremental gain in life-years is 0.38 years. The costs of treating patients with pomalidomide plus low-dose dexamethasone is almost 6 times as high than treating patients with high-dose dexamethasone (£99,134 versus £17,420). Therefore, the undiscounted ICER

is £105,787 per life-year gained. By including quality of life in the model, the ICER of pomalidomide becomes more unattractive (£216,373 per QALY gained). With a standard threshold value for the ICER of £30,000 per QALY gained, pomalidomide would not be considered cost-effective.

Uncertainty

Most data inputs of the model are uncertain. One-way sensitivity analysis was performed to show the impact of single parameters on the ICER. The cost and utility parameters of pomalidomide showed the greatest impact. A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the deterministic model. All parameters were altered according to their distribution. Cost parameters were assumed to have a gamma distribution, utility parameters a beta distribution. Uncertainty surrounding the highly correlated survival parameters was obtained by a Cholesky decomposition assuming a bivariate Normal distribution. Results of the PSA showed almost no variation from the deterministic model. A threshold analysis was performed to seek the appropriate costs of pomalidomide for an ICER under the NHS threshold. It was found that for no price of pomalidomide, the ICER would be acceptable.

Discussion

There was no individual patient level data available to build a micro simulation model, nor information about individual patient characteristics that may influence the outcomes in terms of the ICER. The results of the sensitivity analyses are largely based on the choice of the distributions of parameters. Transferability of the model to other settings may be difficult, because other countries may have no threshold ICER or take another perspective in their analyses. Because pomalidomide can be considered as an end-of-life drug and there is only a small amount of patient eligible for receiving pomalidomide, other considerations than the ICER could play a role in the decision-making process.

Conclusion

The cost-effectiveness of pomalidomide plus low dose dexamethasone compared to high dose dexamethasone for patients with relapsed multiple myeloma refractory to both lenalidomide and bortezomib in the NHS setting is £216,373 per QALY gained. Pomalidomide is not considered cost-effective with a standard threshold value for the ICER of £30,000 per QALY gained.

1 Introduction

Multiple myeloma (MM) is a neoplastic disease of plasma cells (Durie et al. 2006). It is the second most common hematological cancer type with an incidence of 6 per 100,000 persons in Europe (Dimopoulos & Terpos 2010). The malignancy is incurable as nearly all MM patients eventually become resistant (i.e., refractory) to available treatments (Rajkumar 2013). However, new therapeutic options have improved the prognosis among these patients. Current therapies are primarily based on novel agents: a proteasome inhibitor (bortezomib) or an immunomodulatory drug (lenalidomide) (Kaufman et al. 2009). The appropriate therapy depends on patient characteristics such as prior therapies, age, comorbidities and drug safety (Dimopoulos & Terpos 2010). Relapsed patients are either repeatedly treated with the initial treatment or they switch to another therapy. This decision is based on the duration of remission to the initial therapy and by the toxicity profile (Dimopoulos & Terpos 2010). In the end, patients become refractory to all current therapies; this is called relapsed and refractory multiple myeloma (rrMM) (Kumar et al. 2012). Recently, it has been shown that a combination of pomalidomide with dexamethasone has a significant efficacy in patients with relapsed multiple myeloma earlier treated with both bortezomib and lenalidomide (Lacy et al. 2011; Leleu et al. 2013). Until now, the cost-effectiveness of pomalidomide compared to standard clinical management of rrMM without pomalidomide has not been determined. Such analyses can assist decision makers in determining whether pomalidomide as a standard treatment for patients with rrMM provides 'good value for money' using common benchmarks for cost-effectiveness of the National Health Service (NHS) in the United Kingdom (UK). This benchmark is determined as £30,000 pounds per QALY gained. The results of the economic evaluation will be compared to this threshold.

Therefore, the aim of this thesis is to determine the cost-effectiveness of pomalidomide with low-dose dexamethasone compared to standard clinical management, which is high-dose dexamethasone without pomalidomide. The primary research question is:

What is the cost-effectiveness of pomalidomide in combination with low dose dexamethasone compared to high dose dexamethasone for patients with relapsed multiple myeloma refractory to both lenalidomide and bortezomib in the NHS setting?

For clarity reasons, the central research question is divided into four subquestions:

1. What is known about treatment of rrMM patients with bortezomib, lenalidomide and pomalidomide?

2. What is the post progression survival (PPS) for patients refractory to both lenalidomide and bortezomib in the absence of a pomalidomide-based treatment?
3. What is the improvement in PPS with the presence of a pomalidomide-based treatment for rrMM patients treated with bortezomib or lenalidomide?
4. What is the cost-effectiveness of treating rrMM patients with pomalidomide with low-dose dexamethasone compared to the cost-effectiveness of treating rrMM patients with high-dose dexamethasone from the NHS perspective?

This thesis is structured as follows. In chapter 2, background information will be given on MM and its epidemiology, together with an overview of available treatments for MM and their characteristics, as well as the premise and characteristics of economic evaluations. Additionally, a literature review on the cost-effectiveness of those treatments is provided in Appendix A. The survival of MM patients will be the subject in chapter 3; data on clinical outcomes in terms of progression free survival and overall survival will be used to perform a survival analysis for patients with multiple myeloma with the current treatment options lenalidomide and bortezomib, more elaborately discussed in Appendix B. These results will provide a reference for base case survival.

Data and estimates on costs and effects of pomalidomide in combination with low-dose dexamethasone and treatment with high-dose dexamethasone for patients with rrMM will be the input of the economic evaluation performed in this thesis. The specific methods used for economic evaluation in this thesis are provided in chapter 4. The results of the economic evaluation are presented in chapter 5 and discussed with concluding remarks in chapter 6.

2 Background

2.1 Multiple myeloma

Multiple myeloma is a neoplastic disease of plasma cells (Durie et al. 2006). Most often, multiple myeloma is a sequel on a symptomatic pre-malignant stage called monoclonal gammopathy of undetermined significance (MGUS) (Landgren et al. 2009). MGUS occurs in 3% of the population of 50 years and older (Rajkumar 2013). Another pre-state of multiple myeloma is called smoldering multiple myeloma (SMM). Though this stage is asymptomatic, people diagnosed with SMM have a 10% yearly chance to progress to MM (Kyle et al. 2010). The following clinical requirements determine the presence of MM: 10% or more clonal plasma cells on bone marrow examination or a biopsy proven plasmacytoma and end-organ damage clearly related to the plasma cell disorder (Kyle & Rajkumar 2009). There are two systems that can classify the different stages of the disease: the Durie/Salmon system and the International Staging System (Greipp et al. 2005). Treatment of MM relies on risk stratification. Staging MM is therefore only useful to estimate prognostic information and not within the scope of this thesis. The risk-adapted therapy lines are described in section 3 of this chapter.

2.2 Epidemiology

Multiple myeloma is the second most common hematological cancer type, with an incidence of 6 per 100,000 persons in Europe (Dimopoulos & Terpos 2010). The median age at diagnosis is between 63 and 70 years (Dimopoulos & Terpos 2010). Treatment is only required during the symptomatic disease (Dimpoulos & Terpos 2010). The malignancy is incurable as nearly all patients with multiple myeloma eventually relapse (Rajkumar 2013). Outcomes in terms of survival are highly variable and influenced by the treatment each patient is able to tolerate (Dimopoulos & Terpos 2010).

2.3 Treatment of multiple myeloma

Patients with multiple myeloma can be stratified into different risk groups, explained thoroughly elsewhere (Rajkumar 2013), that have separate treatment protocols. The biggest challenge in the treatment of MM is that patients become refractory to their treatment, so a new treatment has to be started to prevent treatment progression and loss of quality of life (Fragoulakis et al. 2013). Treatment options are explained below, and schematically provided in figure 1.

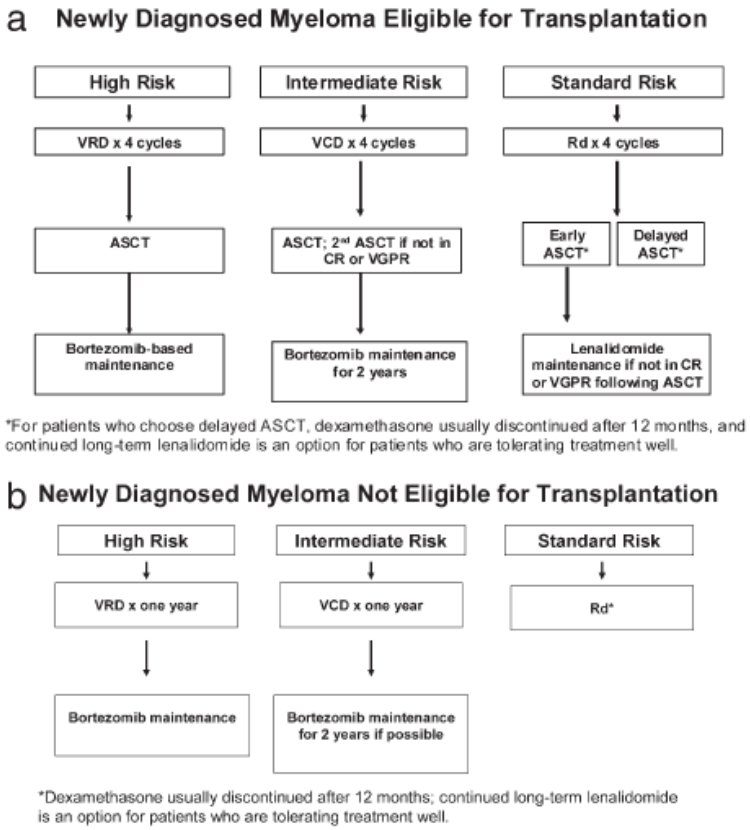

Figure 1: Treatments options given risk profile (from Rajkumar 2013)

2.3.1 Autologous stem cell therapy

Patients are first assessed for whether or not they are eligible for autologous stem cell therapy (ASCT) (Rajkumar 2013). Prerequisites for ASCT include: 1) the patient is less than 65 years-of-age, and 2) without any comorbidity (Dimpoulos & Terpos 2010).

2.3.2 Initial treatment options for those not eligible for ASCT

As a large portion of the MM patient population is greater than 65 years-of-age, most patients are not eligible to receive ASCT (Dimopoulos & Terpos 2010). Non-ASCT patients with a standard risk often receive a combination therapy of lenalidomide with low dose dexamethasone, while patients with an intermediate or high risk receive combination therapy in which bortezomib is combined with other drugs like cyclophosphamide and dexamethasone (Rajkumar 2013).

2.3.2.1 Bortezomib

Bortezomib (BOR) is a proteasome inhibitor (Kaufman et al. 2009). It has a reversible inhibitory effect on the chymotryptic enzymatic site within the proteasome (Kaufman et al.

2009), which causes tumor cell death. The effectiveness of bortezomib is tested in the APEX trial, in which bortezomib monotherapy was compared to high-dose dexamethasone (Richardson et al. 2005). In this trial, bortezomib showed improved effects in terms of response rate (43% versus 9%), time to progression (median of 6.2 months versus 2.5 months) and overall survival (hazard ratio of 0.57 (P=0.001)). The major toxicities occurring in the relapsed setting of the disease are peripheral neuropathy, thrombocytopenia, neutropenia and gastrointestinal events (Dimopoulos & Terpos 2010). Information about the cost-effectiveness of bortezomib is given in appendix A.

2.3.2.2 Lenalidomide

Lenalidomide (LEN) was the first drug to be licensed from the new immunomodulatory (iMID) class (Deniz et al. 2008). In two large trials (MM-009 and MM-010), the effectiveness of lenalidomide in combination with high-dose dexamethasone was tested compared to a placebo in combination with high-dose dexamethasone (Dimopoulos et al. 2007; Weber et al. 2007). Meta-analysis from these trial results show improvement in drug responses (60.6 to 21.9%, P=0.001), time to progression (median of 13.4 vs 4.6 months (P<0.001)) and overall survival (median of 38.0 versus 31.6 months without correction for cross-over from the placebo plus high-dose dexamethasone group to the lenalidomide plus high-dose dexamethasone group (P<0.045)). The most common adverse events in patients receiving lenalidomide plus high-dose dexamethasone are neutropenia, thrombocytopenia, venous thromboembolism and infections (Dimopoulos & Terpos 2010). Information about the cost-effectiveness of lenalidomide is also given in appendix A.

2.3.3 Treatment options in the single refractory stage

As previously mentioned, patients eventually relapse or become refractory to their initial treatment. If patients relapse while treated, they can be retreated with the same therapy after six months. Once patients become refractory to the treatment, the current treatment is discontinued. As a subsequent therapy, a different agent than that previously administered is given to the patient (Rajkumar 2013). Patients therefore often receive lenalidomide when earlier treated with bortezomib and vice versa.

2.3.4 Treatment options in the double refractory stage

MM patients refractory to their second-line treatment currently do not have many additional therapeutic options, and there is currently no drug approved in the UK for patients who

become refractory to lenalidomide and bortezomib. Multiple novel agents are currently being tested in order to determine the most appropriate therapy for patients with multiple myeloma in the double relapsed/refractory setting of the disease (Dimopoulos & Terpos 2010). One candidate novel agents is pomalidomide, which is part of the immunomodulatory class of drugs (Richardson et al. 2013).

2.3.4.1 Pomalidomide

The introduction of both lenalidomide and bortezomib has improved survival outcomes for patients with MM (Kumar et al. 2008), but there is a need for a treatment for patients who become refractory to lenalidomide and bortezomib. As mentioned previously, several novel agents are currently being tested in phase I and phase II trials to fill this treatment gap. among which is pomalidomide. Phase I and II trials on pomalidomide have shown increased survival with an acceptable occurrence of side-effects in patients refractory to both lenalidomide and bortezomib (Lacy et al. 2011; Leleu et al. 2013; Richardson et al. 2013). With a response rate of 35%, and 44% of the patients still alive after 18 months, pomalidomide in combination with dexamethasone has shown to be highly active and can salvage end stage MM refractory to lenalidomide and bortezomib (Leleu et al. 2013). Despite hematologic adverse events occurring in 80% of the patient population, pomalidomide is considered well tolerated (Lacy et al. 2011) and therefore eligible for a phase III trial.

<u>The MM-003 trial</u>

Design and methodology

The MM-003 trial was a randomized, open-label, phase III trial with the aim to compare the efficacy and safety of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone alone for rrMM patients (San Miguel et al. 2013). The patients (n=455) from 93 centers in Europe, Russia, Australia, Canada, and the USA were randomly assigned in a 2:1 ratio to either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone. Stratification factors were age (above or under 75 years), disease status (refractory vs relapsed and refractory vs bortezomib intolerant), and number of previous treatments (two vs three or more). Analyses were done by intention-to-treat, the primary endpoint was progression-free survival (PFS), the main secondary endpoint was overall survival (OS).

Criteria and patient population

592 patients were screened for the MM-003 trial, from which 137 were not included because they did not meet pre-specified inclusion or exclusion criteria. To meet the inclusion criteria, patients had to be refractory to their previous treatments, have refractory or relapsed and refractory MM, must have received treatment with both bortezomib and lenalidomide and had to be at least 18 years old. Exclusion criteria were: previous treatment with pomalidomide, hypersensitivity to thalidomide, lenalidomide, or dexamethasone, or resistance to high-dose dexamethasone. Other exclusion criteria were peripheral neuropathy of grade 2 or more, substantial cardiac disease or laboratory abnormalities that could indicate liver or renal failure (San Miguel et al. 2013). 455 patients were found eligible for the trial. Their characteristics can be found in figure 2.

	Pomalidomide plus low-dose dexamethasone (n=302)	High-dose dexamethasone (n=153)
Age (years)	64 (35–84)	65 (35–87)
>65	135 (45%)	72 (47%)
>75	24 (8%)	12 (8%)
Sex		
Male	181 (60%)	87 (57%)
Female	121 (40%)	66 (43%)
Time from diagnosis (years)	5·3 (0·6–30·0)	6·1 (0·9–21·1)
ECOG performance status score		
0–1	248 (82%)	122 (80%)
2–3	52 (17%)	28 (18%)
Missing	2 (<1%)	3 (2%)
International Staging System		
I–II	197 (65%)	93 (61%)
III	93 (31%)	54 (35%)
Missing	12 (4%)	6 (4%)
Creatinine clearance, <60 mL/min	95 (31%)	59 (39%)
Number of previous treatments	5 (2–14)	5 (2–17)
More than two	285 (94%)	145 (95%)
Previous treatments		
Dexamethasone	295 (98%)	152 (99%)
Thalidomide	173 (57%)	93 (61%)
Autologous stem-cell transplantation	214 (71%)	105 (69%)
Lenalidomide	302 (100%)	153 (100%)
Bortezomib	302 (100%)	153 (100%)
Refractory multiple myeloma	249 (82%)	125 (82%)
Intolerant to bortezomib	45 (15%)	23 (15%)
Refractory to lenalidomide	286 (95%)	141 (92%)
Refractory to bortezomib	238 (79%)	121 (79%)
Refractory to both bortezomib and lenalidomide	225 (75%)	113 (74%)

Data are median (range) or number (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics of patients**

Figure 2: Patient characteristics MM-003 trial (from San Miguel et al. 2013)

Treatment protocol

The protocol of the patients receiving pomalidomide and low-dose dexamethasone consisted of oral 4mg/day pomalidomide on day 1-21 and oral 40mg/day dexamethasone on days 1, 8,

15, 22 within a 28-days cycle. Patients within the high-dose dexamethasone arm received orally 40mg/day dexamethasone on days 1-4, 9-12 and 17-20 in a 28-days cycle. Treatment was stopped when the disease progression occurred or when serious adverse events occurred.

Recently published data from the MM-003 trial on progression and survival of pomalidomide can determine if pomalidomide provides added value in terms of extending survival for patients with multiple myeloma refractory to both lenalidomide and bortezomib. The MM-003 trial reported an overall survival in the comparator arm (high-dose dexamethasone) of 8.1 months (95% C.I. 6.9-10.8).
To date, no economic evaluation on assessing pomalidomide has been published in the PubMed data base. In the next section, background information on economic evaluations is given, after which the methods used to undertake the cost-effectiveness analysis of pomalidomide are described.

2.4 Background for economic evaluation

Health care resources are scarce and need to be allocated in the best possible way. The answers of allocation questions depend heavily on the relative added value of a treatment. Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences (Drummond et al. 2005). In this thesis, pomalidomide plus low-dose dexamethasone is compared to high-dose dexamethasone.

There are three main techniques to perform an economic evaluation[1]. In a cost-benefit analysis, both costs and effects are monetized. The treatment with the highest net monetary benefit is considered as the best treatment option. In a cost-effectiveness analysis (CEA), the effects are quantified in natural units (most often in life years gained). A cost-utility analysis is almost equal to a CEA, but the effects incorporate the preference people have for the effect the treatment causes. This is often described by quality-adjusted life years (QALYs). In this thesis, the effects are quantified as life years gained (LYG) and as QALYs.

Information about costs and effects are often obtained from randomized clinical trials (RCTs). Performing a cost-effectiveness/utility analysis based on a RCT has serious limitations. The

[1] A fourth technique, cost-minimization analysis, is often mentioned as technique for economic evaluation. However, in this technique only costs are compared and effects neglected. Therefore, it cannot be considered as a full economic evaluation.

intervention of interest is not always compared to a relevant treatment, the short follow-up in RCTs results in limited data and not all evidence needed to address cost-effectiveness can be collected with this data (Briggs et al. 2006). Therefore, there is a need for a technique that allows the incorporation of external data and extrapolation of all data over a longer period of time to assess the cost-effectiveness question properly. This can be done by decision analytic modelling.

Decision analytic modelling is referred to as the technique that uses "mathematical relationships to define series of possible consequences that would flow from a set of alternative options being evaluated" (Briggs et al. 2006:6). These possible consequences incorporate the uncertainty around the cost and effect parameters included in the model. How the model in this thesis is designed will be discussed in chapter 4.

Because information about the effectiveness of pomalidomide is hard to obtain and often lacks in providing significant results because of the small patient population (Harousseau et al. 2010), information about the patient population that most resembles the population that will receive pomalidomide will also be determined. This patient population is the MM patients who receive lenalidomide or bortezomib in the single refractory stage of MM. The following chapter will explain how this reference case will assist in obtaining knowledge about the effects of pomalidomide.

3 Survival without pomalidomide

3.1 Introduction

The aim of this chapter is to calculate the post progression survival for patients who are double refractory (after receiving either bortezomib or lenalidomide) in the absence of additional treatment options. Subsequently, the survival improvements associated with administering a third-line treatment (i.e. pomalidomide) after becoming refractory to their second treatment can be determined. If similar patient populations were used in the MM-003 trial as in the APEX and MM-009/010 trials, the overall survival in the comparator arm (DEX) of the model in this thesis should be approximately equal to the post-progression survival in the BOR-arm of the APEX trial and the LEN-arm of the MM-009/010 trials. This is illustrated in figure 3.

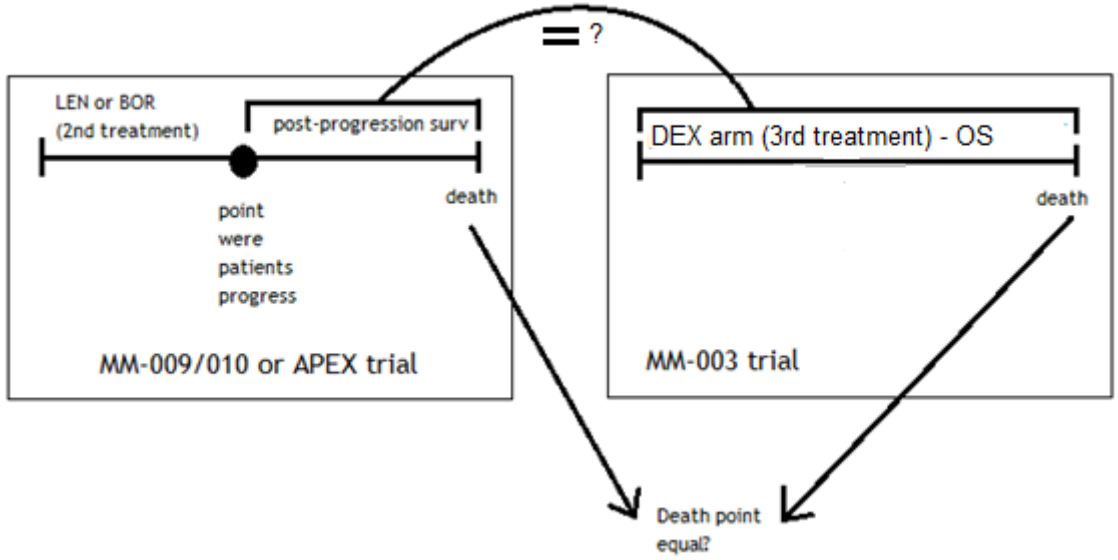

Figure 3: Comparison PPS MM-009/APEX trials and OS comparator arm MM-003 trial

3.2 Post-progression survival after bortezomib and lenalidomide

The goal of treating multiple myeloma is to prevent the patient from progressing while keeping the quality of life (Qol) for the patient as high as possible (Fragoulakis et al. 2013). Survival analysis can be used to assess and compare different survival patterns of different treatment options. Both progression-free survival and overall survival of lenalidomide plus high-dose dexamethasone and bortezomib monotherapy will be analyzed using a parametric time-to-event analysis. To compare the survival of patients progressing from treatment with either lenalidomide or bortezomib, the progression-free survival and overall survival needs to be projected. The post-progression survival, also mentioned earlier as the survival for rrMM patients without the presence of pomalidomide, is the overall survival minus the progression-

free survival. Most analyses that performed a survival analysis to compare results between treating rrMM patients with lenalidomide and bortezomib, report median or mean results (Hornberger et al. 2010; Möller et al. 2011; Fragoulakis et al. 2013). These results cannot capture the post-progression survival. The survival curves of patients treated with lenalidomide or bortezomib are constructed, using only the results from studies where lenalidomide and bortezomib were administered to patients as a second or subsequent treatment line.

3.3 Survival analysis methods

The Kaplan-Meier (KM) survival curves of the applicable studies are digitalized using Engauge Digitalizer©. The x-axes, which denotes the time lapsed, and the y-axes, which denotes the proportion of the study population still progression-free/alive, were scaled. The points extracted from the curve therefore illustrate the proportion of patients still progression-free/alive at defined moments in the trial. Therefore, the proportion of the patient population progressing or dying respectively between two time points could be calculated. This method, also used by Guyot et al. (2012), has the advantage of estimating the difference in survival between the two arms without making assumptions that have to be made when using a hazard ratio.

For the survival analysis a Weibull survival distribution was assumed. Previous studies (Möller et al. 2011; Brown et al. 2013; Fragoulakis et al. 2013) have reported that the Weibull distribution provided the best fit for the survival curves of both lenalidomide and bortezomib. The parameters for the Weibull model were estimated in a two-step procedure. First, candidate Weibull parameters (i.e., shape and scale) were initially chosen in Excel by selecting the parameters that achieved good visual correspondence between the reconstructed Kaplan-Meier survival curve and a Weibull curve. The values obtained in Excel are used as starting values for a maximum likelihood estimation (MLE) in SPSS. The Weibull equation was put into non-linear regression and after confirming all R-squared numbers were close to 1, the Weibull equation was used to perform survival analysis, using the parameters obtained from the non-linear regression for the survival analysis. A hypothetical cohort of 1,000 patients is used to model the progression free survival and the overall survival for both groups. The Weibull approach assumes a monotonically increasing risk of an event. This parametric approach has the advantageous to be sensitive to small changes (i.e. it can incorporate one death per cycle).

3.4 Survival analysis results

The constructed Weibull curves of the progression-free survival and overall survival of lenalidomide and bortezomib are given in figure 4. The shaded region indicates the post-progression survival.

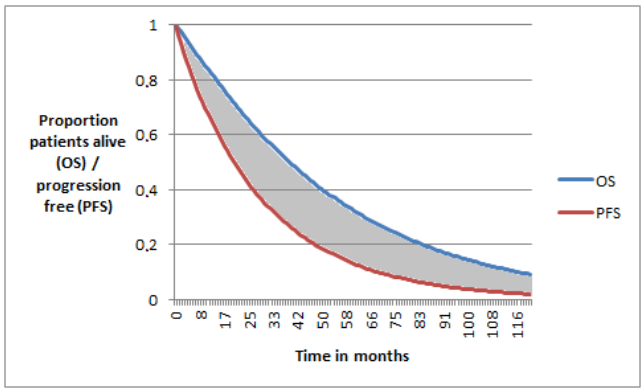

Figure 4a: Constructed Weibull curves lenalidomide

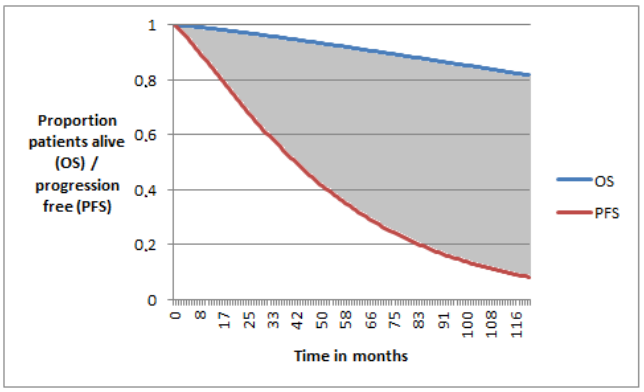

Figure 4b: Constructed Weibull curves bortezomib

Kumar et al. (2012) reported a median post-progression survival of 9 months in rrMM patients in registry data from multiple centers across the United States, Asia and Europe. They did not find significant differences between the bortezomib and lenalidomide sequence of treatment. These results are reconfirmed for lenalidomide in this thesis, with a median PPS after lenalidomide of 8.3 months. With a median PPS after bortezomib of 11.3 months, the post-progression survival estimates of Kumar et al. (2012) are not confirmed in this thesis.

To use information about the patient population of the MM-009/010 and the APEX trial for the analysis of pomalidomide it must be assumed that the fictitious cohorts, representing the bortezomib and lenalidomide plus high-dose dexamethasone receiving patients, have equal patient characteristics with respect to their (event-free) survival probability. These results do not indicate similarity between the cohorts; only the information of the MM-009/010 trials seem reliable to use in the model for pomalidomide. But it is shown by the survival analysis performed in this chapter and evidence from other authors, in the absence of a third line treatment prognosis for this patient groups is poor.

4 Methods for estimating the cost-effectiveness of pomalidomide

4.1 Decision analytic approach

A decision analytic model was built to assess the cost-effectiveness of pomalidomide plus low-dose dexamethasone compared to high-dose dexamethasone. Only cohort level data was available from the MM-003 trial. Based on the taxonomy of Brennan et al. (2006) the best choice of model when no individual-based data is available is to construct a Markov model. It is assumed that there is no interaction between the individuals. Therefore, all dynamic models are not appropriate for the MM-003 trial data (Brennan et al. 2006). The outcomes of the MM-003 trial are time-based (time-to-progression, overall survival). This implies that if a decision tree would be used, this decision tree should be repeated because the chance that patients receive a certain treatment changes over time. A Markov model can simplify this complex decision tree, and explicitly accounts for the timing of events. The model only allows for homogenous cohorts, but can be run for different cohorts of patients, dependent on their patient-specific characteristics and/or previous treatments, to assess the impact of patient heterogeneity. The outcomes of the Markov model are displayed in pounds per life-years and QALYs gained. These outcomes will be compared to the NHS threshold of £30,000 per QALY gained. All costs are reported in 2014 Great British pounds (£); when not available, costs were inflated to 2014 using official UK inflation indices of Hospital & community health services (HCHS) (Curtis 2013). Annual percentages of the pay cost index were used, multiplying the increased costs of the previous year with the following years' inflation. The 2014 was not available. Therefore, the 2013 inflation percentage was also used for 2014.

4.2 Model structure

The model shown below will be used with a 10 years' time horizon comprised of 131[2] 4-week cycles. The model is based on the different health states the patient can experience. These are:

- The progression-free state. In this health state, patients are not relapsed or have become refractory to the treatment regime they receive. They either receive pomalidomide plus low-dose dexamethasone or high-dose dexamethasone.
- The progressed state. In this health state patients are relapsed or have become refractory to either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone. It is assumed that patients from both treatment arms are getting equal

[2] A normal 10 year time horizon divided in 4-week cycle would consist of 130 cycles. Since the Simpson's methods does not allow an even number of cycles, an extra cycle is added to the model. Since this is the last cycle and there is little difference between the amount of patients in the different states between the two arms of the model, this extra cycle will not have an effect on the ICER.

treatment in this health state. Costs and related adverse events (including utility decrements) are included in this state.

– The death state. Because MM is an incurable disease, patients will eventually die from MM or an event related to (the treatment for) MM. Death can also occur from other, non-treatment related, causes.

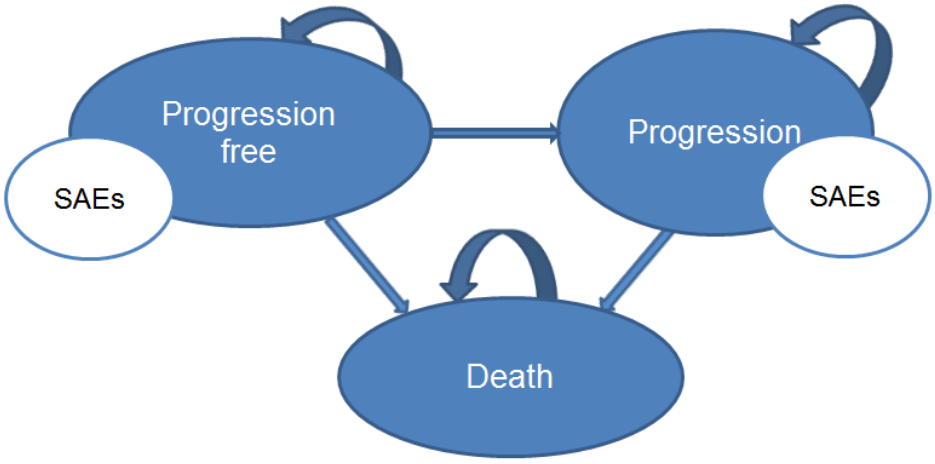

Figure 5: Model

If patients experience a treatment- or disease-related adverse event, the treatment will be discontinued for one treatment cycle. The chance, utility decrements and treatment costs of adverse events are included in this health state. The treatment costs of either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone will be subtracted from the total costs per cycle of this health state.

4.3 Input parameters

4.3.1 Cost parameters

Cost units and resource use were derived from different studies with similar patient populations. An overview of the unit costs is given in appendix C. Arguments for inclusion into the model are subsequently given.

Cost associated with the progression-free health state.

In the progression-free health state, patient receive either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone according to MM-003 trial protocol (San Miguel et al. 2013). The costs of the drug pomalidomide are £8,884.00, as determined by the manufacturer (MIMS 2013). The costs of dexamethasone (£10.90 per cycle) were obtained through the British National Formulary (BNF) (Hoyle et al. 2008). The submission of Celgene

for reimbursement of lenalidomide (2008) was used to determine the monitoring actions of both arms in the MM-003 trial. These costs (£131.17) consisted of a visit to the oncologists and several physical tests, which unit costs were obtained from the NHS reference costs. Monitoring costs were set equal for patients who received pomalidomide plus low-dose dexamethasone and high-dose dexamethasone.

Costs of adverse events

The costs of treating adverse events were obtained from the NHS national reference costs. The distribution of care between inpatient care, polyclinic care and outpatient care is obtained from the Celgene submission for lenalidomide (2008). Costs of treating adverse events are calculated as a multiplication of the probability of experiencing the adverse event (from the MM-003 trial) and the costs of resource use while experiencing an adverse event. Only adverse events that occur in five per cent in both arms of the study population were included. This resulted in the following costs per patient per cycle (table 1).

Averse event	Progression-free pomalidomide	Progression-free dexamethasone	Progressed
Anemia	£122.33	£133.40	£431.65
Febrile neutropenia	£289.65	£0	£502.19
Neutropenia	£90.18	£33.87	£197.62
Thrombocytopenia	£78.58	£84.74	£285.88
Fatigue	£4.11	£22.52	-
Pyrexia	£3.07	£62.78	-
Pneumonia	£19.14	£13.75	-
Bone pain	£61.53	£46.07	-
Leukopenia	£26.93	£9.95	-

Table 1: Overview of total costs of adverse events per patient per cycle

Costs associated with progressing

Costs of initial treatment after progression from either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone, if applicable, will be calculated as transition costs from the progression free state to the progression state. Assumptions needed to be made regarding what these costs consisted of. In this model, it is assumed that progressing costs

consist of the average costs of experiencing an adverse event (£87.21) and monitoring tests (£62.31), since progression is usually determined by clinical thresholds.

Costs associated with the progressed state

Resource use during the progressed stage of the disease is based on a study of Park et al. (2014), who found that a certain treatment combination (DCEP) is effective as a fourth treatment for patients who relapsed on bortezomib and an iMID. DCEP consists of dexamethasone, cyclophosphamide, etoposide and cisplatin (per patient per cycle £1,966.54 including administration and concomitant medications). These are drugs that were given to MM patients before the novel agents were on the market. As discussed elsewhere (Kumar et al. 2012), older drugs for treating MM are often placed further in the treatment sequence as last resort treatment. In the paper of Park et al (2014), the occurrence of adverse events were also given. These are also included in the model. Because the treatment cycle in the study of Park et al. (2014) is three weeks, all related costs and effects are divided by 21 and multiplied by 28 to equalize it to the 4-week cycle in this model. The same amount of monitoring as in the progression-free state was included in the progressed state.

End-of-life costs

End of life costs will be calculated as the transition costs from the progression state to the death state. For simplicity reasons, it has to be assumed that patients either die while being treated for an adverse event, or they run out of eligible treatments and die while receiving palliative care (on average £549.46 per patient per cycle). Therefore, the average costs of the inpatient treatments of known MM-related AEs is calculated (£2,104.85), reflecting the transition costs to death.

Several cost-specific adjustments were required, and are as follows. Not all costs were up-to-date; therefore, all costs were adjusted to 2014 prices using the price converter of hospital & community health services (Curtis 2013).

The future value of health benefits and costs are valued lower than the present value of the benefits and costs. To adjust the future costs to present value in accordance with NICE guidelines, a discount rate of 3.5% was applied to both health benefits and costs.

4.3.2 Utility parameters

There is little information about the QoL of relapsed patients with multiple myeloma refractory to both lenalidomide and bortezomib. Until now, the study of Van Agthoven et al. (2004) is the best estimate for the quality of life of MM patients. The results of this study are utility values of 0.81 for the progression-free state of MM and 0.644 for the progressed state of the disease. However, because of several arguments these values cannot be used directly for this model. Firstly, the study population in the paper of Van Agthoven et al. (2004) was newly diagnosed with MM. The average time from diagnosis in the MM-003 trial was respectively 5.3 years for the POM arm and 6.1 years for the DEX arm. Moreover, the study population was on average ten years younger (mean of 54 years compared to a 64 years mean in the MM-003 trial (San Miguel et al. 2013)). There is a need to adjust these values. Within this model, the utility value for the progressed state of Van Agthoven et al. (2004) is chosen as the progression-free state. This assumption will be elaborated on in the discussion section of this thesis. The utility for the progressed state needed to be calculated. If linearity in utility estimation could be assumed, the difference between 0.81 and 0.644 could be subtracted from 0.644 to obtain the utility for the progressed state of this model. However, the crucial condition of the linear QALY model, risk neutrality with respect to life duration, is often violated (Bleichrodt, Pinto & Wakker (2001)). People often show risk averse preferences (i.e. they are not willing to give up a lot of time for an increase in quality of life), which is shown by a concave utility function as in figure 5. The multiplicative QALY model usually holds for chronic disease states (Miyamoto et al. 1998). However, the curvature of the QALY model for MM is not known. The best estimate for the utility value of the progressed state in this model is assumed to be the non-linear QALY model. The calculation for the progressed state of rrMM is further explained in figure 6. The calculation resulted in a utility value of 0.537096.

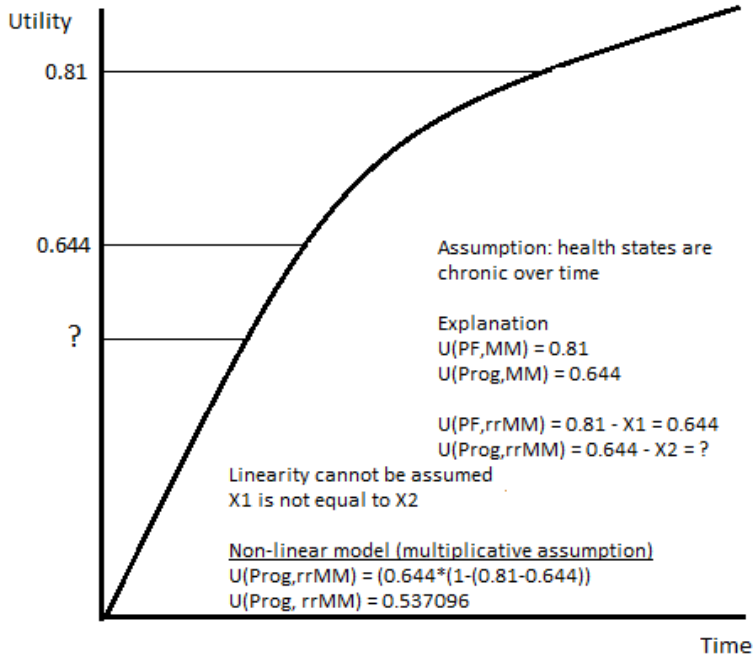

Figure 6: Utility adjustment rrMM (non-linear)

Utility adjustments due to experiencing adverse events are determined as the probability of experiencing an adverse event multiplied by the utility decrement of the adverse event. The utility decrements of different adverse events will be obtained from other studies with similar patient populations or malignancies. The probability of experiencing an adverse event differs between treatments (pomalidomide plus low-dose dexamethasone, high-dose dexamethasone, DCEP (after progression)) and therefore will have an effect on the ICER. An overview of the utility adjustment is given in table 2.

Adverse event	Utility decrement	Occurrence per cycle pomalidomide	Occurrence per cycle high-dose dexamethasone	Occurrence per cycle DCEP
Anemia	0.31	0.054690459	0.053195669	0.172128111
Febrile neutropenia	0.09002	0.025903075	0	0.090978538
Neutropenia	0.145	0.053195669	0.017900856	0.104453799
Thrombocytopenia	0.31	0.02696129	0.025903075	0.083172131
Fatigue	0.07346	0.0313387	0.023827304	-
Pyrexia (fever)	0.11	0.023827304	0.019828724	-
Pneumonia	0.2	0.012376333	0.008890042	-
Bone pain	0.069	0.01417668	0.010614685	-
Leukopenia	0.09	0.010614685	0.003922806	-
Utility after adjustment		0.599310867	0.610088778	0.434617236

Table 2: Utility decrements from experiencing adverse events

4.3.3 Transition probabilities

The following probabilities are possible in the model that is constructed for this thesis:

1. The probability of staying in the progression free state;
2. The probability of transferring from the progression free state to the progression state (disease progression);
3. The probability of transferring from the progression free state to the death state;
4. The probability of staying in the progression state;
5. The probability of transferring from the progression state to the death state;
6. The probability of staying in the death state. The death state is the absorbing state in the model. That is, once a patient enters this health state, the patient remains in this state.

Both the progression free survival (probability 1) and the overall survival (probability 1 to 4) change over time and can be calculated for each cycle in the model by the Weibull equation ($S(t) = e^{-\lambda t^{\gamma}}$). The value of 't' is defined by the time passed since the starting point of the trial, defined in months. The scale (λ) and shape (γ) parameters are determined through digitalizing the survival curve from the MM-003 trial. The coordinates from the digitalized curves are put into a non-linear regression analysis, and by maximum likelihood estimation (MLE) the Weibull parameters are obtained.

Patients who were first in the high-dose dexamethasone arm had the possibility to receive pomalidomide as monotherapy after they progressed on high-dose dexamethasone. Approximately 50% of the patients did (Morgan et al. 2014). San Miguel et al. (2013) reported a median overall survival in the high-dose dexamethasone arm of 8.1 months, Morgan et al. (2014) reported a median overall survival of 5.7 months after correcting for this cross-over. Because cross-over to pomalidomide monotherapy is possible after progression on high-dose dexamethasone, cross-over only affects the overall survival of in the dexamethasone arm. Therefore, the overall survival curve of patients receiving high-dose dexamethasone is adjusted. The survival parameters are adjusted in a way that the median overall survival is altered from 8.1 to 5.7, while keeping the shape of the curve (i.e. the relative proportion of patients dying) equal. The difference in the overall survival of dexamethasone is graphically described in figure 7.

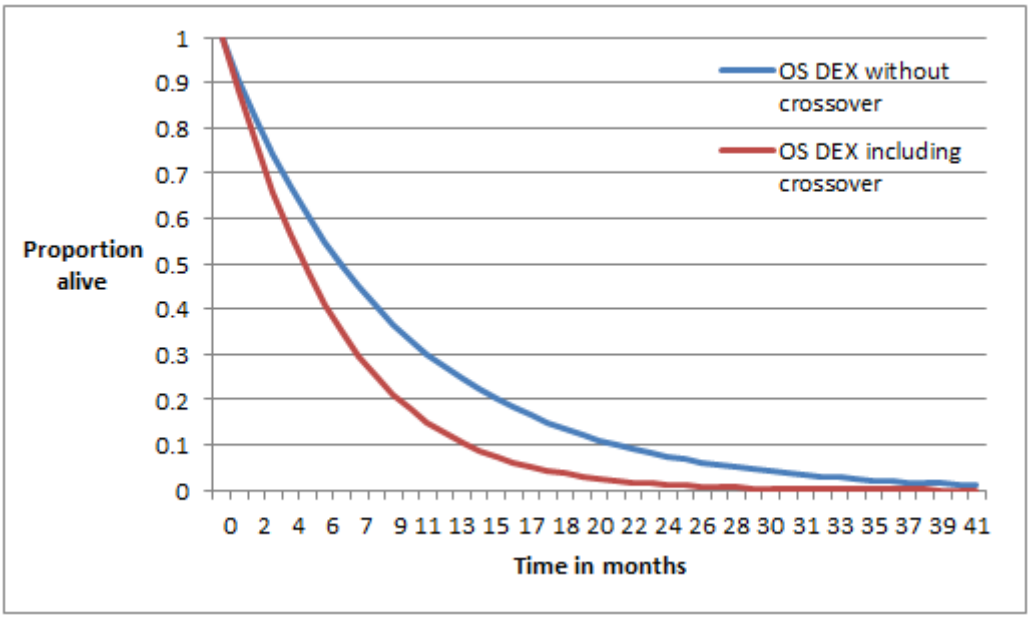

Figure 7: Adjustment OS DEX for cross-over MM-003 trial

The amount of patients in each health state in each cycle can be determined as follows:

- Progression free health state: the initial study population multiplied by the Weibull equation for progression free survival;
- Progression health state: the initial total study population minus the parts of the population either in the progression free health state or the death state at that moment of time;
- Death state: the total initial study population multiplied by one minus the Weibull equation for overall survival.

Generally, a half-cycle correction is performed to correct for the Markov model's characteristic that all events are modelled to happen either at the beginning of end of the cycle in the model. However, the Simpson's method has the advantage to account for the curvature of usual survival curves[3]. The adjustment is shown graphically in figure 8.

[3] With normal half-cycle correction, the costs and effects of the first and last cycle are divided by two. Using the Simpson's method, the first cycle is multiplied by 1/3, followed by a multiplication of each cycle by 4/3, 2/3, 4/3, 2/3 etcetera. The last cycle will be multiplied by 1/3.

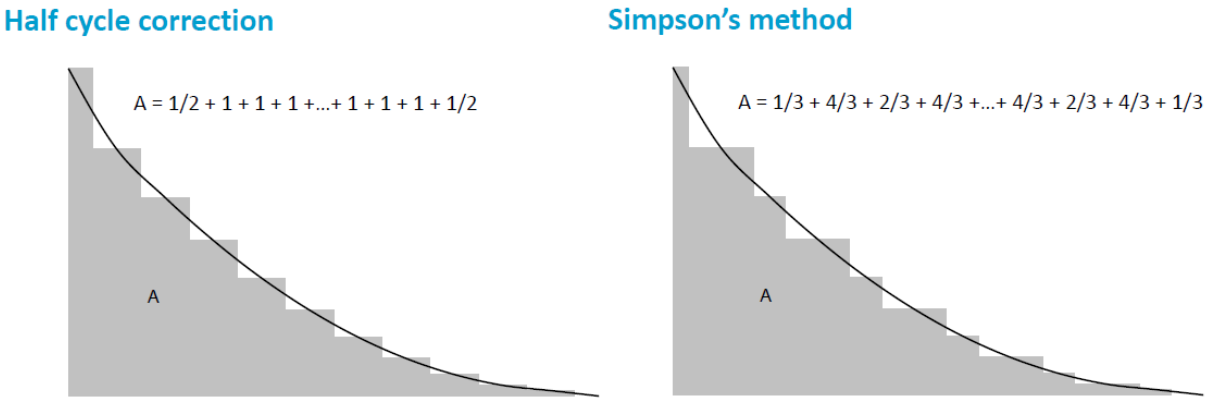

Figure 8: Difference half cycle and Simpon's method for cycle correction (from Wisløff (2011))

Median progression-free survival and overall survival of both treatment arms are given in chapter 5. These median results are estimated with the Weibull equation set to 0.5. This allows to calculate the only unknown parameter (i.e. time in months) in the Weibull equation.

4.4 Model assumptions

A model aims to resemble reality. Due to structural limitations of the model and knowledge-based limitations on disease and treatment, certain assumptions need to be made:

1. A patient can only be at one health state per cycle;
2. A patient can only transfer to another cycle once per cycle;
3. The probability of progressing or dying is irrespectively from the individual time within a cycle;
4. All AE's are independent events that are not related to other AE's;
5. Each kind of AE can only occur once per cycle;

4.5 Uncertainty

Most data used as input parameters in this model are obtained from sources that do not directly relate to the MM-003 trial or the patient population of interest in this thesis. Therefore, these inputs are uncertain. To test the robustness of the model, different sensitivity analyses were conducted.

4.5.1 One-way sensitivity analyses

The majority of the parameters involved in the model are uncertain. In a one-way sensitivity analysis (OSA), all parameters are kept constant while one parameter at a time is varied to a minimum and maximum value. Like this, the impact of varying a single parameter can be observed. Standard errors of 10% of the deterministic value for utility parameters and 20% of

the deterministic value for cost parameters were used. The standard error for cost parameters is assumed to be higher than for utility parameters because these consist of many elements which are all uncertain. The survival parameters are not included in the OSA because they do not have a clear increasing or decreasing effect on the ICER due to their non-linear characteristics.

4.5.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the deterministic model. A PSA differs from OSA because all parameters are changed simultaneously. These changes in the individual parameters are determined by the distributions of those parameters. Due to the characteristics of some of the parameters, normal distribution cannot be assumed. Therefore, probabilistic sensitivity analysis is performed using the Bayesian approach of uncertainty intervals. This is done by a Monte Carlo simulation. The distribution of the parameters are adapted from earlier studies and standards given by Briggs et al. (2006).

Distribution survival parameter

Lambda and gamma parameters of the Weibull distribution are assumed to be Normally distributed together. This bivariate Normal distribution is not equal to the combination of two Normally distributed parameters, but one of the parameters is conditionally Normal distributed on the other parameter. The scale (lambda) and shape (gamma) parameters are highly correlated (see table 3). The conditional distribution is based on the correlation between the two parameters and its variance. Therefore, a Cholesky decomposition is performed to correct for the correlation between two parameters. It is inherent which Weibull parameter is conditionally distributed on another, so in this thesis the gamma parameter is conditionally distributed on the lambda parameter. The conditional mean is determined by:

$$\mu_{y|x} = \mu_y + \rho_{xy} * (\sigma_y/\sigma_x) * (X - \mu_x)$$

in which μ_y is the mean of the lambda parameter, the σ represent the variance, ρ_{xy} is the correlation between the lambda and the gamma parameter (given with the results of the MLE when estimating the parameters). X is a random value drawn from the lambda parameter.

The standard errors of the survival parameters were estimated in the MLE of the parameters themselves. There are, however, two factors that influence the uncertainty around the survival estimates. First, there is the normal uncertainty of the KM-curves. Secondly, the survival points extracted from the KM-curves do not exactly reflect the survival curve (i.e. these points

also include uncertainty around them). Therefore, the standard error estimated by the maximum likelihood is doubled.

The probabilistic values of the Weibull parameters are given by a Normal distribution of the lambda parameter and a conditional Normal distribution of the gamma parameter. The results of the probabilistic sensitivity analyses are displayed through a cost-effectiveness plane and a cost-effectiveness acceptability curve in section 5.2.2 of this thesis.

Correlation matrix OS POM

	Lambda_OS_POM	Gamma_OS_POM
Lambda_OS_POM	1.000	-.980
Gamma_OS_POM	-.980	1.000

Correlations Matrix OS DEX

	Lambda_OS_DEX	Gamma_OS_DEX
Lambda_OS_DEX	1,000	-,964
Gamma_OS_DEX	-,964	1,000

Correlation Matrix PFS POM

	Lambda_PFS_POM	Gamma_PFS_POM
Lambda_PFS_POM	1.000	-.946
Gamma_PFS_POM	-.946	1.000

Correlation Matrix PFS DEX

	Lambda_PFS_DEX	Gamma_PFS_DEX
Lambda_PFS_DEX	1.000	-.871
Gamma_PFS_DEX	-.871	1.000

Table 3: Correlation between lambda and gamma parameters Weibull distribution

Distribution unit costs

A gamma distribution was chosen to represent the variation in costs. It is most likely that this distribution fits the variation of the cost parameters because no negative values can occur. Moreover, the gamma distribution can adapt many forms depending on the mean and standard error of the parameter. This distribution was also chosen by Celgene in their submission for lenalidomide (2008) and considered as an acceptable distribution by the review commission (Hoyle et al. 2008). The alpha and beta for the gamma distribution are calculated as follows:

$$\alpha = \frac{\mu^2}{s^2} \qquad \beta = \frac{s^2}{\mu}$$

Where μ^2 is the square of the mean (μ) and S^2 is the square of the standard deviation.

Distribution utility parameters

To represent variability in the utility values calculated in section 4.3.2, the beta distribution was used. The beta distribution is restricted to values between 0 and 1, a restriction often used

for utility values. This distribution was also used for the lenalidomide submission of Celgene (2008). The alpha and beta for the beta distribution are calculated as follows:

$$\propto = \mu + (\left(\frac{\mu * (1-\mu)}{s^2 * S^2}\right) - 1)$$

$$\beta = (1-\mu) * (\left(\frac{\mu * (1-\mu)}{s^2 * s^2}\right) - 1)$$

Where μ is the mean and S^2 is the square of the standard deviation of this mean.

4.6 Result representation

The results of the model will be presented in terms of the deterministic ICER and probabilistic ICERs by the cost-effectiveness plane (CE-plane). The CE-plane is a graphical representation of the incremental costs and effects (ICERs). The results can be divided in four quadrants. The northeast quadrant represents the situation in which the new treatment is dominated. The new treatment is dominant if the ICER is in the southwest quadrant. In the northwest and southeast quadrants, the new treatment can be accepted based on its' ICER and the threshold. While the cost-effectiveness plane gives some information about the acceptability of the cost-effectiveness of pomalidomide. Therefore, there is a need to set a limit on the ICER and see whether that limit is acceptable for the ICERs given by the PSA. This can be realized by the cost-effectiveness acceptability curve (CEAC), which shows the probability that the true ICER will be below several threshold ICERs (Al 2013).

5 The cost-effectiveness of pomalidomide: results

5.1 Model results

Tables 4a and 4b present the deterministic model outcomes in terms of costs, life years and QALYs by therapy arm. These undiscounted and discounted results represent a patient population as similar as possible to those included in the MM-003 trial. According to the analysis, pomalidomide plus low-dose dexamethasone provided slightly better clinical outcomes than high-dose dexamethasone, with an incremental gain of life-years of 0.38 years. The costs of treating patients with pomalidomide plus low-dose dexamethasone is almost 6 times as high than treating patients with high-dose dexamethasone (£99,134 versus £17,420). Therefore, the undiscounted ICER (£105,787 per life-year gained) is primarily driven by high drug costs associated with pomalidomide plus low-dose dexamethasone. The limited difference in quality of life for patients treated with pomalidomide plus low-dose dexamethasone or with high-dose dexamethasone (0.64 versus 0.26). By including quality of life in the model, the ICER of pomalidomide becomes more unattractive (£216,373 per QALY gained). With a standard threshold value for the ICER of £30,000 per QALY gained, pomalidomide would not be considered cost-effective.

Results (deterministic) undiscounted			
Treatment	**Costs**	**QALY**	**LY**
POM+ldDEX	£99,134	0.64	1.29
hdDEX	£17,420	0.26	0.52
Increment	**£81,714**	**0.38**	**0.77**
ICERs:		**incremental costs/ QALY**	**incremental costs/ LY**
POM+ldDEX vs hdDEX		**£216,373**	**£105,787**

Table 4a: undiscounted deterministic results

Results (deterministic) discounted			
Treatment	**Costs**	**QALY**	**LY**
POM+ldDEX	£96,232	0.62	1.24
hdDEX	£17,063	0.26	0.51
Increment	**£79,169**	**0.36**	**0.73**
ICERs:		**incremental costs/ QALY**	**incremental costs/ LY**
POM+ldDEX vs hdDEX		**£220,580**	**£108,210**

Table 4b: discounted deterministic results

The effect of discounting is somewhat detrimental for the ICER in terms of pounds per life year gained and in pounds per QALY gained. All subsequent results will be compared with the discounted ICER, since discounting is applied in the NHS perspective.

The model predicts a median progression-free survival for pomalidomide plus low-dose dexamethasone of 4.39 months compared with 2.09 months for the high-dose dexamethasone group. The difference in progression-free survival between the two treatment arms is graphically presented in figure 9.

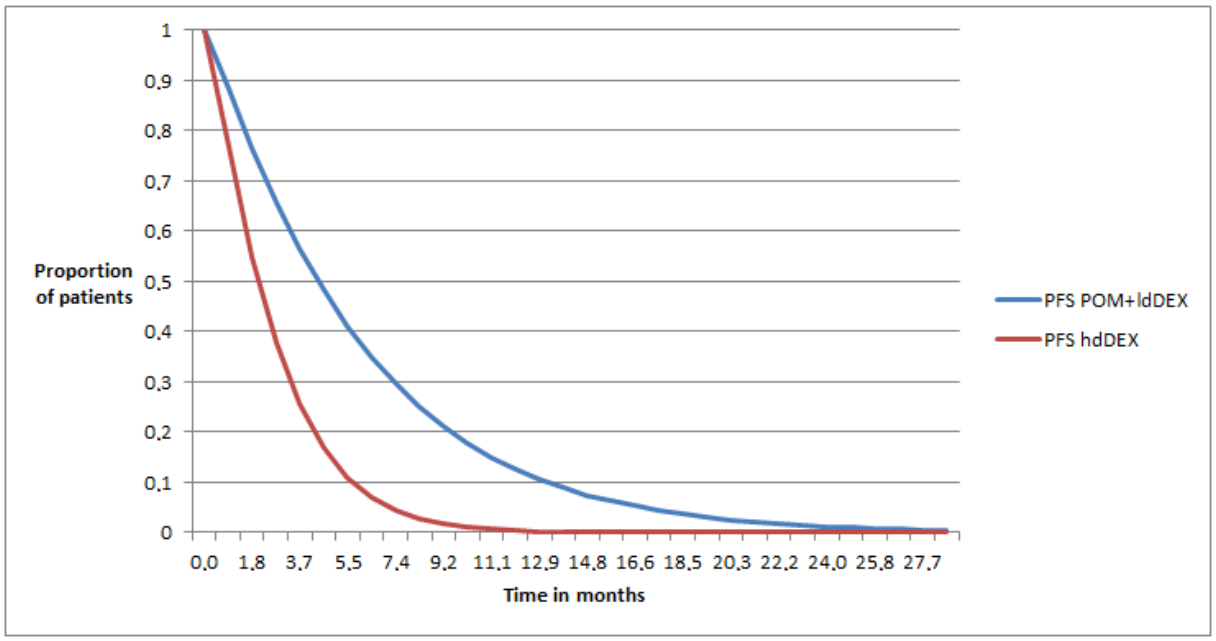

Figure 9: Difference in PFS between POM+ldDEX and hdDEX

5.2 Statistical analyses

5.2.1 One-way sensitivity analyses

The one-way sensitivity analyses were performed using Microsoft Excel©, the discounted results are shown in the tornado plot (figure 10). The x-axis represents the ICER values. The y-axis represents the ICER for the situation where one parameter is minimized (the blue bar) or maximized (the red bar), while all other parameters remain by their deterministic value.

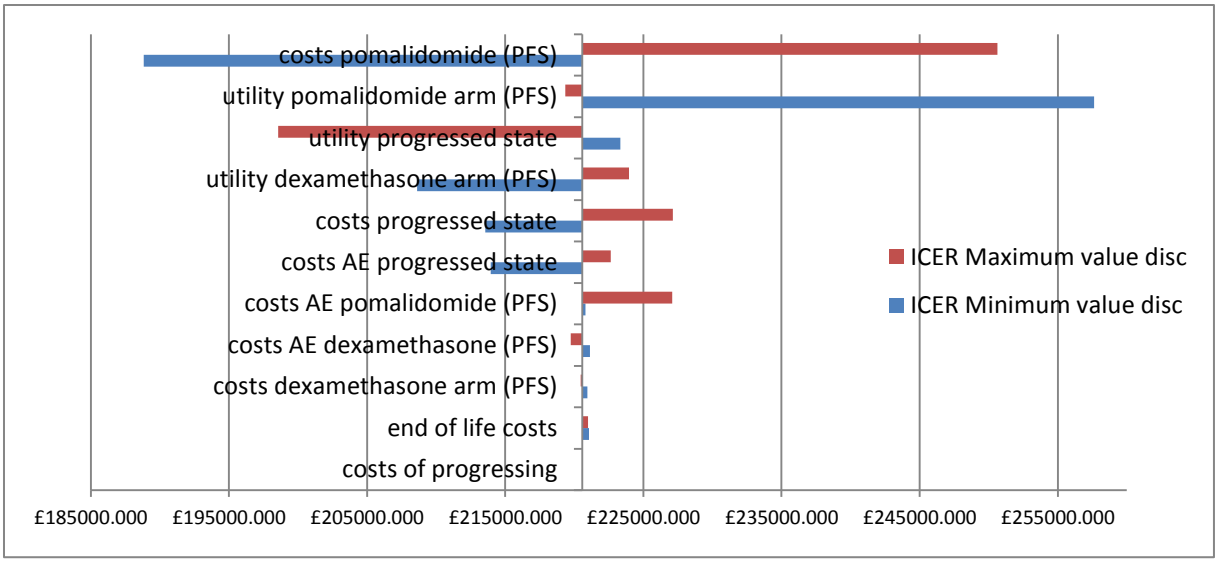

Figure 10: Tornado plot OSA

As shown in the tornado plot, there are parameters that are more influential on the ICER than other parameters, like the utility and costs of people receiving pomalidomide plus low-dose dexamethasone. Some parameters show an inverse effect: if the parameter is maximized, the ICER is lower and vice versa. The costs of treating patients with high-dose dexamethasone have little effect on the ICER, as well as the costs of progressing and dying. Table 5 provides the value of the minimum and maximum value of the ICER from the OSA.

Description	Value (£/QALY)	Difference with deterministic ICER
Deterministic ICER	£220,580	
Minimum ICER OSA	£188,842 (Minimum value of costs of pomalidomide (PFS))	**-£31,738**
Maximum ICER OSA	£257,621 (Minimum value of utility of pomalidomide (PFS))	**£37,041**

Table 5: Extreme values of ICERs from OSA

5.2.2 Probabilistic sensitivity analysis

The mean results of the PSA are given in table 6, including the difference with the deterministic ICER.

	Deterministic	Probabilistic (mean)	Difference
Incremental costs	£79,169	£79,280	**-£111**
Incremental LYs	0.73	0.73	**0**
Incremental QALYs	0.36	0.36	**0**
ICER (£/LYs)	£108,210	£108,170	**£40**
ICER (£/QALYs)	£220,580	£220,687	**-£107**

Table 6: Deterministic and probabilistic incremental outcomes and ICERs

The ICER associated with each of the 1,000 Monte Carlo simulations is provided in the cost-effectiveness plane (figure 11).

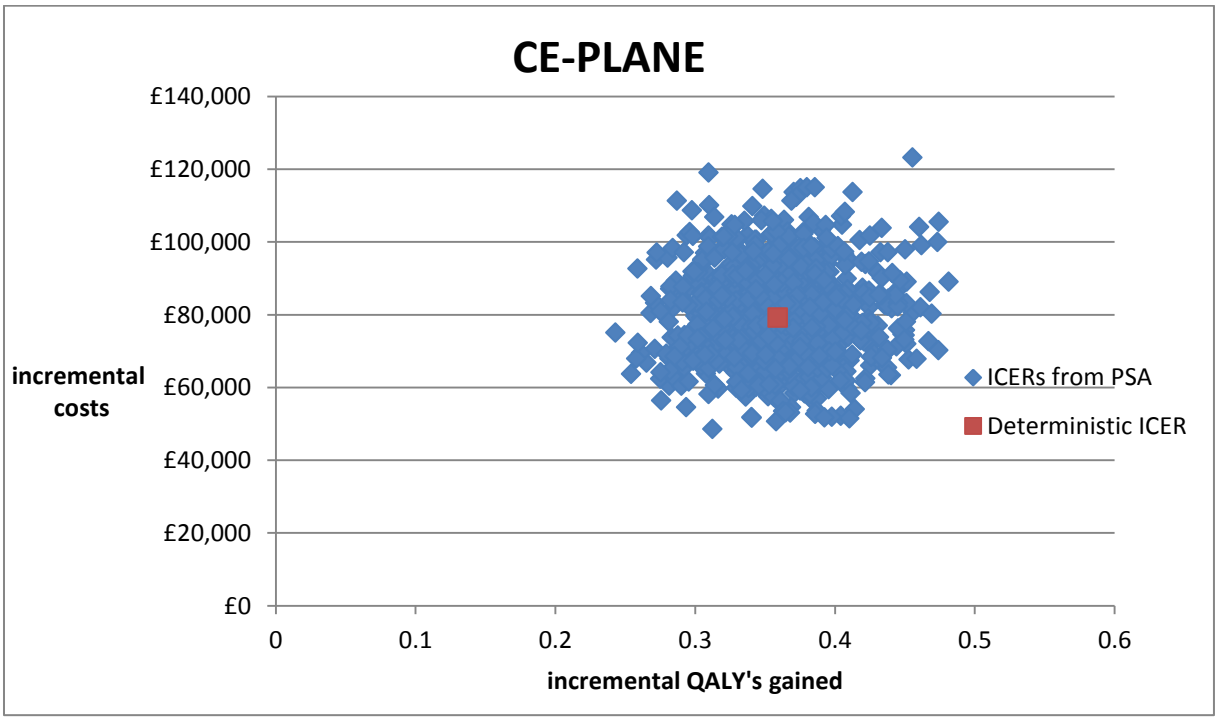

Figure 11: CE-plane of PSA results

The cost-effectiveness plane for pomalidomide reveals the spread of uncertainty around the deterministic ICER. The ICERs from the PSA show that in all cases patients treated with pomalidomide have slightly better results in terms of QoL, but the costs of treating rrMM patients with pomalidomide are substantially higher. Therefore, all the ICERs that represents the result of the incremental costs of pomalidomide over dexamethasone per incremental QALYs gained are situated in the northeast quadrant of the cost-effectiveness plane. The northwest quadrant represents the situation in which the new treatment (pomalidomide) is more costly but also yields more effects. There are no ICERs situated in the northwest, southwest, and southeast quadrants, which implies that there is no evidence that

pomalidomide can be a cost-saving and/or less effective compared to high-dose dexamethasone. There is a higher possibility that pomalidomide is cost-effective when the threshold ICER increases. This is show in the CEAC (Figure 12).

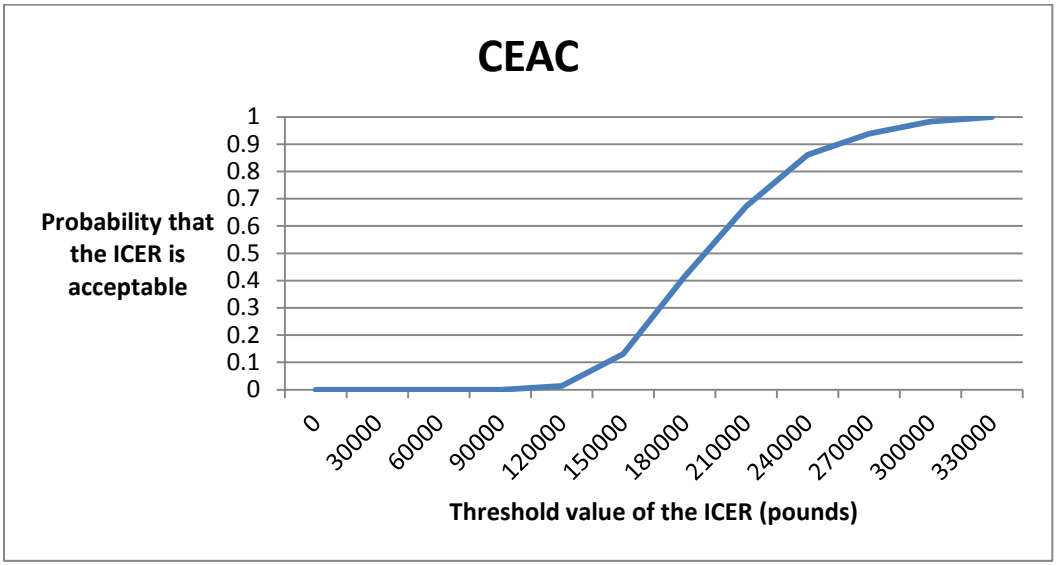

Figure 12: Cost-effectiveness acceptability curve

When the threshold value of the ICER is equal to the NHS threshold (£30,000), the probability that pomalidomide is cost-effective is 0. The deterministic and probabilistic results show that the ICER of pomalidomide is much higher than the threshold ICER and that the OSA shows that the ICER is primarily driven by the high costs of pomalidomide itself. Therefore, a threshold analysis is performed to estimate what the costs of pomalidomide should be to have an ICER under or equal to £30,000.

5.3 Threshold analysis

The threshold analysis shows the maximum costs of pomalidomide for the ICER to be acceptable according to the NHS standard of £30,000. The incremental QALYs gained 0.36. The following equation shows that the incremental costs are equal to £10,800.

$$\frac{\Delta C}{0.36} = £30{,}000$$

Since the costs of treating patients with high-dose dexamethasone is estimated on £17,063, the total costs of treating patients with pomalidomide plus low-dose dexamethasone cannot exceed £27,863.

Element	Subelements	Cost elements	ICER
Deterministic value costs pomalidomide arm per cycle		£8,728	£220,580
	Deterministic value costs pomalidomide arm per cycle without adjustment for adverse events	£8,978	
	Drug costs pomalidomide	£8,884	
	Other costs of pomalidomide arm per cycle	£94	
Threshold analysis costs pomalidomide			
	Costs of pomalidomide	0	
	Costs per cycle if costs of pomalidomide = 0	£94	
	Total costs per patient if costs pomalidomide = 0	£87,563	£68,057

Table 7: Threshold analysis for the costs of pomalidomide

When the costs of pomalidomide are set to zero pounds, the ICER of pomalidomide is twice as big as the threshold ICER, since the total costs exceed £27,863. Treating rrMM patients with pomalidomide is not cost-effectiveness regardless of its price.

6 Discussion

Measuring and valuing outcomes is an imperfect science (Lehoux 2006). In the first part of this chapter, the differences between deterministic and probabilistic outcomes will be discussed. By decision analytic modeling, it is aimed that the model represents reality in the best possible way. It is known that this resemblance cannot be perfect because of modeling restrictions. These limitations are explained in the second section. After the methods and outcomes are handled, other considerations in the use of the model on pomalidomide are given. This chapter will be concluded by recommendations for further research.

6.1 General findings

In this thesis, a Markov model was built to assess the cost-effectiveness of pomalidomide plus low-dose dexamethasone compared to high-dose dexamethasone for rrMM patients. The model was built using a NHS perspective with using data from the MM-003 trial and reference data with a patient population as close as possible to the patient population in the MM-003 trial. The ICER was determined as £220,580 per QALY gained in the deterministic model.

The impact of the parameters on the ICER was evaluated by OSA and PSA. The results from the OSA varied from £198,555 to £257,621, mostly influenced by the utility parameters and the costs of treating people with pomalidomide.

The significant effect of the costs of pomalidomide plus low-dose dexamethasone can be explained by two arguments. First, the costs of pomalidomide plus low-dose dexamethasone are very high compared to other cost parameters. Secondly, because patients are most likely to stay longer in the progression-free state when they receive pomalidomide plus low-dose dexamethasone, the total costs of pomalidomide plus low-dose dexamethasone are high. Differentiation in this parameter therefore is likely to have a big effect on the ICER.

The inverse effect of the OSA on the ICER (i.e. a lower ICER than the deterministic ICER when a parameter is maximized) is due to the equation of the ICER. For example, if the utility of the progression-free state of pomalidomide plus low-dose dexamethasone is maximized, more increment QALYs are gained. This reduces the ICER. The utility parameters have, beside to the pomalidomide plus low-dose dexamethasone costs, a greater effect on the ICER. Because the incremental costs are determined by more parameters than the incremental effects, this is not directly due to a greater uncertainty in the utility parameters. The progressing and dying parameters have the smallest impact on the ICER. The costs of the parameters themselves are relatively low, and the period they transfer is limited to one cycle.

The PSA showed slightly different results than the deterministic results with a mean ICER of the PSA is £220,687 (deterministic value is £220,580). As shown in table 6 of the result section, the probabilistic results yield higher incremental costs. This can be explained by the gamma distribution which is chosen for the costs, because of which the costs cannot be negative, but are most likely to be skewed to the right. This is represented by the difference between the deterministic ICER and the probabilistic mean of 1,000 ICERs. According to Claxton et al. (2005), probabilistic results are more appropriate to use in medical decision making, because these results incorporate uncertainty. Since real life costs and effects of pomalidomide are uncertain, the probabilistic results present are more realistic than the deterministic results.

6.2 Limitations

In order to build the model in this thesis, multiple assumptions and model-related choices needed to be made. These assumptions and choices have led to limitations in the model, which will be discussed in the following subsections.

6.2.1 Model structure

The cycle length of the model was determined by clinical standards in which pomalidomide and dexamethasone were administered. This 4-week cycle may yield some limitations in the sensitivity of the progression-free survival and the overall survival of both arms. While through Simpson's method there is corrected for between-state transition time point, a smaller cycle length would specify the time of transition more precisely, what could influence the ICER.

Because the model has a Markov structure, the Markovian assumption had to be made. This implies that the chance of transferring to another state is independent on the time spent in the current state. In other words, the Markov model on pomalidomide includes no history. However, the model is a cohort model and the survival curve can predict the probability of transferring for every cycle. So it must be assumed that this resembles the effect of a model in which history is included. As said, the Markov model on pomalidomide is a cohort model. There was no individual patient level data available to build a micro simulation model, nor information about individual patient characteristics that may influence the outcomes in terms of the ICER. The Markov model therefore gives the best representation of the outcomes of rrMM patients. As seen in the survival analysis of bortezomib and lenalidomide, there is a

difference in PPS. This implies that subgroup analysis based on the last treatment administered can result in differences in terms of effectiveness of pomalidomide.

Another assumption that had to be made is that patients can experience all adverse events, but only one time per cycle. Patients were, for example, only treated for fatigue one time per cycle. There is limited information about the distribution of occurrence of adverse events, because often only overall rates of occurrence are given. The costs of adverse events are added per probability per cycle. It might occur that a patient experiences multiple adverse events at once, which might lead to a decrease in costs (i.e. only one hospital admittance, while a hospital admittance is calculated for every adverse event). This overestimation of costs for adverse events may compensate for the underestimation that only one specific adverse event can occur once per cycle.

The last limitation of the model structure is that the model on pomalidomide does not allow for retreatment with pomalidomide once a patient has progressed on pomalidomide. While also not reported in the MM-003, in clinical reality MM patients are often retreated with the same drug they relapsed on (until they become refractory to it). If rrMM patients are retreated with pomalidomide, the model should be built in a way that it allows patients to transfer from the progressed state to the progression-free state.

6.2.2 Parameters

As seen in the OSA, the individual parameters in the model have differential influence on the outcomes of the model. The largest group of parameters consist of the cost parameters. These include the parameters of combined costs within a health state or costs considering the transition to another health state. While the costs of pomalidomide were given by Celgene, the other costs are based on assumptions. The monitoring activities and costs are based on the technology appraisal on lenalidomide (Hoyle et al. 2008). The patient population considered in this thesis has MM in a more advanced stage than the patients receiving lenalidomide. Therefore, it is likely that the monitoring costs are underestimated. If these would be equal in both arms, the effect on the ICER would be minimal.

While the costs of adverse events are discussed in the previous paragraph, they are not included in the progressing costs in the model. Since eligibility for treatment in the progression-free state is often determined by blood counts (Kumar et al. 2012). Therefore, it must be assumed that an adverse event can cause progression due to bad blood counts, but is captured in the health state the patient was previously in.

The treatment in the progressed state, DCEP, was chosen because MM patients are often treated with 'old' drugs when they become refractory to the novel agents (Kumar et al. 2012). However, there is considerable evidence that rrMM patients are retreated with bortezomib, even when they were considered refractory to it (Conner et al. 2008; Warzocha et al. 2008; Sood et al.2009). Bortezomib would be more costly than treating patients in the progressed state with DCEP. As seen in the OSA, increasing the costs of the post-progressive state reduces the ICER. If the rrMM patients are treated with a more expensive drug in the progressed state, the ICER must be reconsidered. There is no evidence on retreatment with lenalidomide. Lenalidomide is effective when patients have become refractory to thalidomide, which is also an iMID (Weber et al. 2007). However, the effectiveness to own refractory population for lenalidomide not yet determined.

Patients were included in the MM-003 trial based on several clinical criteria. These criteria excluded patients with other diseases or critical health states. In daily clinical practice, these patients are often treated with the same drugs as patients in better health states because there is simply no alternative. It can therefore be assumed that both the results in the intervention as the comparator arm are worse than the results from the MM-003 trial. This can be confirmed by obtaining real life data.

It is known from the KM-curves in the MM-003 that the estimated survival parameters are biased due to censoring (Guyot et al. 2012). Censoring was not incorporated in the estimation of the survival parameters. It is assumed that this bias is captured by the enlarged standard error of the survival parameters.

Because different stage of MM in the study of Van Agthoven et al. (2004) and the MM-003 trial, the utility values could not directly be used in this model . Therefore, the utility value of the progressed state of Van Agthoven et al. (2004) are altered for the model in this thesis. A non-linear QALY model was used, with an exponential function to calculate the utility for the progressed health state. Appendix D shows the utility values and the deterministic ICER when the linear QALY model is used. When the utility value is estimated linearly (and therefore is lower), the total amount of QALYs gained per person is higher in the high-dose dexamethasone arm and lower in the pomalidomide plus low-dose dexamethasone arm. This implies that patients progressed on pomalidomide are relatively shorter alive than patients who progressed on dexamethasone (respectively to the time they were in the progression-free state). The adjustments of the utility values contain a higher degree of uncertainty, since these are rough estimates based on assumptions. However, the utility estimates in this model are likely to be more accurate than using the values of Van Agthoven et al. (2004). The OSA

shows that the utility values of the progression-free state have a substantial impact on the ICER. There is little difference in quality of life between the intervention and comparator group in the model. Therefore, altering one of the utility values has a major effect on the ICER. But when the parameters are altered at the same time (in the PSA), the incremental QALYs do not differentiate from the deterministic results. The limited effect of the utility parameters on the ICER can justify the rough estimates from the utility adjustments.

6.2.3 Sensitivity analyses

The results of the sensitivity analyses are largely based on the choice of the distributions of parameters. The distributions of the parameters were estimated on a variance of 10% of the deterministic utility values and 20% of the deterministic cost values. There was no information on uncertainty surrounding the parameters from real life data, which is preferred in economic evaluation standards (Briggs et al. 2012). If the uncertainty around the parameters is higher than the 10 or 20 per cent, the uncertainty in this model is underestimated. If the uncertainty is higher, the CE-plane is more scattered. This influences medical decision making, depending on the part of the CE-plane than is below the threshold.

The threshold analysis shows that for any price of pomalidomide, treating pomalidomide would not be considered cost-effective. Despite the high costs of pomalidomide itself, main costs drivers are also the costs concerned with treating adverse events. These costs are higher for the pomalidomide arm (£696 per cycle) than for the dexamethasone arm (£407 per cycle).

6.3 Transferability to other settings

In this paragraph, the possibility to use this model in other settings than the NHS setting will be discussed. The transferability of the model depends on multiple aspects. The first important part of the model are the unit costs used. These unit costs are all based on NHS costs, since the model was built with a NHS perspective. However, these unit costs can easily be adjusted to other national prices. This adjustment is not complete. Different countries have different clinical standards, which may result in different amounts of monitoring activities, other activities, and different administration schedules of the drugs.

As shown in appendix C, the unit costs, the use of the unit per 4-week cycle, and the references are given. This transparency improves the possibility to make this model eligible to other health care settings.

Different countries have different thresholds in terms of willingness to pay for the ICER in their decision making process. This threshold can easily be adjusted to the national setting.

But different countries take different perspectives for their CEAs. This model is based on the NHS setting, which is common in the UK, while other countries, like the Netherlands, have adopted a broader societal perspective (Rutten-van Mölken et al. 2010). This changes the cost and utility attributes involved and therefore the model outcomes. Not all countries have adopted cost-effectiveness as a criterion in their medical decision making. Moreover, even countries that have adopted cost-effectiveness as a criterion, do not always have a fixed threshold ICER. Therefore, other considerations in decision-making than cost-effectiveness will be discussed in the next paragraph.

6.4 Other considerations in decision-making

This thesis focused on the cost-effectiveness of pomalidomide in order to assist the decision-making process whether to accept reimbursement of the drug within the UK health care system (NHS). However, cost-effectiveness is only one of the criteria that decision makers face. Not all criteria that are used for medical decision making will be discussed here, but only the criteria that are most important for the decision making on pomalidomide.

Pomalidomide is recently approved for MM patients that are relapsed and/or refractory on bortezomib and lenalidomide. Without pomalidomide, rrMM patients' life expectancy is limited. Since pomalidomide extend this life expectancy, it can be referred to as a last resort option. The overall survival for patients treated with pomalidomide is less than 16 months (1.24 years on average). Therefore, pomalidomide can also be considered as an end-of-life drug. These drugs are often accepted with a higher ICER than the usual threshold.

NICE accepted a higher threshold ICER for end-of-life drugs (Moise 2011). Not only the cost-effectiveness, but also the total budget impact is a quantified aspect that is often considered in the decision-making process. The budget impact is determined by the costs of the treatment, and by the amount of patients that is eligible to receive the treatment. It can be assumed that the patient population with MM that survived initial treatment and a second therapy is small and the budget impact is limited. Since pomalidomide is likely to fit these special criteria, and the CE-threshold is bigger, there is a chance that pomalidomide will be accepted within the NHS.

6.5 Future research

There is limited information on the (cost-)effectiveness of pomalidomide. To assess the cost-effectiveness of pomalidomide more accurately, recommendations on future research will be given.

First, the MM-003 trial shows some evidence that there is a difference in the survival between patients that were last treated with lenalidomide or bortezomib. This implicates that subgroup analysis could be a useful way to determine for which groups of patient pomalidomide is more effective. The total patient population of the MM-003 trial consists of 355 patients. More information on subgroups could become available if a trial was performed on a bigger patient population.

In this thesis, the utility parameters are estimated from the values from Van Agthoven et al. (2004). These estimates are highly uncertain. Therefore, there is a need for more accurate utility measurement for MM patients in the double refractory stage of the disease.

The use of dexamethasone as comparator drug in this CEA is questionable, since it was states by NICE than pomalidomide plus low-dose dexamethasone would be compared to standard clinical management without pomalidomide. Drummond & Jefferson (1996) stated that the comparator in economic evaluation must be the best treatment option currently available. This results in "the most widely used alternative" (Drummond & Jefferson 1996). The incremental effects would therefore be more realistic if pomalidomide is compared to a combination of old agents, which is commonly applied in health care practice (Park et al. 2014).

All data on medical surveillance, costs of treating adverse events, treatment once the patients are progressed and end-of-life care are based on previous economic evaluations. Therefore, this data will not fully match the clinical reality. To obtain the real-life health care costs of treating rrMM patients with pomalidomide, data from clinical practice could be gathered.

7 Conclusion

This chapter will give a concluding overview of the answers given to the research questions of this thesis.

Little is known about treatment of rrMM patients with pomalidomide. Studies on cost-effectiveness are not published (yet), the studies on the effectiveness, safety and efficacy are scarce. Often the studies are performed with a small study sample. More information about the characteristics of MM patients (i.e. survival, toxicity) can be obtained from the studies performed with bortezomib and/or lenalidomide. The patients who receive bortezomib or lenalidomide in the single refractory stage of MM are the closest resemblance to the patients who are eligible to receive pomalidomide (double refractory). Therefore, data on these patients is often the best available data to use when assessing pomalidomide.

The post progression survival of patients refractory to both lenalidomide and bortezomib is poor, due to the progressive character of MM and the absence of an available treatment of MM patients in this stage of the disease. As shown in the survival analysis of this thesis, the post progression survival after treatment with lenalidomide as treatment in the single refractory stage is 8.3 months. For bortezomib this is 11.3 months.

The improvement in post-progression survival with the presence of a pomalidomide-based treatment for rrMM patients depends mostly on the period that patients receive pomalidomide. Once they progress, their post-progression survival is quite similar to the control group. The improvement in survival is 0.73 years, which is nearly 9 months.

This improvement in survival yields an increase of costs for treating rrMM patients. The average total costs of treating patients with pomalidomide, and the treatment after progression from pomalidomide to the patient's death are estimated on £96,350 per patient. For high-dose dexamethasone, with which pomalidomide is compared, this is £17,070.

The cost-effectiveness of pomalidomide in combination with low dose dexamethasone compared to high dose dexamethasone for patients with relapsed multiple myeloma refractory to both lenalidomide and bortezomib in the NHS setting is determined in incremental pounds per life year gained and pounds per QALY gained. The deterministic value of the ICER is £220,580. The probabilistic mean of the ICER is £220,687. This high ICER is mostly influenced by the high costs of pomalidomide and the limited difference in QALYs with dexamethasone. This is far above the £30,000 NHS threshold, but other considerations, like the budget impact and limited availability of other treatment options may change this standard threshold.

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Appendix A – systematic review CEA's on bortezomib and/or lenalidomide

Introduction

The systematic literature review aims to get insights in the strengths and weaknesses on CEAs performed on a population as close as the population eligible to receive pomalidomide.

Methods systematic review

A literature review on the economic evaluations for both lenalidomide and bortezomib was performed. The search engines used were Pubmed and Cochrane database for systematic review. Search terms included: multiple myeloma or plasma cell myeloma; economic or cost; and budget or expenditure and adding 'lenalidomide' or 'bortezomib' to the search term (following Gaultney et al. 2011).

Inclusion and exclusion criteria were**:** (1) the patients subject to the treatment were all diagnosed with multiple myeloma; (2) either the main comparator drug or the main intervention drug within the study was bortezomib or lenalidomide; (3) studies that contained previously untreated patients (/initial therapy) were excluded; and (4) only research articles in the English language were considered. Reviews and abstracts were excluded after search for the relevant studies in the reference list.

Papers were included after the title and abstract was read and the following elements were mentioned: (1) a costing element, inherent in the valuta used and the perspective taken; (2) an effectiveness element, either in response rates, survival or quality adjusted life years (QALYs). The stage of treatment in the studies was either maintenance or relapse/refractory.

3 full economic evaluation that met all criteria were found. Next to that, four reviews were found (Messori et al. (2011); Scott & Lyseng-Williamson (2011);Gaultney et al. (2012); Moeremans & Annemans (2006)); two additional economic evaluations were found in the reference lists of the reviews. The characteristics of the papers are given in Appendix A.

In all relevant papers, lenalidomide and bortezomib were compared to each other. In all papers, data from the MM-009/010 trials for lenalidomide, and data from the APEX trial for bortezomib was used. All studies were defined as cost-effectiveness analyses. Perspectives varied from 2 years to a lifetime perspective. The effectiveness outcome in all studies was given by an incremental cost-effectiveness ratio (ICER), in life years gained and in quality-adjusted life years (QALYs) gained. The costs were reported in pounds, euros, Swedish mint or Norwegian mint. All costs were converted to pounds. All studies in the papers were funded by pharmaceutical companies. An overview is given in table 8.

Study	*Hornberger et al. 2010*	*Brown et al. 2013*	*Deniz et al. 2008*	*Fragoulakis et al. 2013*	*Möller et al. 2011*
Intervention	BOR	LEN+ldDEX	LEN+ldDEX	LEN+ldDEX	LEN+ldDEX
Comparator	hdDEX or LEN+ldDEX	hdDEX	hdDEX	BOR	BOR
Perspective	Swedish NHS	UK NHS	UK NHS	Greece public providers	Norwegian NHS
Source of effectiveness estimation	RCT	RCT	RCT	RCT	RCT
Sample size (I/C)	669/704				
Type of evaluation	CEA	CEA	CEA	CEA	CEA
Time horizon	10 year	Lifetime	2 year base case	Lifetime	2 year base case
Discount rate	Costs and effects: 3%	Costs and effects: 3.5%	Costs and effects: 3.5%	Costs and effects: 3.5%	Costs and effects: 4%
Effectiveness outcomes	ICER	ICER	ICER	ICER	ICER
Incremental effects (LYG)	8.3; 0.46	2.2	1.8	0.79	0.76
Incremental costs	902,874; CS (SEK) = £80,722.81	£66.483	£52.336	€ 38.268,00 = £30,974.40	247,078 (NOK) = £24,596.17
Funding sources	Johnson & Johnson	Celgene	Celgene	Genesis Pharma Hellas	Celgene

Table 8: Overview of CEA on bortezomib and/or lenalidomide

Critical assessment

In order to assess the quality of each of the economic evaluations, a standardized checklist for reporting of CEAs was used (Drummond et al 2009). Certain issues are relevant for the model built to assess the cost-effectiveness of pomalidomide. In all papers, patients characteristics of both the intervention group and the control group were given or referred to. There is some patient heterogeneity which is sometimes mentioned, but not incorporated in the analysis. Moreover, differences in trial setting can result in different outcomes for the LEN and BOR group. All papers used the article of Van Agthoven et al. (2004) as a reference for their utility values. This choice will be further discussed in section 4.3.2. Little to nothing is mentioned about how the patients are treated after they relapse or become refractory to either lenalidomide or bortezomib. Both in the APEX and the MM-009/010 trial, a great amount of patients crossed over from the comparator group to the intervention group after progression. As Ishak et al. (2011) discussed thoroughly, this cross-over has a biased effect on the estimated overall survival in the comparator arm of the study.

The transferability of study settings in the economic evaluations is low. This, also reported by the authors themselves, decreases the use of the studies for reimbursement questions to the setting the study was performed in. In most studies only hazard ratios of Kaplan-Meier curves were given for the progression-free survival and the overall survival of the patients. Hazard

ratios, as discussed, rely on the assumption of proportional hazards. Because the post-progression period has a median of 9 months (Rajkumar et al. 2013), healthcare-related costs could be high and might differentiate between different groups.

Criteria Drummond et al. 2009	
Q1	Was a well-defined question posed in answerable form?
Q2	Was a comprehensive description of the competing alternatives given?
Q3	Was the effectiveness of the programs or services established?
Q4	Were all relevant costs/consequences for each alternative identified in light of viewpoint?
Q5	Were costs and consequences measured in appropriate physical units?
Q6	Were costs and consequences valued credibly?
Q7	Were costs and consequences adjusted for differential timing (i.e. discounted)?
Q8	Was an incremental analysis of costs and consequences of alternatives performed?
Q9	Was the impact of uncertainty in the estimates of costs and consequences examined?
Q10a	Was the conclusion easily interpretable and based on objective comparison in terms of costs and effect difference?
Q10b	Were the results compared with those of others and allowance made for methodological difference?
Q10c	Did the study discuss the generalizability of the results to other settings/patient groups?
Q10d	Did the study allude to or take account of other important factors in the choice of decision under consideration?
Q10e	Did the study discuss issues of implementation and whether free resources could be redeployed to other programs?

Figure 13: Criteria critical assessment CEAs on bortezomib and/or lenalidomide (from Drummond et al. 2009)

The results of the critical assessment are given table 9.

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10a	Q10b	Q10c	Q10d	Q10e
Hornberger et al. 2010	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No
Brown et al. 2013	No	No	Yes	Yes	Only consequences	Yes	Yes	Yes	Yes	Yes	Only response	No	Yes	No
Deniz et al. 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Only costs	Yes	No	No	No	No
Fragoulakis et al. 2013	Yes	Yes	Yes	Only costs	Only costs	Only costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Möller et al. 2011	Yes	No	Yes	Yes	No	Only costs	Yes	Yes	Yes	Yes	Yes	Yes	No	No

Table 9: Results of CEAs on bortezomib and/or lenalidomide on assessment of figure 12.

Appendix B – Survival analysis lenalidomide and bortezomib

Introduction

The survival analysis on bortezomib and lenalidomide used in the single refractory stage of MM is performed to assist chapter 3, in which the survival of MM patients without pomalidomide is assessed. The survival of MM patients without pomalidomide is determined as the post-progression survival after being treated with lenalidomide or bortezomib as a second treatment line. The post-progression survival is calculated as the overall survival minus the progression free survival, as shown in figure 14.

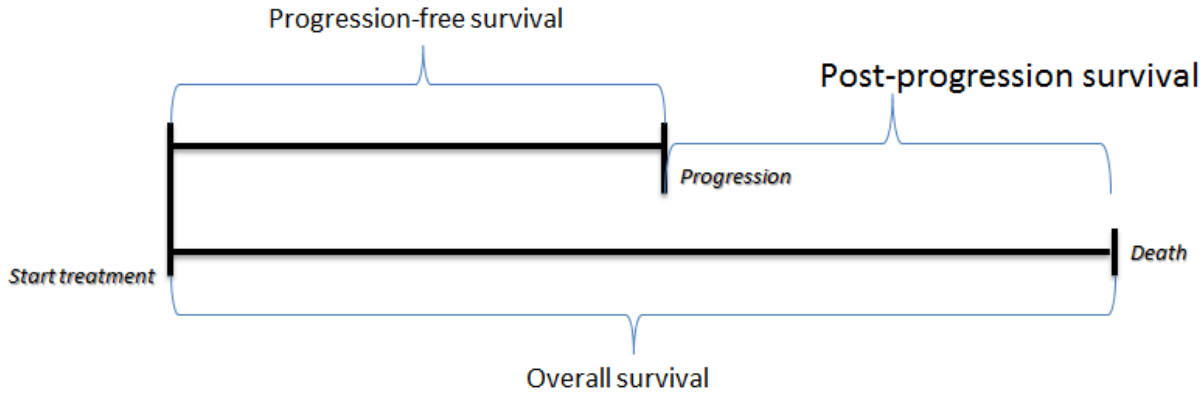

Figure 14: Post-progression survival as overall survival minus progression-free survival

Progression free survival

Progression free survival is usually measured through the time to progression, determined as the period from the treatment initiation until the patient progresses according to clinical guidelines. The progression free survival needs to be calculated to estimate the post-progression survival of patients in both trials. As discussed in chapter 4 of this thesis, the progression-free survival curve is digitalized. This digitalized curve is rebuilt in office Excel©, after which a Weibull curve with the scale (λ) and shape (γ) parameter were chosen as close as the survival curve. The curves are given in figure 15a and 15b.

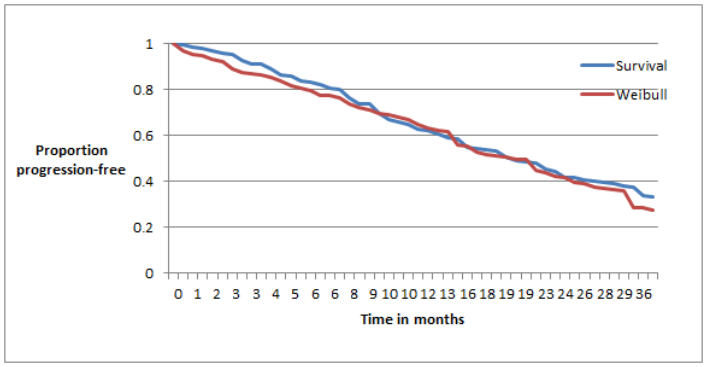

Figure 15a: PFS lenalidomide and fitted Weibull curve

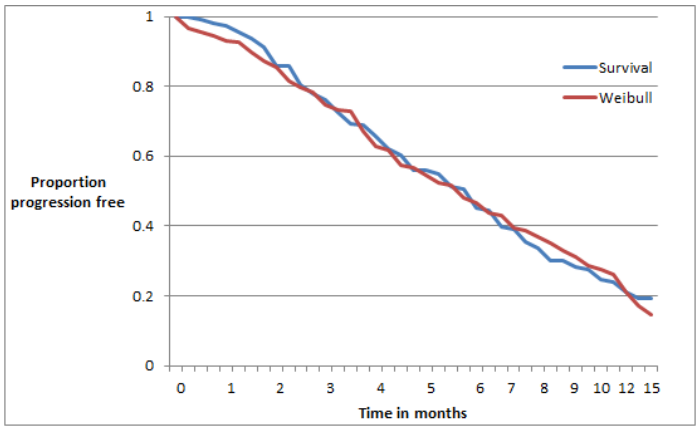

Figure 15b: PFS bortezomib and fitted Weibull curve

The chosen values for the Weibull parameters were put into a maximum likelihood estimation (MLE) together with These values are given in table 10.

	PFS lenalidomide	PFS bortezomib
Scale parameter (λ)	0.012	0.019
Shape parameter (γ)	0.92	1.11

Table 10: estimated PFS Weibull parameters for MLE

Overall survival

Because there is no cure for multiple myeloma, most patients eventually die from progression of MM (Fragoulakis et al. 2013). The overall survival incorporates the probability that patients will die during the period they receive the treatment of interest and the post-progression survival. The overall survival is estimated in the same way as the progression-free survival, with the survival curves in figure 16a and b, and the estimated Weibull parameters in table 11.

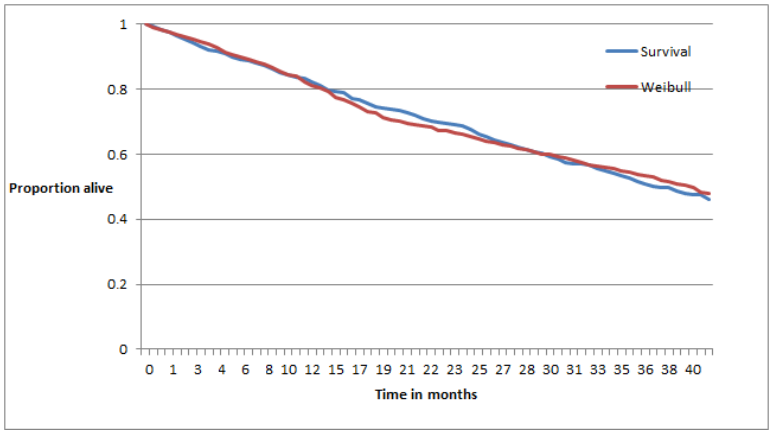

Figure 16a: OS lenalidomide and fitted Weibull curve

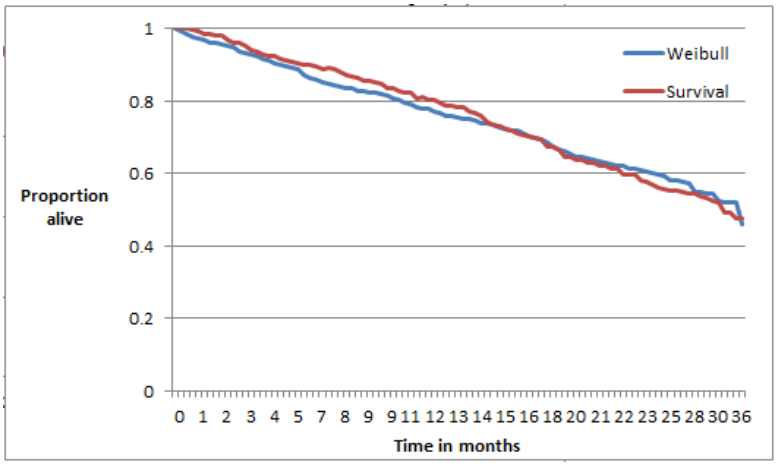

Figure 16b: OS bortezomib and fitted Weibull curve

	OS lenalidomide	OS bortezomib
Scale parameter (λ)	0.004	0.002
Shape parameter (γ)	1	1.2

Table 11: estimated OS Weibull parameters for MLE

The outcomes of the MLE estimated are given in table 12.

	PFS lenalidomide	OS lenalidomide	PFS bortezomib	OS bortezomib
Scale parameter (λ)	0.009	0.003	0.002	0.001
Shape parameter (γ)	0.967	1.089	1.203	1.195

Table 12: Weibull parameters as used for survival analysis

Appendix C – Resource use and unit costs in model

Unit costs drugs

Drugs	Stage of care	Unit costs per cycle (2014)	Reference unit costs	Reference resource use
Pomalidomide	Progression-free state	£8,884.00	Celgene (2013)	ESNM32
Dexamethasone	Progression-free state, progressed state	£2.39	Hoyle et al. (2008)	ESNM32; Park et al. 2014
Cyclophosphamide	Progressed state	£4.47	Hoyle et al. (2008)	Park et al. 2014
Etoposide	Progressed state	£224.81	Hoyle et al. (2008)	Park et al. 2014
Cisplatin	Progressed state	£11.34	Hoyle et al. (2008)	Park et al. 2014

Table 13: unit costs drugs

Monitoring costs

Test / Unit	Unit costs (2014)*	Use per cycle (PFS)**	Use per cycle (progressing)**	Use per cycle (progressed)**	Reference costs and use
Monitoring outpatient	£123.93	0.923076923	1	0.923076923	NHS reference costs 2005, clinical haematology
Routine blood counts (RBC)	£3.74	0.823076923	1.546153846	0.823076923	NHS reference costs 2005, pathology services test data (TPATH) - haematology
Clotting	£3.74	0.084615385	0.3	0.084615385	NHS reference costs 2005, pathology services test data (TPATH) - haematology
INR	£3.74	0.223076923	0.2	0.223076923	NHS reference costs 2005, pathology services test data (TPATH) - haematology
Biochemisrty (U&Es)	£2.03	0.746153846	1.330769231	0.746153846	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Liver function tests (LFTs)	£2.03	0.584615385	1.123076923	0.584615385	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Erythrocyte sedimentation (ESR)	£3.74	0.107692308	0.2	0.107692308	NHS reference costs 2005, pathology services test data (TPATH) - haematology
Plasma Viscosity	£2.03	0.023076923	0.123076923	0.023076923	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Uric Acid (Urate)	£2.03	0.107692308	0.207692308	0.107692308	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Immunoglobin (Igs)	£2.03	0.492307692	0.746153846	0.492307692	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Paraprotein Measurements (PP)	£2.03	0.584615385	0.853846154	0.584615385	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Protein Electrophoresis	£2.03	0.515384615	0.738461538	0.515384615	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Serum β2 microglobin	£2.03	0.230769231	0.384615385	0.230769231	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
C-reactive protein	£2.03	0.123076923	0.253846154	0.123076923	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Serum erythropoietin level	£2.03	0.007692308	0.038461538	0.007692308	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Immunofixation (SIF)	£2.03	0.261538462	0.369230769	0.261538462	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Creatinine-clearance (CRCL)	£2.03	0.053846154	0.176923077	0.053846154	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Glomerular filtration rate (GFR)	£2.03	0.253846154	0.546153846	0.253846154	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Serum Free	£2.03	0.223076923	0.315384615	0.223076923	NHS reference costs 2005,

Light Chains (SFLC)					pathology services test data (TPATH) - Biochemistry
Routine urineanalysis	£2.03	0.130769231	0.338461538	0.130769231	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
24-hour urine measurement (24hr UR)	£2.03	0.1	0.230769231	0.1	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
24-hour urine for creatinine (24hr UrCr)	£2.03	0.046153846	0.107692308	0.046153846	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Total Urine Protein (24hr TUP)	£2.03	0.107692308	0.246153846	0.107692308	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Urine protein electrophoresis/ light chains	£2.03	0.207692308	0.376923077	0.207692308	NHS reference costs 2005, pathology services test data (TPATH) - Biochemistry
Urine Immunofixation	£23.71	0.076923077	0.161538462	0.076923077	NHS reference costs 2005 - Radiology services test data (TRADIO)
Skeletal Survey by X-Ray	£23.71	0.007692308	0.123076923	0.007692308	NHS reference costs 2005 - Radiology services test data (TRADIO)
Skeletal Survey by X-Ray individual sites	£3.74	0.007692308	0.123076923	0.007692308	NHS reference costs 2005, pathology services test data (TPATH) - haematology
MRI	£399.85	0	0.069230769	0	NHS reference costs 2005, pathology services test data (TPATH) - histology/histopathology
Bone Densitometry (BMD)	£8.11	0	0.007692308	0	NHS reference costs 2005, pathology services test data (TPATH) - Microbiology / virology
Bone Marrow Trephine (BMT)	£2.03	0.015384615	0.161538462	0.015384615	NHS reference costs 2005, pathology services test data (TPATH) - haematology
Neuropathy	£2.03	0.015384615	0.153846154	0.015384615	NHS reference costs 2005, pathology services test data (TPATH) - haematology
Bacterial investigation	£3.74	0.007692308	0.007692308	0.007692308	NHS reference costs 2005, pathology services test data (TPATH) - haematology

Table 14: Monitoring costs

Adverse events costs

Adverse event	Treatment	Unit costs	Reference
Anaemia	Inpatient	£1,569.56	NHS reference costs 2005
	Day-case	£550.08	NHS reference costs 2005
	Outpatient	£123.93	NHS reference costs 2005
Febrile neutropenia	Inpatient	£2,295.56	NHS reference costs 2005
Neutropenia	Inpatient	£2,295.56	NHS reference costs 2005
	Day-case	£600.51	NHS reference costs 2005
	Outpatient	£123.93	NHS reference costs 2005
Thrombocytopenia	Inpatient	£1,992.61	NHS reference costs 2005
	Day-case	£700.03	NHS reference costs 2005
	Outpatient	£123.93	NHS reference costs 2005
Fatigue	Outpatient	£506.93	NHS reference costs 2009-2010
Pyrexia	unknown	£480.54	NHS reference costs 2009-2010
Pneumonia	Inpatient	£1,417.42	NHS reference costs 2009-2010
Bone pain	unknown	£440.95	NHS reference costs 2009-2010
Leukopenia	unknown	£517.93	NHS reference costs 2009-2010

Table 15: Adverse events costs

End-of-life costs

Unit	How often per cycle	Part patient population	Unit cost	Reference
Adverse event	1.00	1	£2,104.85	estimation
Hospice care	3.73	0.2	£394.77	Expert estimate in STA cabazitaxel; SD04A: Medical Specialist Palliative Care Attendance 19 years and over

Palliative home care - nurse	4.80	0.5	£29.69	Expert estimate in STA cabazitaxel; PSSRU 2010, Cost of Community Nurse per home visit73
Palliative home care - nurse	1.20	0.5	£131.96	Expert estimate in STA cabazitaxel; PSSRU (2010), Cost of GP per home visit lasting 23.4 minutes including travel time73
Palliative outpatient visits	0.75	0.5	£279.31	Expert estimate in STA cabazitaxel; National Schedule of Reference Costs (2009–10) – NHS Trusts Specialist Palliative Care: Outpatient50

Table 16: end-of-life costs

Appendix D - Linear extrapolation of utility estimates

The utility values in this thesis are adjusted values from the study of Van Agthoven et al. (2004), who obtained the EQ-5D utility values from MM patients who were recently diagnosed. In this thesis, the assumption is made that the utility value of the progressed state of Van Agthoven et al. (2004) is equal to the utility in the progression-free state when concerning rrMM patients who received at least two previous treatments. It is also assumed that the utility decrement of progressed rrMM patients cannot be equal to the utility decrement of progression-free rrMM patients, because a linear QALY model cannot be assumed. Therefore, the exponential QALY model is used to estimate the utility value for the progressed state in this thesis. However, it is possible that the linear QALY model holds and using the exponential QALY model gives the wrong results in terms of the ICER. Figure 17 shows that when the linear QALY model is applied, the estimated utility value of the progressed state is equal to 0.488 (for comparison, the exponential model result was 0.537).

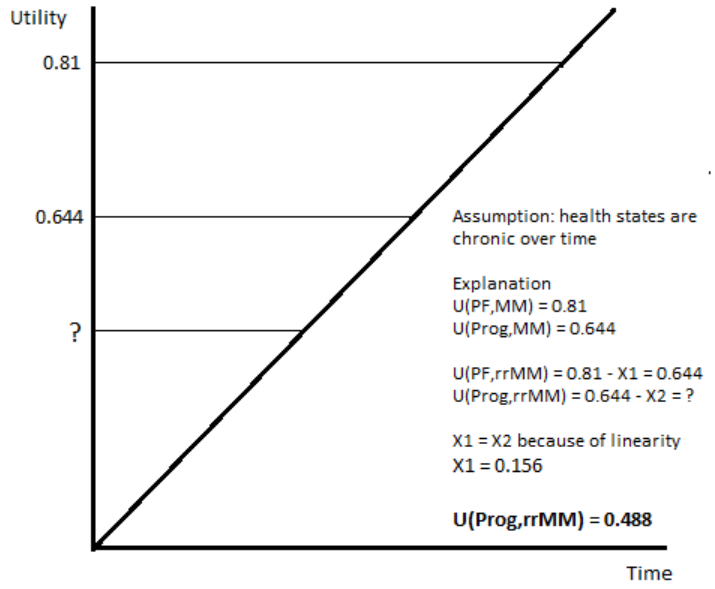

Figure 17: Utility adjustment rrMM (linearly)

Because patients also experience adverse events in the progressed health state (when receiving DCEP), the utility value is adjusted for the utility decrement of common adverse events, multiplied by the probability a patient will experience an adverse event per cycle. This results in an utility value of the progressed state of 0.37 (table 17).

Adverse event	Utility decrement	Occurrence per cycle
Anaemia	0.31	0.17
Febrile neutropenia	0.09	0.09
Neutropenia	0.145	0.10
Thrombocytopenia	0.31	0.083
Adjusted utility progressed state	**0.37**	

Table 17: Utility adjustment for adverse events for the linear uProgression

As seen in the OSA, the utility of the progressed state has effect on the ICER. Because costs stay equal, the ICER is higher (£239,010 v. £220,580) (table 18) and therefore, estimating the utility values linearly is less favorable for the ICER.

Results (deterministic) discounted			
Treatment	**Costs**	**QALY**	**LY**
POM+ldDEX	£96,232	0.57	1.24
hdDEX	£17,063	0.24	0.51
Increment	**£79,169**	**0.33**	**0.73**
		incremental costs/ QALY	**incremental costs/ LY**
ICERs: POM+ldDEX vs hdDEX		**£239,010**	**£108,210**

Table 18: ICER when utility values are estimated linearly