2011

A cost-effectiveness analysis of two anti-EGFR monoclonal antibodies (cetuximab and panitumumab) plus best supportive care versus best supportive care alone as third-line treatment of advanced chemorefractory metastatic colorectal cancer

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A cost-effectiveness analysis of two anti-EGFR monoclonal antibodies (*cetuximab* and *panitumumab)* plus best supportive care versus best supportive care alone as third-line treatment of advanced chemorefractory metastatic colorectal cancer

(Spine title: Cost-effectiveness analysis of anti-EGFR monoclonal antibodies)
(Thesis format: Monograph)

By

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Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

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ABSTRACT

Introduction

The National Cancer Institute of Canada Clinical Trials Group CO. 17 trial and the Open-Label Phase III trial showed that the addition of new anti-EGFR monoclonal antibodies (*cetuximab and panitumumab*) to best supportive care as third-line treatments prolong the life of patients with advanced metastatic colorectal cancer, but have also introduced a unique set of toxicities and increased costs. In a resource constrained environment this prompts the need for tools to identify the patients who are likely to benefit from these therapies in a more efficient and cost-effective way.

We developed an economic model using analytic decision modeling to assess the cost-effectiveness of two anti-EGFR monoclonal antibodies (cetuximab and panitumumab) plus best supportive care versus best supportive care alone as third-line treatment in advanced chemorefractory metastatic colorectal cancer.

Methods

We constructed a Markov model based on the efficacy data obtained from the National Cancer Institute of Canada Clinical Trials Group CO. 17 trial and the Open-Label Phase III trial studies. Costs for physician visits, blood products, emergency department visits, hospitalizations and toxicity management were obtained published literature and expert opinion. Drug costs were obtained from London Health Sciences Center (LHSC) drug formulary intranet. The primary outcome of the model is the incremental cost-utility ratio of adding anti-EGFR monoclonal antibodies (panitumumab and cetuximab) to best supportive care as third-line therapies in treatment of advanced metastatic chemo-refractory colorectal cancer, expressed as cost per quality-adjusted life year (QALY) gained. A series of deterministic and probabilistic sensitivity analyses were also performed to account for uncertainty in the model parameters.

Results

Adding panitumumab to best supportive care (with KRAS test) resulted in a mean gain of 0.087 QALYs with a mean incremental cost utility ratio of $269,703 per QALY gained (95% CI = $135,432 to $766,072 per QALY gained). The addition of cetuximab to best supportive care (with KRAS test) resulted in a mean gain of 0.068 QALYs with a mean incremental cost-utility ratio of $352,046 per QALY gained (95% CI = $151,916 to $949,342 per QALY gained). In subset of patients with wild-type KRAS, the addition of panitumumab to best supportive care resulted in a mean gain of 0.16 QALYs with a mean incremental cost-utility ratio of $236,469 per QALY gained (95% CI = $125,259 to $557,750 per QALY gained).

Conclusions

From a health economic perspective, both anti-EFGR therapies (panitumumab and cetuximab) showed very high Incremental cost-utility ratios and were not cost-effective at a willingness-to-pay threshold of $100,000 per QALY. The cost-utility ratios were much more favorable in subset of patients with wild-type KRAS. This suggests that personalizing advanced metastatic colorectal cancer treatment based on KRAS mutation status could not only save health care system substantial sums but also spare thousands of patients with metastatic colorectal cancer from side effects of the anti-EGFR therapies that are unlikely to benefit from the treatment.

Keywords

Epidermal growth factor receptor, Anti-EGFR monoclonal antibodies, KRAS oncogene, Colorectal, Incremental cost-utility ratio, Quality-adjusted life year, Probabilistic sensitivity analysis.

DEDICATION

This thesis is dedicated to oncology research

ACKNOWLEDGEMENTS

I would like to thank my thesis supervisor, Dr. Greg Zaric and co-supervisor, Dr. Muriel Brackstone for their support and assistance during the development, execution and writing of the thesis.

Mr. Malek Bassam Hannouf for his advice on analytic model building.

Mr. Benjamin Ofori, Regional Medical Liaision, AMGEN Canada Inc., for his support in database search and release of clinical trial information.

Mr. Robert Toman, specialty Representative Oncology, Bristol-Myers Squibb Canada., for his advice on database search.

Dr. Ian Arra for his great support as a friend and his advice on thesis format.

Finally, I would like to thank my wife and daughter for their love, support, and encouragement.

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LIST OF ABBREVIATIONS AND UNITS

EGFR	Epidermal growth factor receptor
IgG	Immunoglobulin G
QALY	Quality adjusted life year
GTP	Guanine Tri-Phosphate
GDP	Guanine Di-Phosphate
PCD	Programmed cell death
SNPs	Single-nucleotide polymorphisms
HER	Human epidermal growth factor receptor
NSCLC	Non-small-cell lung cancer
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CMA	Cost-minimization analysis
CBA	Cost-benefit analysis
ICER	Incremental cost-effectiveness ratio
HUI	Health Utilities Index
EQ-5D	Euroqol 5D
QWB	Quality of well-Being
HRQoL	Health-related quality of life
ECOG	Eastern Cooperative Oncology Group
PFS	Progression-free survival
OS	Overall survival
PCR	Polymerase chain reaction
BSC	Best supportive care

NCIC CTG	National Cancer Institute of Canada Clinical Trials Group
OL Phase III	Open Label Phase III study
CPI	Consumer price index
LHSC	London Health Sciences Center
CIHI	Canadian Institute for Health Information
IV infusion	Intravenous infusion
ER visit	Emergency room visit
AE	Adverse Events
ICE	Incremental cost-effectiveness
CDR	Canadian Common Drug Review
CEDAC	Canadian Expert Drug Advisory Committee

Chapter 1: Introduction

Colorectal cancer is the third most common cancer and the second most common cause of death due to cancer among Canadians [1]. According to Statistics Canada, in 2010 an estimated 22,500 Canadians will be diagnosed with colorectal cancer and 9,100 will die from it [1].

The life expectancy of metastatic colorectal cancer patients who receive best supportive care without chemotherapy is about five to six months [2-3]. The current use of standard chemotherapy such as 5-fluourouracil and leucovorin along with adjuvant chemotherapy such as irinotecan, oxaliplatin, and bevacizumab as first-line or second-line treatment for metastatic colorectal cancer have resulted in median survival rates of about 18 months to 21 months [3-8], but most patients eventually become chemo-refractory to these therapies [8-9] and die of their disease [8-9].

The treatment of advanced metastatic colorectal cancer, which involves conventional chemotherapy, is very costly and each year millions of dollars are spent for treating patients with colorectal cancer in Canada [10-12]. The rising cost of treatment along with increasing rate of treatment failure is becoming a significant financial burden on a publicly funded health-care system [10-11]. The current situation poses a great challenge for clinicians, researchers, and policy makers to find new cost-effective ways for the treatment of advanced metastatic colorectal cancer.

Epidermal growth factor receptor (EGFR) is a 170-kDa trans-membrane tyrosine kinase receptor and belongs to human epidermal growth factor receptor (HER) family [13]. EGFR is present in most epithelial tissues and is widely expressed in different types of cancer such as colorectal cancer, breast cancer, stomach cancer and oesophageal cancer [13]. The over expression EGFR is associated with increased risk of cancer recurrence, metastasis and poorer survival along with resistance to chemotherapy [13].

According to recent research, the therapies targeting EGFR have shown activity in chemorefractory metastatic colorectal cancer [8-9, 13-14] especially in patients with the wild-type KRAS oncogene [13, 15-18]. These therapies include anti-EGFR monoclonal antibodies such as *cetuximab* (Erbitux®) and *panitumumab (*Vectibix®). The anti-EGFR monoclonal antibodies specifically bind to cysteine-rich extracellular domain of EGFR and compete with the other natural ligands for binding to the receptor, thus preventing ligand-induced activation of EGFR intracellular signalling pathway [13-18].

The KRAS gene plays an important role in the EGFR signalling pathway and activating mutations in the KRAS gene are predictive of response to anti-EGFR therapy in EGFR-expressing metastatic colorectal cancer [13-18]. These activating mutations lead to an independent and uncontrolled activation of downstream EGFR intracellular signalling pathways which results in increased tumour cell growth, proliferation, metastasis, protection against apoptosis, and activation of tumour induced angiogenesis [13-19].

Both cetuximab and panitumumab are anti-EGFR monoclonal antibodies [8-9] but they have significant structural differences. Cetuximab is a chimeric monoclonal antibody with a significant amount of mouse protein [20-21]. The presence of this foreign protein increases the chance of antibody development against the monoclonal antibody which also increases the chance of infusion reactions [22]. Panitumumab, on the other hand, is a fully humanized antibody [8, 23]; therefore, its use poses a low risk of anti-panitumumab antibody formation and infusion reactions [22, 24-25].

Furthermore, cetuximab is an immunoglobulin G1 (IgG1) monoclonal antibody [20-21], whereas panitumumab is an immunoglobulin G2 (IgG2) monoclonal antibody [8, 21, 23]. These differences are of clinical significance, as dissimilar immunoglobulin subtypes affect complement activation and antibody-mediated cytotoxicity differently [26].

In clinical practice, there is no therapeutic preference for using cetuximab versus panitumumab either as immunotherapy or in combination with chemotherapy as treatment of advanced metastatic colorectal cancer primarily due to lack of trials directly comparing cetuximab versus panitumumab [21]. The introduction of these new anti-EGFR therapies (panitumumab and cetuximab) have shown to prolong the life of patients with advanced metastatic colorectal cancer [8-9] but have also introduced a unique set of toxicities and increased costs [8, 9, 27-30]. In a shrinking health care resources environment, this prompts the need for tools in form of economic analysis to identify the patients who are likely to benefit from these therapies in a more efficient and cost-effective way.

I developed an economic model using analytic decision modeling to assess the cost-effectiveness of two anti-EGFR monoclonal antibodies *(cetuximab and panitumumab)* plus best supportive care versus best supportive care alone as third-line treatment in advanced chemorefractory metastatic colorectal cancer patients. I also compared the cost-effectiveness of panitumumab plus best supportive care versus cetuximab plus best supportive care as third-line treatment using a cross-trial comparison method. Owing to the importance of KRAS gene mutation in EGFR-expressing metastatic colorectal cancer [13-19], I assessed the cost-effectiveness of KRAS testing by comparing the cost and effectiveness both anti-EGFR therapies plus best supportive care with and without KRAS testing.

The rationale for conducting a cost-effectiveness analysis using Markov decision modeling is that it will offer an explicit and transparent approach to quantify the costs and benefits of treatment strategies being compared by using a common denominator i.e. quality-adjusted life years (QALYs). The resulting cost-utility ratios can then be compared across conditions with each other or with a willingness-to-pay threshold value, with the goal of identifying the most efficient ways of maximizing health at the population level. This approach has the potential advantage of facilitating a deliberative, systematic, and data-driven decision-making process for the allocation of public resources.

The remainder of this thesis is organized as follows. In chapter 2, I have discussed the literature review part of the thesis. In chapter 3, I have enumerated the primary and secondary research questions related to the thesis. In chapter 4, I have explained the materials and methods used to conduct my cost-effectiveness analysis. In chapter 5, I have shown the results of my economic analysis along with deterministic and probabilistic sensitivity analyses. I conclude in chapter 6.

Chapter 2: Literature Review

The first half of this chapter covers the biology and significance of KRAS gene and epidermal growth factor receptor (EGFR) in advanced metastatic colorectal cancer. Furthermore, it explains in detail the role of KRAS gene mutations and response to anti-EGFR therapies in patients with advanced metastatic colorectal cancer. The second half of the chapter describes different types of economic analysis and decision analytic models used for health economic evaluation.

2.1 Background / Biology & Significance of the KRAS gene

2.1.1 Location of the KRAS gene

The KRAS gene is also known as v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog [31-32]. Its cytogenetic location is on the short arm (p) of chromosome 12 at position 12.1 (12p12.1) and its molecular location is from base pair 25, 249, 446 to base pair 25, 295, 120 on chromosome 12 [31-33].

2.1.2 Functions of the KRAS gene

The KRAS gene is a member of the RAS subfamily [31]. Like other members of RAS subfamily such as HRAS and NRAS, it is involved in many cellular signal transduction pathways such as the EGFR (epidermal growth factor receptor) signalling cascade [17-18, 33-35]. These signalling transduction pathways are carried out through the KRAS protein encoded by the KRAS gene and lead to important cell functions such as cell division, cell maturation, cell differentiation and apoptosis (also known as the process of programmed cell death "PCD") [17-18, 33-35]. The KRAS protein is GTPase in nature and converts GTP (Guanine Tri-Phosphate) to GDP (Guanine Di-Phosphate) by cleaving the terminal phosphate of the nucleotide [18, 35].

The binding of the KRAS protein to cell membranes occurs due to the presence of an isoprenyl group on its C-terminus [13, 18]. The KRAS protein acts like a control switch and it is activated by binding with GTP and deactivated when GTP is converted to GDP [13, 18]. Once GTP is converted to GDP and the KRAS is binded to GDP, it stops relaying any signals to the cell nucleus [13, 18].

2.1.3 Mutations in the KRAS gene

Somatic mutations in the KRAS gene play an important role in the development of several types of cancer such as colorectal cancer [36], pancreatic cancer [37] and lung cancer [38]. These activating point mutations result from substitution of a single amino acid or single-nucleotide polymorphisms (SNPs) such as p.Gly12Val in a critical part of oncogene structure known as codons and leads to a block of the GTP hydrolytic activity of the *K-ras*-p21 protein [13, 18]. This results in a continuous activation of the KRAS protein and this persistent activation of the KRAS protein is non-responsive to particular regulatory signals from outside the cell and results in an uncontrolled and continuous cell growth, cell proliferation and cell division [13, 18]. About 90% of activating mutations in the KRAS oncogene which are related to development of different types of cancer especially colorectal cancer, occur in codons 12 (CGT) and 13 (GGC) [13, 18]. According to recent studies some rare mutations also occur at codons 61(CAA) and 146 [13, 17-18].

2.2 Background / Biology & Significance of the EGFR

2.2.1 EGFR (Epidermal growth factor receptor)

The EGFR (Epidermal growth factor receptor) is a 170-kDa trans-membrane tyrosine kinase receptor and belong to human epidermal growth factor receptor (HER) family [13]. EGFR is present in most epithelial tissues and is widely expressed in different types of cancer such as colorectal cancer, breast cancer, stomach cancer and oesophageal cancer [13]. The over expression of

EGFR is associated with increased risk of cancer recurrence, metastasis and poorer survival along with resistance to chemotherapy [13].

2.2.2 Domains of the EGFR

Domains are the units of protein structure and sequence in a receptor which can evolve, function, and exist independently of the rest of the protein chain. Each domain forms a compact three-dimensional structure and may vary in length from about 25 amino acids up to 500 amino acids [39]. The EGFR has five domains.

1) a ***cysteine-rich extracellular domain***, which recognizes and binds ligands such as epidermal growth factor (EGF), transforming growth factor (TGF)-α and amphiregulin [39].

2) a ***hydrophobic transmembrane domain***, which is mainly involved in interactions between cell surface receptors and plays an important role in anchoring the receptor to the lipid bilayer of the cell [39].

3) a ***tyrosine kinase domain,*** which can cross-phosphorylate tyrosine residues of other receptors and plays an important role in functional activation and induction of EGFR signalling pathways [39].

4) an ***internalization domain***, which regulates ligand internalization and receptor sorting [39].

5) a ***cytoplasmic domain*** also known as C-terminal domain, which includes autophosphorylated tyrosine residues and plays an important role in internal regulation of tyrosine kinase activity [13, 39].

2.2.3 Activation of the EGFR Signalling Pathway

The activation of EGFR signalling pathway occurs in a sequential manner. In the first step, the binding of specific ligands to extracellular domain of EGFR occurs, this results in the formation of a functionally active EGFR dimer (an association of two identical molecules linked together) with another ligand-bound EGFR or with one of the EGFR related receptors such as HER2 (human

epidermal growth factor receptor 2), HER3 (human epidermal growth factor receptor 3), or HER4 (human epidermal growth factor receptor4) [13, 40]. Finally, this receptor dimerization results in auto-phosphorylation of tyrosine kinase within the C-terminal domain of the receptor which leads to the activation of several downstream signalling cascades such as RAS-MAPK pathway, P13K-Akt pathway and STAT pathway. These signal transduction pathways control gene transcription, cell growth and proliferation, angiogenesis, and invasion [13, 40].

The KRAS gene plays an important role in the EGFR signalling pathway. Activating mutations in the KRAS gene leads to an independent and uncontrolled activation of downstream EGFR intracellular signalling pathways which results in increased tumour cell growth, proliferation, invasion and activation of tumour induced angiogenesis [13-19].

2.3 EGFR antagonists

Due to the important role of EGFR in cancer development and progression, two types of EGFR antagonists have been developed to block the downstream EGFR intracellular signalling which can potentially lead to inhibition of tumour cell growth, proliferation and metastasis [13].

1) The first type includes ***anti-EGFR monoclonal antibodies*** such as *cetuximab* (Erbitux®) and *panitumumab* (Vectibix®). These anti-EGFR antibodies specifically bind to Cysteine-rich extracellular domain of EGFR and compete with other natural ligands for binding to the receptor, thus preventing ligand-induced activation of EGFR intracellular signalling pathway [13].

2) The second type includes ***small-molecule EGFR-Tyrosine kinase inhibitors*** such as *gefitinib* (Iressa®) and *erlotinib* (Tarceva®). These EGFR-Tyrosine kinase inhibitors compete with ATP for binding to the intracellular cytoplasmic domain also known as C-terminal domain of the EGFR, thus inhibiting EGFR tyrosine phosphorylation [13]. This inhibition

of EGFR tyrosine phosphorylation suppresses the activation of the downstream EGFR intracellular signalling pathway [13].

2.4 EGFR gene mutations & Response to anti-EGFR therapy

The two types of EGFR antagonists such as anti-EGFR monoclonal antibodies (cetuximab and panitumumab) and EGFR-Tyrosine kinase inhibitors (gefitinib and erlotinib) have been evaluated extensively for the treatment of different types tumours with EGFR over-expression [13, 34]. These tumours include colorectal cancer, metastatic non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and pancreatic cancer [13, 34].

The EGFR gene and the KRAS gene mutations generally occur independently and are predictive of response to EGFR-targeted treatments depending on the type of cancer [13]. The EGFR gene mutations are strongly correlated with phosphorylation of the EGFR at tyrosine 992 (pEGFR-tyr992) and are predictive of response to EGFR-Tyrosine kinase inhibitors (gefitinib and erlotinib) in metastatic non-small-cell lung cancer [13, 41-43]. However, the EGFR gene is rarely mutated (less than 1 %) in patients with colorectal cancer and therefore it is a poor predictor of response to EGFR-targeted therapy in such patients [13, 44].

2.5 KRAS gene mutations and response to anti-EGFR therapy

The KRAS gene mutation is predictive of response to EGFR-targeted therapy in almost all EGFR-related cancers, particularly colorectal cancer and non-small-cell lung cancer [13]. The KRAS gene is mutated in approximately 30 - 40% of colorectal cancers [13], 20 - 30% of non-small-cell lung cancers [45], and 70 – 90% of pancreatic cancers [46]. Recent studies have shown that advanced metastatic colorectal cancer patients with the mutated KRAS gene respond poorly to anti-EGFR monoclonal antibodies such as cetuximab and panitumumab [13-19, 47]. Similarly, studies evaluating the KRAS gene mutation status in non-small-cell lung cancer (NSCLC) patients have shown that mutations in the KRAS

gene are strongly predictive of resistance to EGFR-Tyrosine kinase inhibitors such as gefitinib and erlotinib [48-50].

2.6 Economic evaluation

Economic evaluation is defined as the comparative analysis of actions in terms of both their costs and consequences in order to assist policy decisions [51]. In the context of healthcare, the main purpose of economic evaluation is to "identify, measure, value and compare the costs and health outcomes of alternative treatment strategies being considered" [51] to inform "value for money" judgments about a treatment strategy [52].

2.6.1 Stages of Economic Evaluation

The following are the main stages of an economic evaluation [51-52].

1. Research Question
2. Assessment of Costs and Consequences
3. Analysis
4. Variability and Uncertainty

2.6.2 Research Question

The first stage is to state the research question to be addressed by the economic evaluation in a well defined and answerable form relevant to the decision facing the target audience [52]. The research question also defines the target population in terms of their condition (e.g., stage or severity of the disease or tumour) along with appraising the alternative treatment strategies (comparators) relevant to the study [52]. The primary perspective of the study (e.g., public payer) and relevant secondary research questions are also defined [52].

2.6.3 Assessment of costs and consequences

The 2nd stage of an economic evaluation is the identification, measurement and valuation of all type of costs and consequences (health outcomes) related to the study with best available evidence and methods [51-52].

2.6.4 Analysis

The 3rd and most important stage of an economic evaluation is analysis. The selection of appropriate type of analysis is entirely based on nature of the research question, the condition of interest, and the availability of data on outcomes [51-52]. There are four main types of methods for economic evaluation discussed below:

1. Cost-effectiveness analysis (CEA)
2. Cost-utility analysis (CUA)
3. Cost-minimization analysis (CMA)
4. Cost-benefit analysis (CBA)

2.6.5 Cost-effectiveness analysis (CEA)

According to the literature [52], the term "cost-effectiveness" is usually used to refer to economic evaluations in general. In the context of healthcare, the cost-effectiveness is a type of economic evaluation in which costs are expressed in monetary terms and the health outcomes in natural health units such as life-years gained, adverse events avoided, and reduction in blood pressure etc [51-52]. The result of a cost-effectiveness analysis is expressed as incremental cost-effectiveness ratio (ICER = incremental cost ($C_A - C_B$) / ($E_A - E_B$) incremental effectiveness) [51-52]. The net benefits approach may be used as an additional measure to ICER especially when the incremental effectiveness is very small (ICER becomes very large) and a willingness-to-pay threshold has been assumed [52]. The willingness-to-pay is defined as the maximum amount a person would be willing to pay to acquire a good /service or to avoid an undesired event [51].

2.6.6 Cost-utility analysis (CUA)

Cost-utility analysis is based on the same principle as the cost-effectiveness analysis [51]. Costs are measured in monetary terms and health outcomes as health-related preferences (combined in to a weighted index; valued as utilities) such as quality-adjusted life year (QALY) [51-52]. Multi-attribute utility instruments such as Health Utilities Index (HUI), Euroqol (EQ-5D), and Quality of well-Being (QWB) are used to assign quality of life scores (utilities) to health states [51].

Cost-utility analysis is method of choice when there are significant differences in health-related quality of life (HRQoL) among treatment strategies being compared [52]. The use of a generic health outcome measure in a cost-utility analysis not only permits policy and decision makers to make broad comparisons across treatment strategies but also facilitate the allocation of resources based on maximizing health gains [52]. The result of a cost-utility analysis is expressed as incremental cost-utility ratio (similar to ICER) [51-52]. The net benefits approach may be used as an additional measure to incremental cost-utility ratio especially when the incremental effectiveness is very small (incremental cost-utility ratio becomes very large) and a willingness-to-pay threshold has been assumed [52].

2.6.7 Cost-minimization analysis (CMA)

Cost-minimization analysis is a type of economic study in which two or more treatment strategies with same effectiveness or efficacy are compared in terms of net costs in order to establish least costly alternative [51-52]. In the context of healthcare, a cost-minimization analysis can be regarded as an extension of cost-utility or cost-effectiveness analysis, where the health outcomes of treatment strategies being compared are demonstrated to be equivalent in all aspects and only the costs of alternatives are being compared [52].

2.6.8 Cost-benefit analysis (CBA)

Cost-benefit analysis is a type of economic study where both costs and consequences (health outcomes) are measured in monetary terms [51-52]. In the context of healthcare, the use of cost-benefit analysis in healthcare policy and decision making is very limited due to methodological difficulties with measuring health outcomes in monetary terms, and ethical issues arising from assigning cost values to health outcomes [52].

2.6.9 Variability and uncertainty

This the final stage of economic analysis in which series of deterministic and probabilistic sensitivity analyses are performed to verify the robustness of results and to account for variability and uncertainty surrounding important parameters in economic evaluation such as health outcomes, costs, probabilities, timing and resource utilization [51-52].

2.7 Economic Evaluation Using Decision Analytic Modelling

Economic evaluation using decision analytic modelling is a logical mathematical framework that permits the integration of a series of possible consequences in the form of health and economic outcomes of patients that would flow from the alternative courses of actions being evaluated [51].

In the context of health economic evaluation, decision analytic modeling allows a rational, feasible, scientific, and timely approach to measure the efficiency new medical interventions in health care by using the best available evidence of various sources and produces detailed estimates of the clinical and economic consequences [53].

The main purpose of economic evaluation using decision analytic modelling is to structure all relevant evidence on clinical and economic outcomes to help inform decisions about clinical practice and health-care resource allocation under conditions of uncertainty, and to make these decision explicit while considering the consequences of these decisions [51, 53].

2.7.1 Stages in the development of decision analytic model

There are three main stages of development of a decision analytic model [51]. First stage is to define the decision problem in terms of a research question considering possible alternatives and payoffs [51, 53]. The second stage is to define model boundaries and parameters which include choice of perspective, appropriate measures of cost and effectiveness, time horizon and various other implications of intervention under consideration [51, 53]. The final stage is the structuring of model based on timing of events, changes in probabilities, extrapolation in to future and incorporation of all relevant costs and effects [51, 53].

2.7.2 Types of decision analytic models

There are three main types of decision analytic models [51]:

1. Decision Tree
2. Markov Model
3. Microsimulation Model

2.7.3 Decision Tree

A decision tree uses a tree like graph or model of decisions and their possible consequences [51]. The events are ordered from left to right and different kinds of events are distinguished using three different shapes called "nodes" [51].

- Square "■" – a decision node indicating a choice and typically at the start of the tree. The branches from a decision node represent the set of alternative strategies being considered for evaluation [51].
- Circle "●" – a chance node representing an event which has multiple possible outcomes and is not under the decision maker's control [51, 53]. The branches from a chance node represent the set of possible

outcomes of the event which must be mutually exclusive and collectively exhaustive [51]. The probabilities of these outcomes must sum to 1.0.

- Triangle "◄" – a terminal node which denotes the endpoint of a scenario. A terminal node has no emanating branches and referred to generically as payoff [51]. The payoff can be costs or effectiveness (LY's or QALYs) [51].

2.7.4 Markov Model

Markov models also known as state transition models are used for events that occur repeatedly over time such as chronic or progressive diseases, cycles of screening or treatment etc [51, 54]. Markov models can handle both costs and outcomes which make them a powerful tool for economic evaluation modeling [51]. The main characteristics of a Markov model are shown below:

- States – A Markov model consists of a set of mutually exclusive states which must be defined. The states can be transient, temporary or absorbing [51, 54].
- Cycles – A Markov model is run for a fixed time period and is broken up in to any number of cycles of fixed length (e.g., week, month, and year) [51]. At the end of each cycle, patients either remain in the same state or move in to a new state and then start over again in a new cycle [51, 54].
- Transition probabilities – A Markov model consists of a set of transition probabilities among states which determine the % of members of state that transition to different states to start the next cycle [51, 54]. The state transition probabilities can be constant or time-dependent [51, 54].
- Rewards – The patients in each state accumulate rewards (e.g., costs, utilities, event counts) at every cycle or at specific transitions defined in the model [51, 54].

2.7.5 Microsimulation Model

Microsimulation models are based on Monte Carlo simulation technique that generates individual patient histories [51]. A set of rules (transition probabilities) are applied to individual patients leading to simulated changes in state and behaviour [51]. The rules can be deterministic (probability = 1) or stochastic (probability < = 1). Individual patients (trials) randomly walk through the model and generate individual outcomes [51]. By analyzing the aggregate results for a set of trials, not only the expected value can be estimated but also the variability among individual outcomes can be examined [51, 54].

In contrast to standard Markov cohort analysis where expected valued is based on entire cohort, the Microsimulation model generates individual outcomes (cost and effectiveness) for individual patients (trials) based on each random walk [51]. Microsimulation models can be used to track individual patient characteristics (e.g., Age, gender, tumour type, tumour size etc) and individual patient events (e.g., number of adverse events, apply chemotherapy treatment etc) [51]. A standard Markov cohort analysis cannot account for such individual patient characteristics because cohort is homogenous [51]. Microsimulation models are expensive to build and rely on heavily comprehensive databases and sometimes it is difficult to interpret the simulation results.

Chapter 3: Research Questions

3.1 Primary research question

To assess the cost-effectiveness of adding the anti-EGFR monoclonal antibodies (*cetuximab* and *panitumumab*) to best supportive care as third-line therapy in treatment of advanced metastatic chemo-refractory colorectal cancer.

3.2 Secondary research questions

1. To analyze the effect of KRAS gene mutation status on the cost-effectiveness of *cetuximab* and *panitumumab* as third-line therapy in treatment of advanced metastatic colorectal cancer.
2. To analyze the cost-effectiveness of KRAS gene testing prior to treatment with *cetuximab* and *panitumumab* as third-line therapy in treatment of advanced metastatic colorectal cancer.
3. To evaluate the cost-effectiveness of anti-EGFR therapies (cetuximab and panitumumab) plus best supportive care at various willingness-to-pay threshold values.
4. To determine the sensitivity of primary model output (incremental cost-utility ratio) to various parameters in the economic model.

Chapter 4: Materials & Methods

I developed an economic model using Markov decision modeling to assess:

1. The cost-effectiveness of two anti-EGFR monoclonal antibodies (*cetuximab* and *panitumumab)* plus best supportive care versus best supportive care alone as third-line treatment in advanced chemorefractory metastatic colorectal cancer patients.

2. The cost-effectiveness of KRAS testing by comparing the cost and effectiveness of both anti-EGFR therapies (*cetuximab* and *panitumumab)* plus best supportive care with and without KRAS testing.

I used the efficacy data from two multi-center clinical trials for my cost-effectiveness analysis. The first study, NCIC CTG (National Cancer Institute of Canada Clinical Trials Group) CO. 17 trial compared the efficacy of cetuximab plus best supportive care versus best supportive care alone as third line treatment of patients with advanced metastatic colorectal cancer [9, 16]. The second study, Open-Label Phase III trial compared the efficacy of panitumumab plus best supportive care versus best supportive care alone as third line treatment of patients with advanced metastatic colorectal cancer [8, 15].

I also compared the cost-effectiveness of cetuximab plus best supportive care versus panitumumab plus best supportive care as third-line treatment using a cross-trial comparison method. This is an indirect comparison owing to the absence of a direct head to head trial of cetuximab plus best supportive care versus panitumumab plus best supportive care as third-line treatment in advanced metastatic colorectal cancer patients.

4.1 Patient characteristics in clinical trial studies

The demographics and baseline characteristics of the patients were quite similar across both studies [8, 9], as shown in Table 4.1. Eligible patients in both studies had advanced metastatic colorectal cancer expressing epidermal growth factor receptor (EGFR) which was refractory to all recommended chemotherapy and detectable by immunohistochemistry [8, 9].

The patients in both trials had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 to 2 and the random assignment of patients in to treatment (anti-EGFR therapy plus best supportive care) and control (best supportive care alone) groups was stratified by ECOG performance status (0 or 1 vs. 2) [8, 9]. The ECOG performance status is a measure of how well a patient is able to carry on ordinary daily activities while living with cancer [55]. The ECOG performance status is ranged from 0 to 5 with 0 being the best scenario (Fully active, able to carry on all pre-disease performance without restriction) and 5 being the worst scenario (dead) [55]. The ECOG performance status is widely used in oncology practice because of its correlation with patient survival duration and response to treatment, as well as their quality of life and co-morbidity [55]. The ECOG performance status scoring system is also used to decide which patients are physically suitable for treatment or entry into a clinical trial [55].

Table 4.1. Demographics and Baseline characteristics of the patients

	NCIC CTG - CO. 17 Trial				Open-Label Phase III Trial			
Characteristic	**Cetuximab + BSC (N=287)**		**BSC Alone (N=285)**		**Panitumumab + BSC (N=231)**		**BSC Alone (N=232)**	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	63	-----	63.6	-----	62	-----	63	-----
Range	28.6 - 88.1	-----	28.7 - 85.9	-----	27.0 - 82.0	-----	27.0 - 83.0	-----
Sex								
Male	186	64.8	182	63.9	146	63	148	64
Female	101	35.2	103	36.1	85	37	84	36
ECOG performance status								
0	72	25.1	64	22.5	107	46	80	34
1	148	51.6	154	54	94	41	115	50
2	67	23.3	67	23.5	29	13	35	16
Previous adjuvant chemotherapy								
	108	37.6	103	36.1	86	37	78	34

Abbreviations: NCIC CTG (National Cancer Institute of Canada Clinical Trials Group), BSC (Best Supportive Care), ECOG (Eastern Cooperative Oncology Group).

4.2 Structure of the Markov model

Three separate Markov models were developed to achieve the primary and secondary objectives of the economic analysis. The Markov models were constructed using TreeAge Pro Suite 2009 (TreeAge Software Inc., Williamstown, MA). The Markov models consist of three mutually exclusive health states with state transitions at the end of each model cycle.

1. progression free
2. progression
3. death

The Markov model 1 was developed to evaluate the cost-effectives of anti-EGFR therapies (panitumumab and cetuximab) plus best supportive care versus best supportive care alone without KRAS testing prior to treatment. The patient population was distributed in to treatment arms based on the population distribution of KRAS gene mutation status (as shown in Figure 4.1). I assumed a population distribution for KRAS mutation status as 60% KRAS wild-type and 40% mutant-type KRAS based on evidence from literature [13-18].

The Markov model 2 was developed to evaluate the cost-effectiveness of KRAS testing by comparing the cost and effectiveness of anti-EGFR therapies (panitumumab and cetuximab) plus best supportive care with and without KRAS testing. The patient population was distributed in to treatment arms based on the sensitivity and specificity of KRAS testing (as shown in Figure 4.2). In both trial studies, real-time PCR (polymerase chain reaction) technology (DxS TheraScreen™ kit in Open-Label Phase III trial and QIAamp DNA Mini Kit in CO. 17 trial) [15, 16], was used to detect KRAS mutation status with a validated sensitivity of 0.95 and specificity of 1.0 [56-58].

The Markov model 3 was developed to evaluate the cost-effectiveness of anti-EGFR therapies (panitumumab and cetuximab) plus best supportive care in subset of patients with wild-type KRAS gene only (as shown in Figure 4.3).

Figure 4.1. Markov model 1

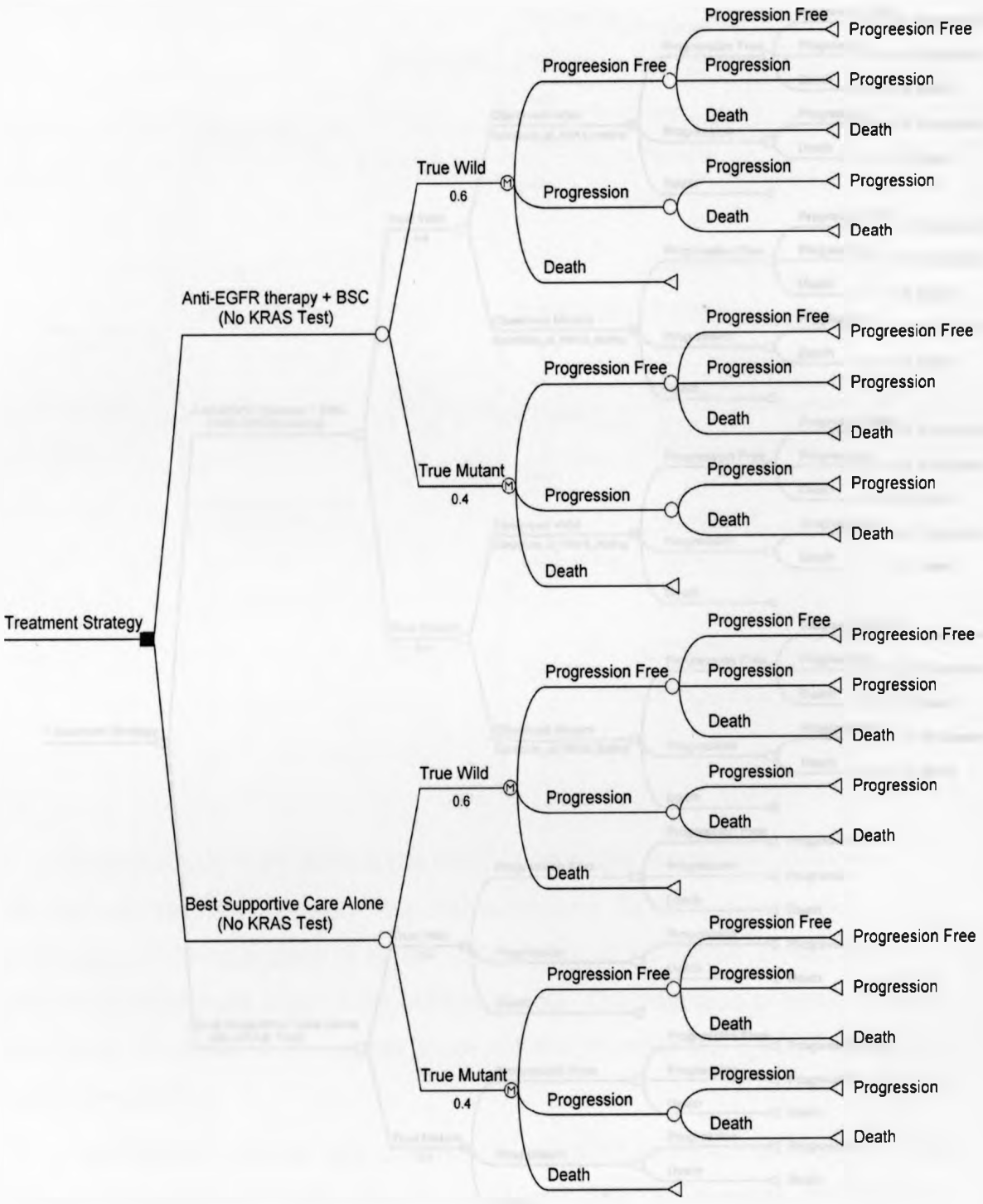


Figure 4.2. Markov model 2

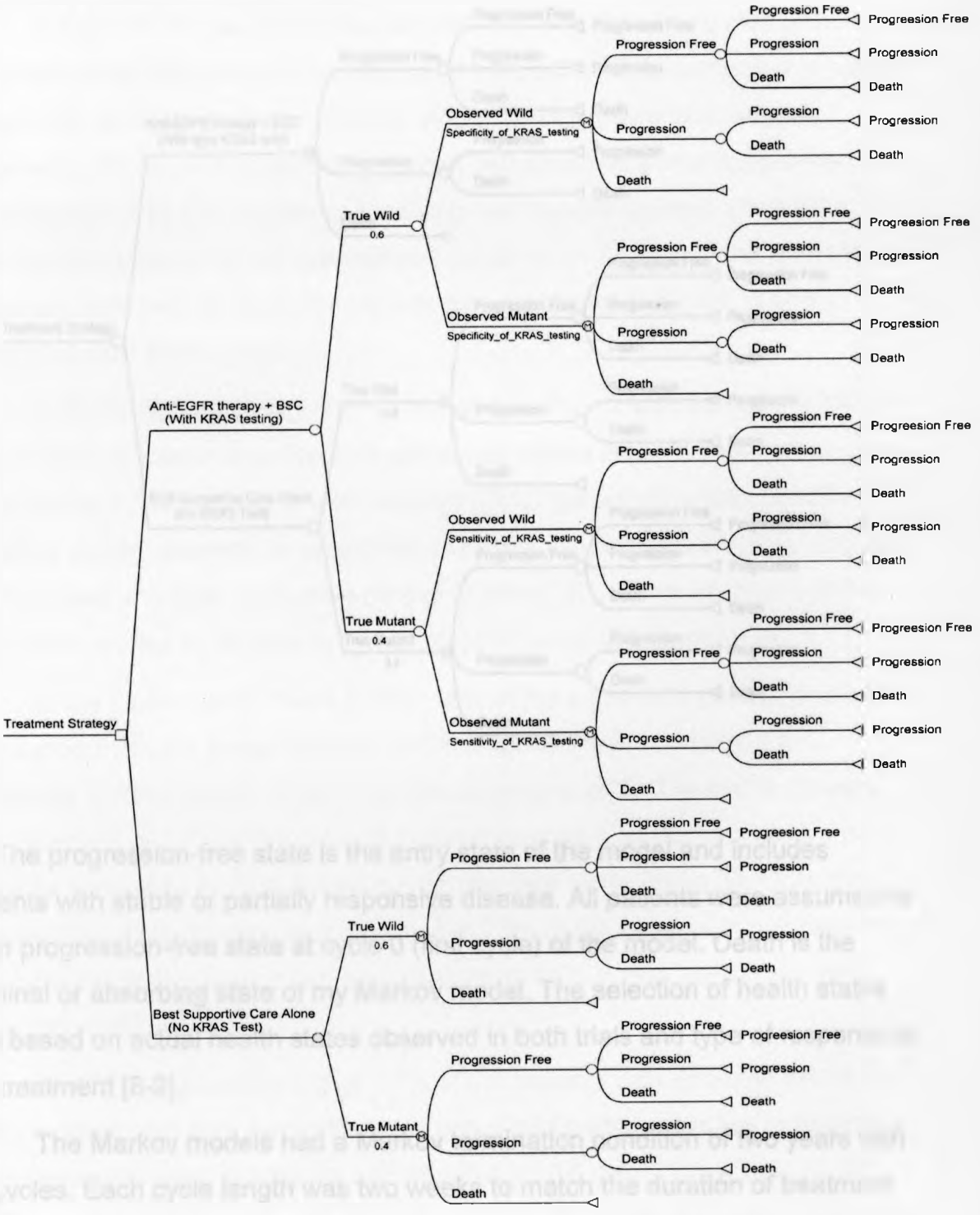
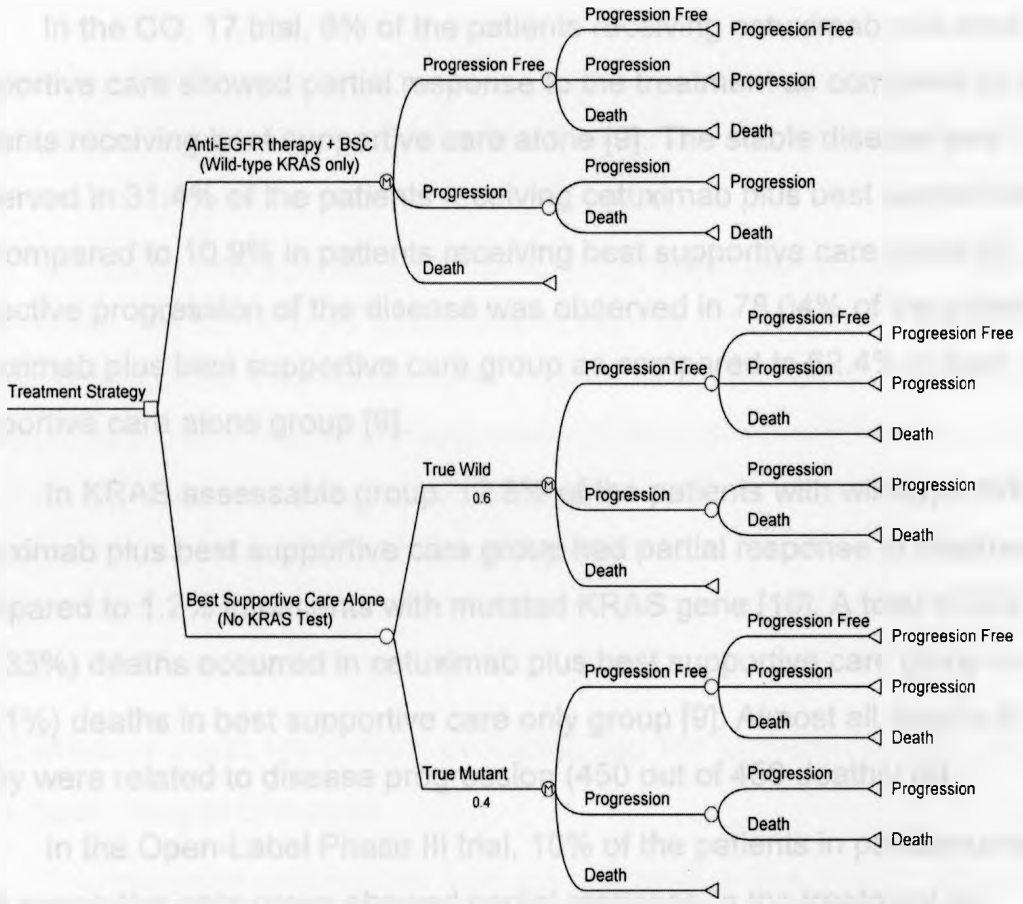


Figure 4.3. Markov model 3



The progression-free state is the entry state of the model and includes patients with stable or partially responsive disease. All patients were assumed to be in progression-free state at cycle 0 (first cycle) of the model. Death is the terminal or absorbing state of my Markov model. The selection of health states was based on actual health states observed in both trials and type of response to the treatment [8-9].

The Markov models had a Markov termination condition of two years with 52 cycles. Each cycle length was two weeks to match the duration of treatment cycles in both trial studies. The Markov termination condition was based on maximum time of follow up in both trial studies. The maximum time of follow-up was 1.58 years (median follow-up time = 70.4 weeks) for the CO.17 trial and 1.9 years (median follow-up = 72 weeks) for the Open-Label Phase III trial [8-9].

4.3 Response rates

In the CO. 17 trial, 8% of the patients receiving cetuximab plus best supportive care showed partial response to the treatment as compared to none in patients receiving best supportive care alone [9]. The stable disease was observed in 31.4% of the patients receiving cetuximab plus best supportive care as compared to 10.9% in patients receiving best supportive care alone [9]. Objective progression of the disease was observed in 78.04% of the patients in cetuximab plus best supportive care group as compared to 62.4% in best supportive care alone group [9].

In KRAS assessable group, 12.8% of the patients with wild-type KRAS in cetuximab plus best supportive care group had partial response to treatment as compared to 1.2% in patients with mutated KRAS gene [16]. A total of 222 (77.35%) deaths occurred in cetuximab plus best supportive care group and 234 (82.1%) deaths in best supportive care only group [9]. Almost all deaths in the study were related to disease progression (450 out of 456 deaths) [9].

In the Open-Label Phase III trial, 10% of the patients in panitumumab plus best supportive care group showed partial response to the treatment as compared to none in best supportive care alone group [8]. The stable disease was observed in 27% of the patients in panitumumab plus best supportive care group as compared to 10% in best supportive care alone group [8]. Objective progression of the disease was observed in 75% of the patients in panitumumab plus best supportive care group as compared to 85% in best supportive care alone group [8].

In KRAS assessable group, 17% of the patients with wild-type KRAS in panitumumab plus best supportive care group had partial response to treatment as compared to none in patients with mutated KRAS gene [15]. A total of 186 (81%) deaths occurred in panitumumab plus best supportive care group and 194 (84%) deaths in best supportive care only group [8]. Almost all deaths in the study were related to disease progression [8].

4.4 Markov model probabilities

The Markov state transition probabilities were derived from progression-free survival (PFS) and overall survival (OS) Kaplan-Meier plots. In both studies time-to-event variables (progression-free survival and overall survival) were summarized using Kaplan-Meier plots [8-9, 15-16].

Based on the cycle length of the Markov model, the probability value for progression-free survival (PFS) and overall survival (OS) was calculated at each following two weeks from Kaplan-Meier plots until the end point of 104 weeks (52 cycles, 2 years) was reached. For progression-free survival (PFS) and overall survival (OS) Kaplan-Meier plots where maximum follow-up was less than 104 weeks (2 years), the last probability value recorded at the end of follow-up period was carried forward. The state transition probabilities were derived separately for wild-type KRAS and mutant-type KRAS in each treatment group.

4.4.1 Markov state transition probabilities for anti-EGFR therapies plus best supportive care

The transition probabilities from the progression-free state to progression and from the progression state to death at the end of each Markov cycle were derived using the progression-free survival (PFS) and the overall survival (OS) Kaplan-Meier plots for wild-type KRAS and mutant-type KRAS in each trial study [15, 16]. Though most of the deaths in both trials were related to disease progression [8-9, 15-16], there were some deaths due to causes other than disease progression. Therefore, to derive the Markov state transition probabilities from the progression-free state to death, I used annual mortality rates from Canadian life tables for particular mean age in each treatment group [59].

4.4.2 Markov state transition probabilities for best supportive care alone

To derive the state transition probabilities for best supportive care alone arm in my Markov model, I combined the data from the progression-free survival (PFS) and the overall survival (OS) Kaplan-Meier plots for wild-type KRAS and mutant-type KRAS in best supportive care alone group from both trials to get averaged progression-free survival (PFS) and overall survival (OS) Kaplan-Meier plots [15, 16], as shown in Figure 4.4 and Figure 4.5.

The state transition probabilities from the progression-free state to progression and from the progression state to death at the end of each Markov cycle were calculated using averaged progression-free survival (PFS) and averaged overall survival (OS) Kaplan-Meier plots for wild-type KRAS and mutant-type KRAS in best supportive care alone group. The Markov state transition probabilities from the progression-free state to death were calculated using annual mortality rates from Canadian life tables for particular mean age in best supportive care alone group [59].

Figure 4.4. Averaged progression-free Survival (PFS) Kaplan-Meier plot for best supportive care alone (BSC Alone), upper graph – 4.4a (wild - type KRAS), lower graph – 4.4b (mutant - type KRAS).

Figure 4.4a

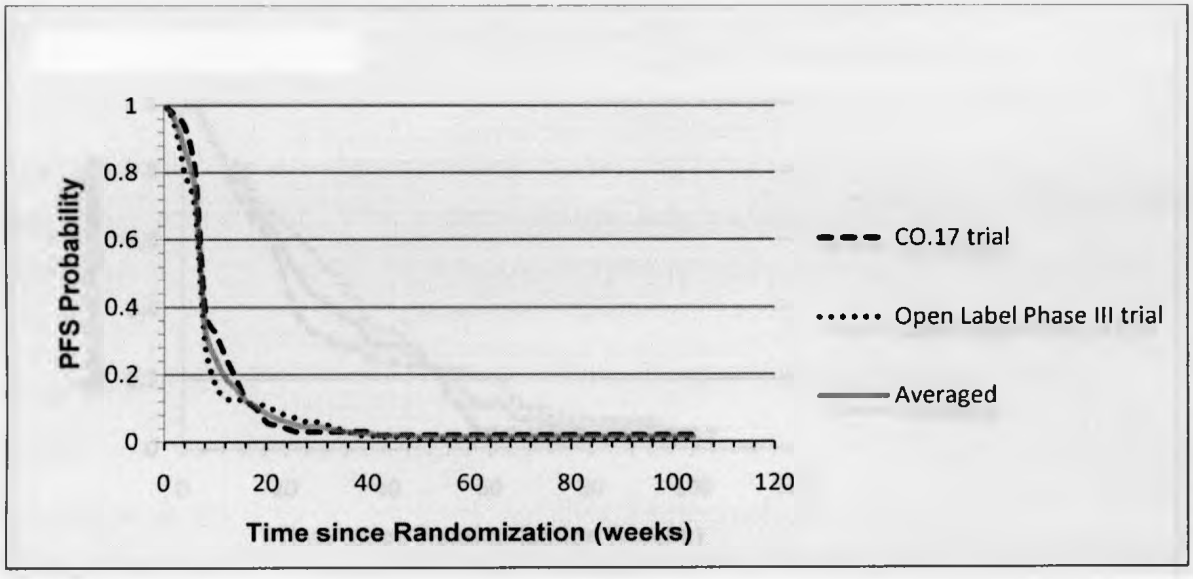


Figure 4.4b

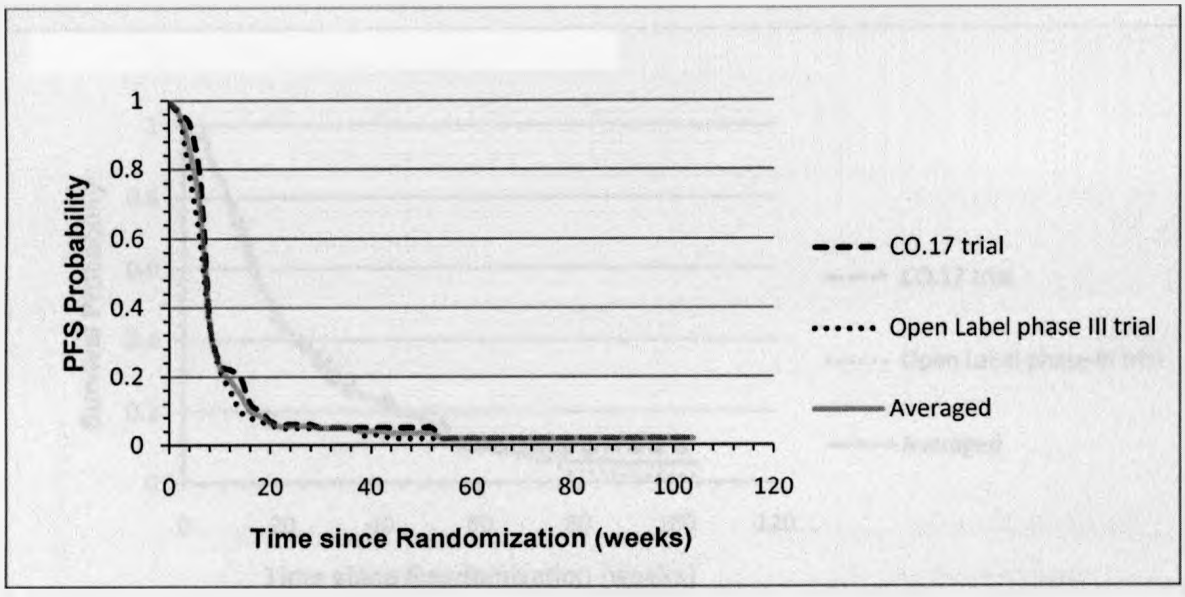


Figure 4.5. Averaged overall survival (OS) Kaplan-Meier plot for best supportive care alone (BSC Alone), upper graph – 4.5a (wild - type KRAS), lower graph – 4.5b (mutant - type KRAS).

Figure 4.5a

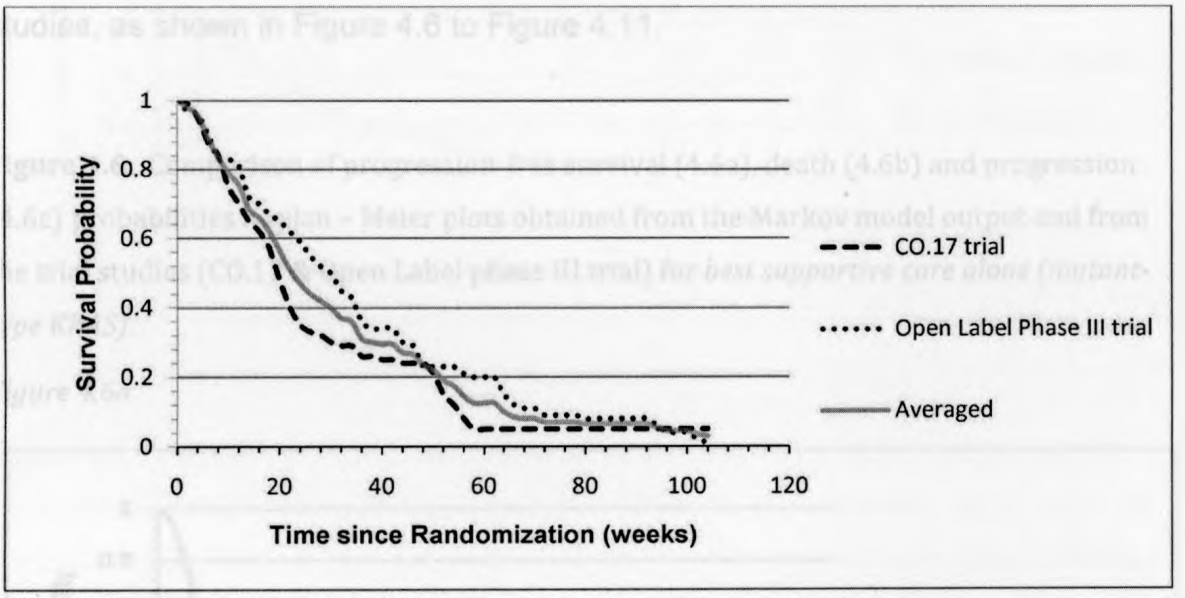
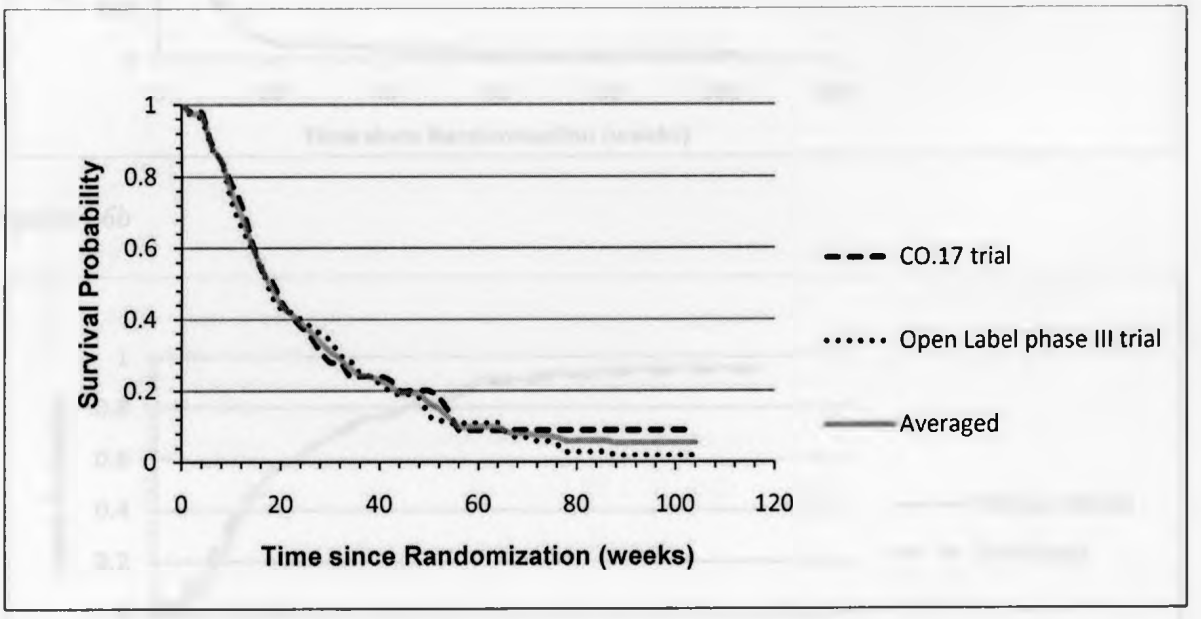


Figure 4.5b



4.5 Validation of the Markov model

The fit and accuracy of the Markov model was ascertained by comparing the probability values for progression-free survival, progression and death produced by the Markov model with the probability values obtained from trial studies, as shown in Figure 4.6 to Figure 4.11.

Figure 4.6. Comparison of progression-free survival (4.6a), death (4.6b) and progression (4.6c) probabilities Kaplan – Meier plots obtained from the Markov model output and from the trial studies (CO.17 & Open Label phase III trial) for *best supportive care alone (mutant-type KRAS)*.

Figure 4.6a

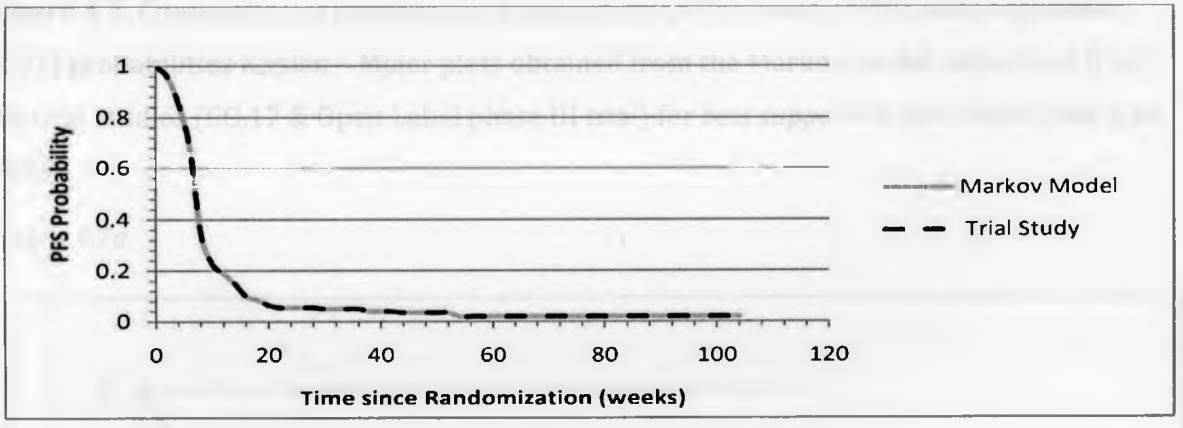


Figure 4.6b

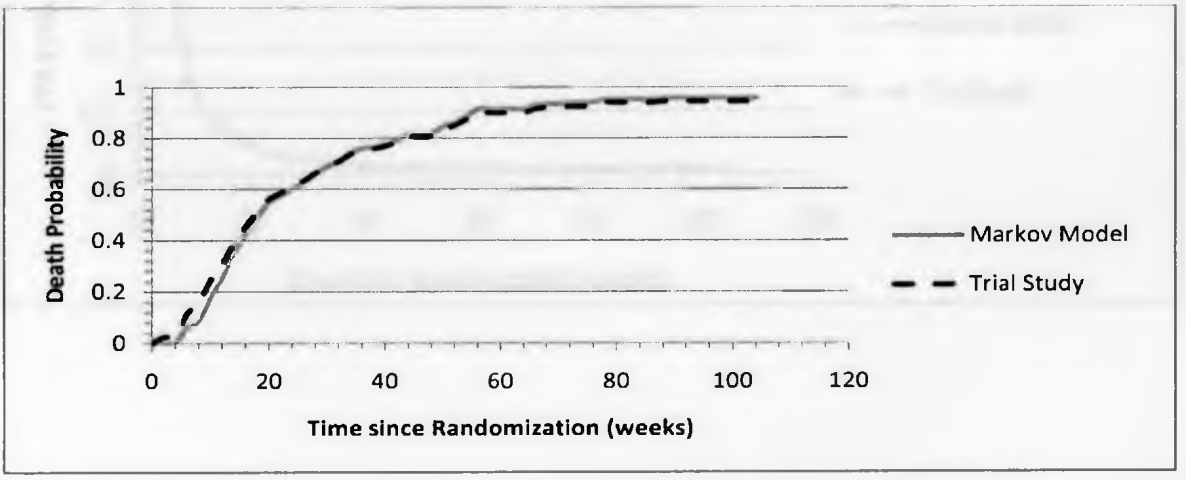


Figure 4.6c

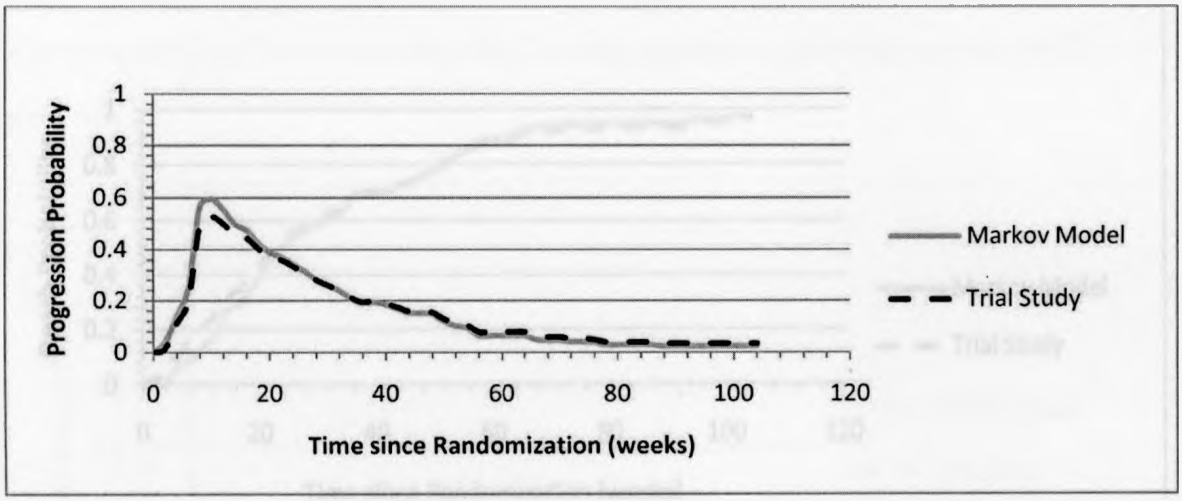


Figure 4.7. Comparison of progression-free survival (4.7a), death (4.7b) and progression (4.7c) probabilities Kaplan – Meier plots obtained from the Markov model output and from the trial studies (CO.17 & Open Label phase III trial) for *best supportive care alone (wild-type KRAS).*

Figure 4.7a

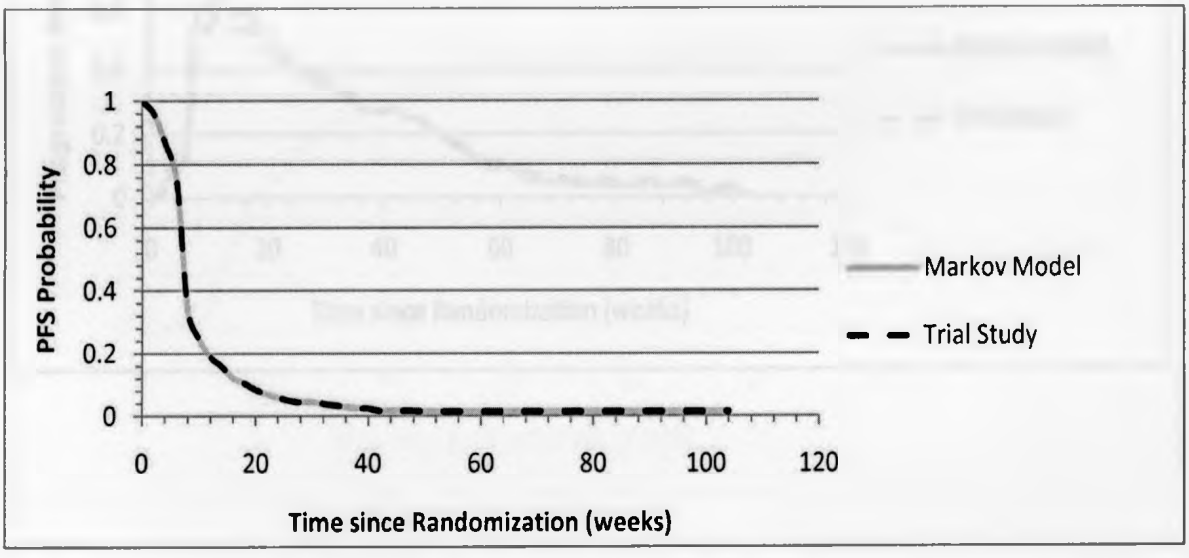


Figure 4.7b

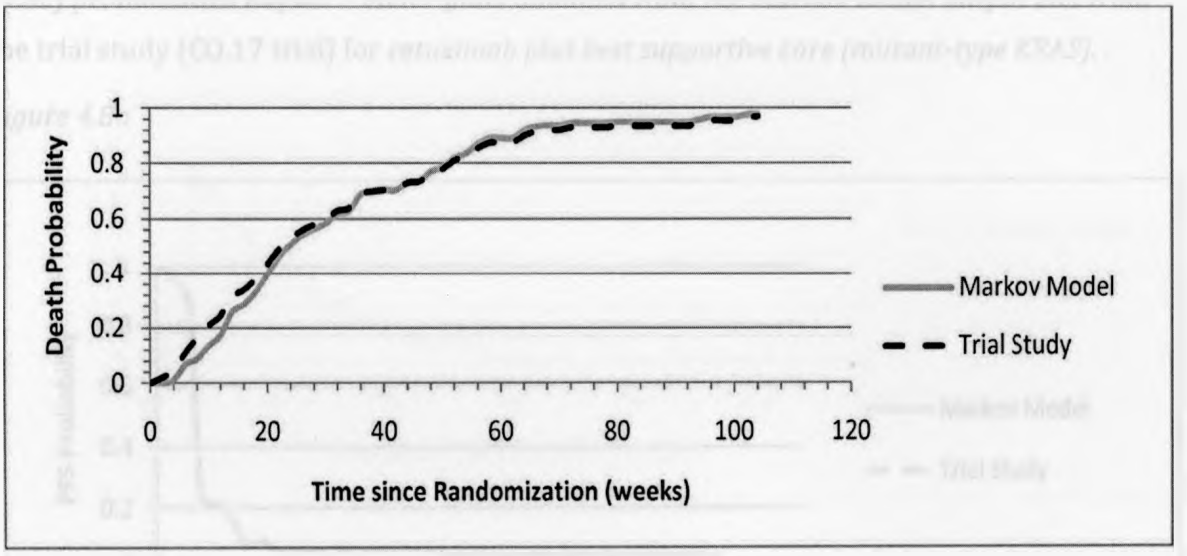


Figure 4.7c

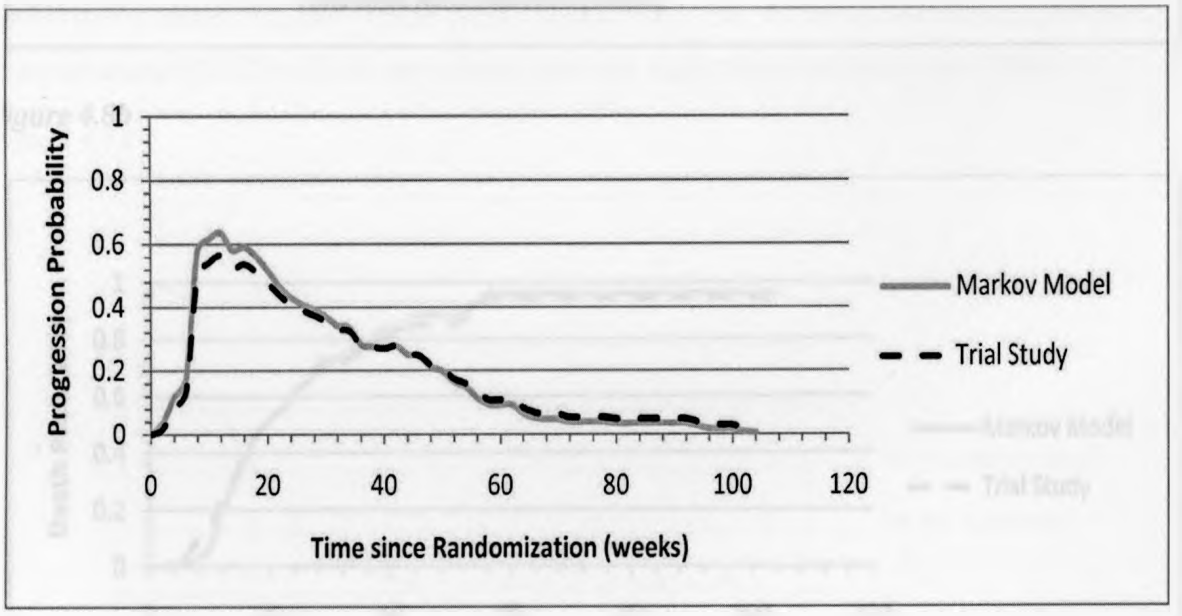


Figure 4.8. Comparison of progression-free survival (4.8a), death (4.8b) and progression (4.8c) probabilities Kaplan – Meier plots obtained from the Markov model output and from the trial study (CO.17 trial) for *cetuximab plus best supportive care (mutant-type KRAS).*

Figure 4.8a

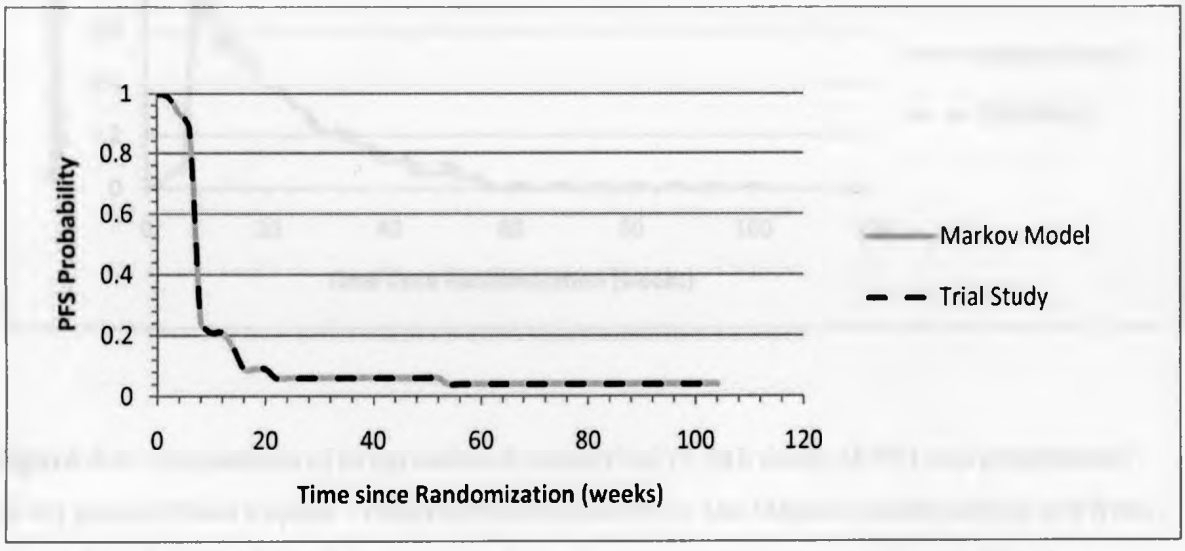


Figure 4.8b

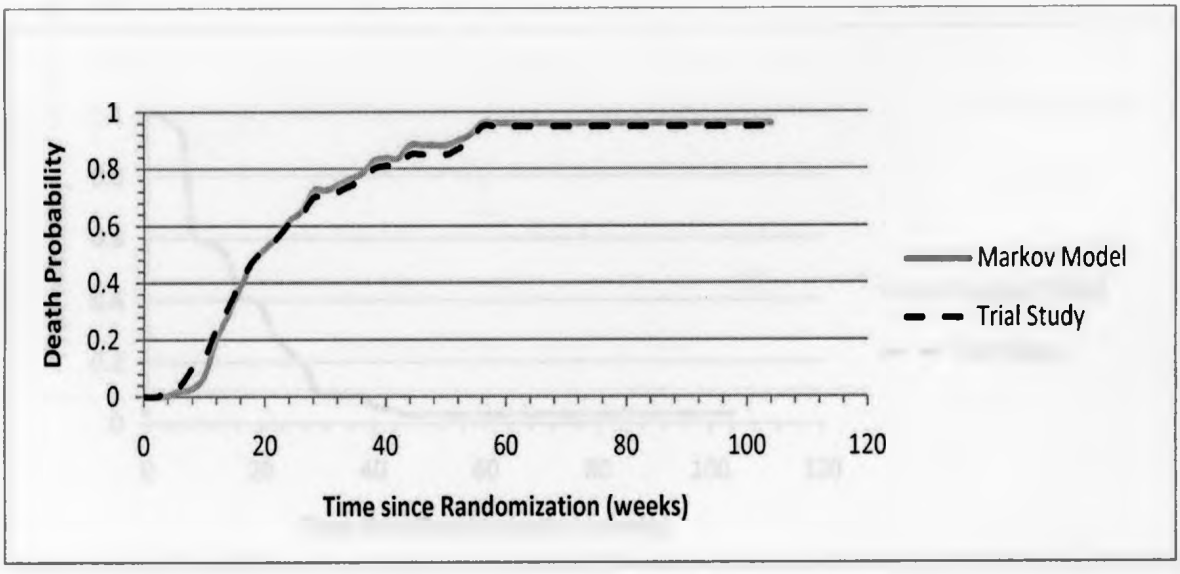


Figure 4.8c

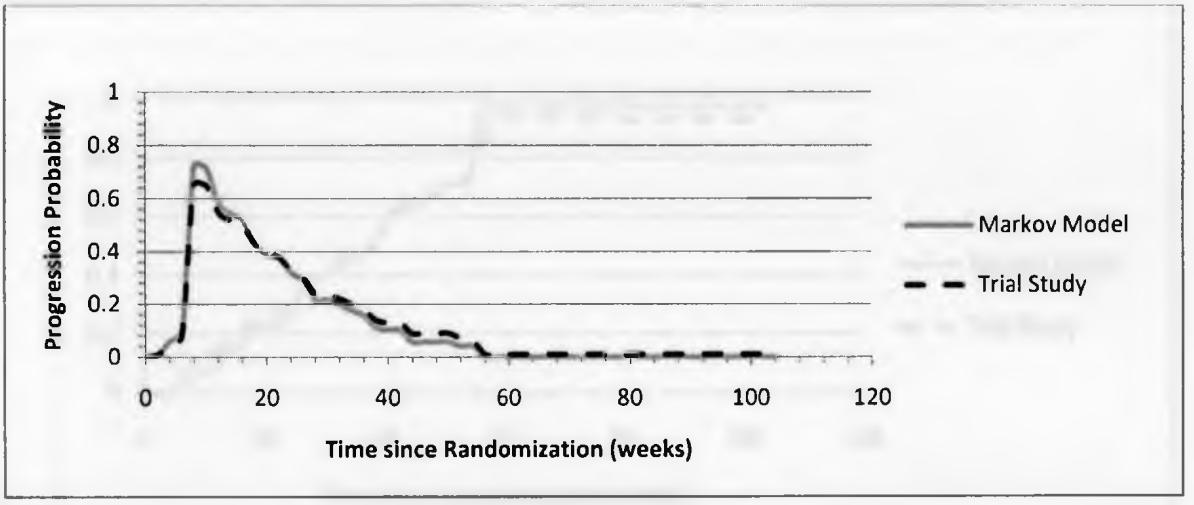


Figure 4.9. Comparison of progression-free survival (4.9a), death (4.9b) and progression (4.9c) probabilities Kaplan – Meier plots obtained from the Markov model output and from the trial study (CO.17 trial) for *cetuximab plus best supportive care (wild-type KRAS).*

Figure 4.9a

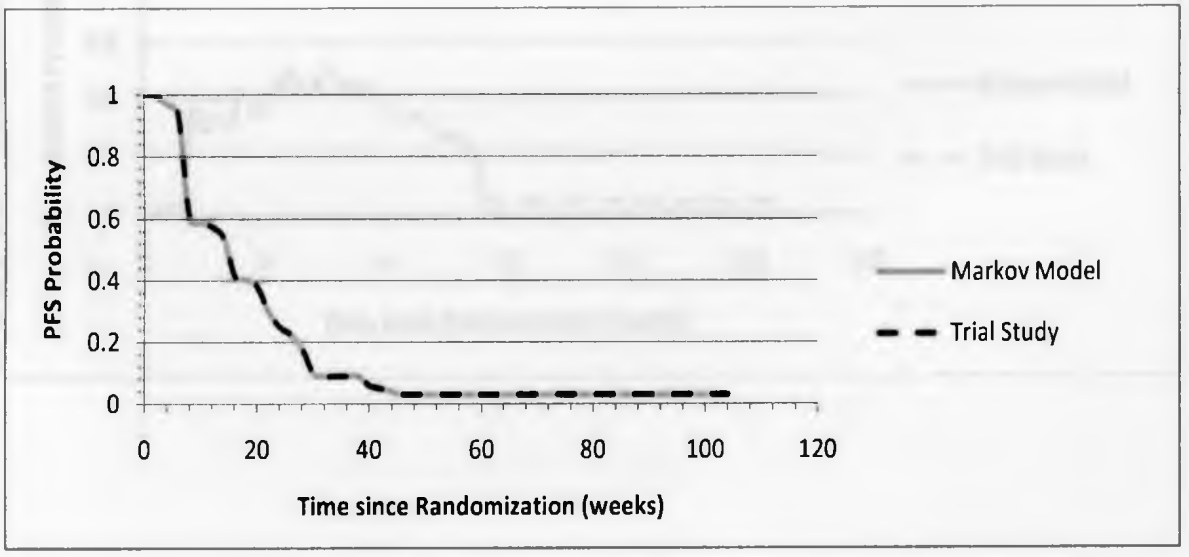


Figure 4.9b

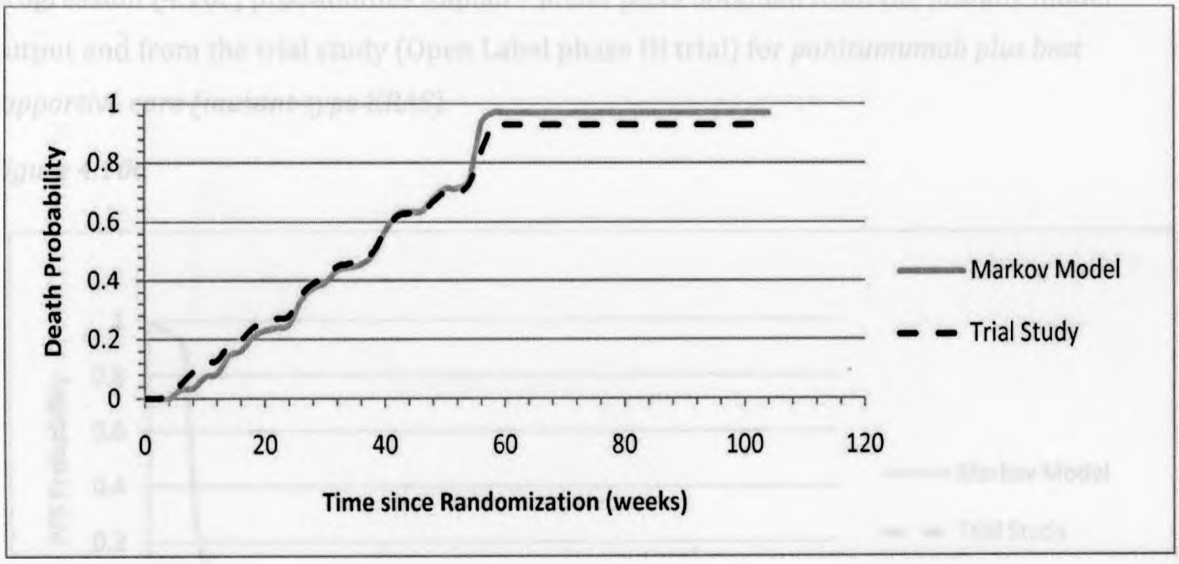


Figure 4.9c

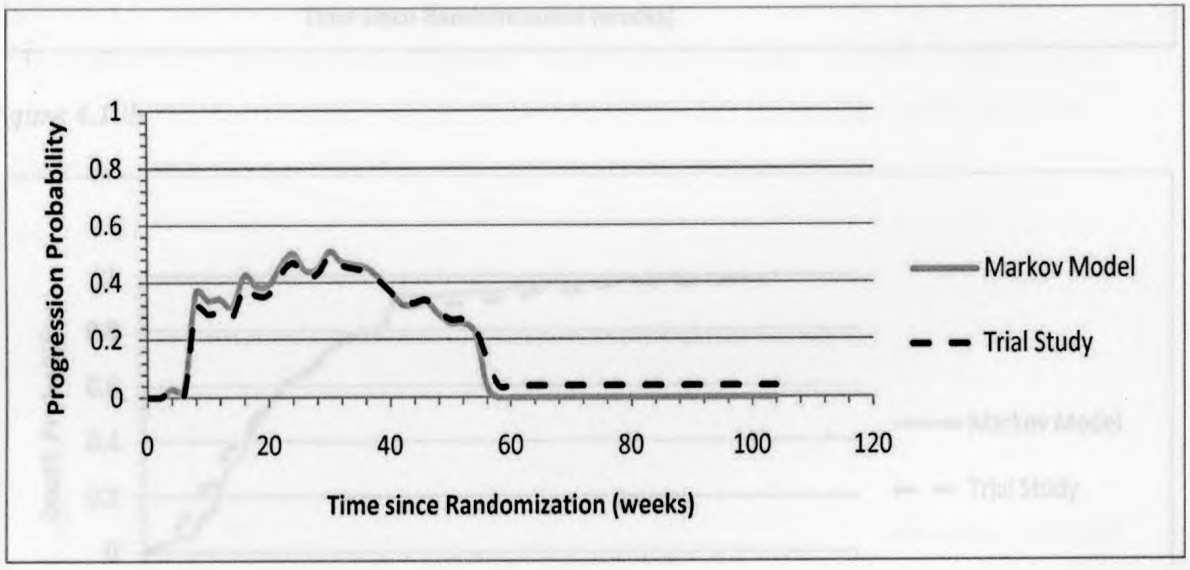


Figure 4.10. Comparison of progression-free survival (4.10a), death (4.10b) and progression (4.10c) probabilities Kaplan – Meier plots obtained from the Markov model output and from the trial study (Open Label phase III trial) for *panitumumab plus best supportive care (mutant-type KRAS).*

Figure 4.10a

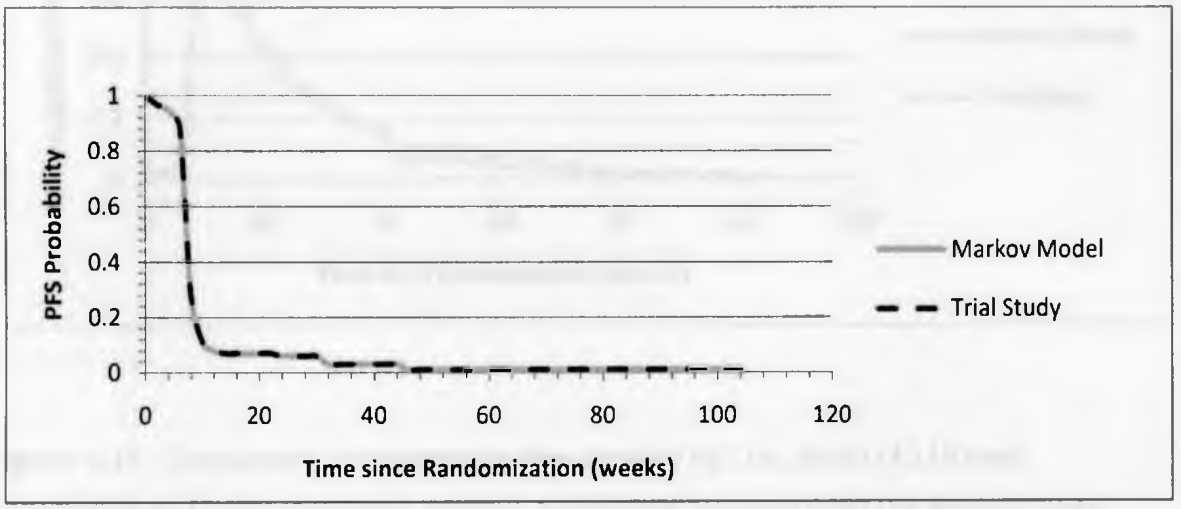


Figure 4.10b

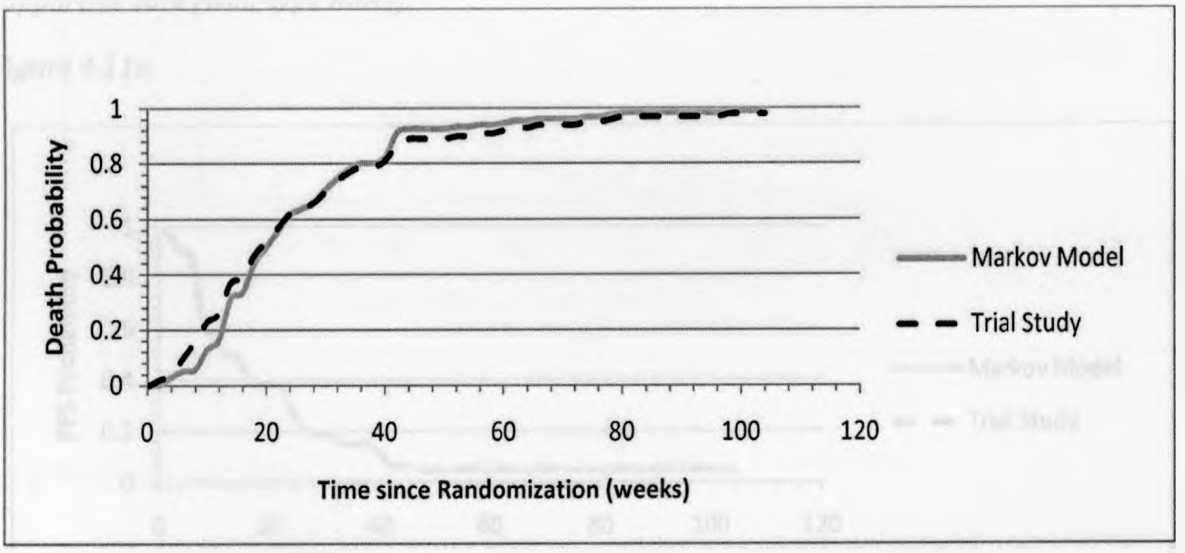


Figure 4.10c

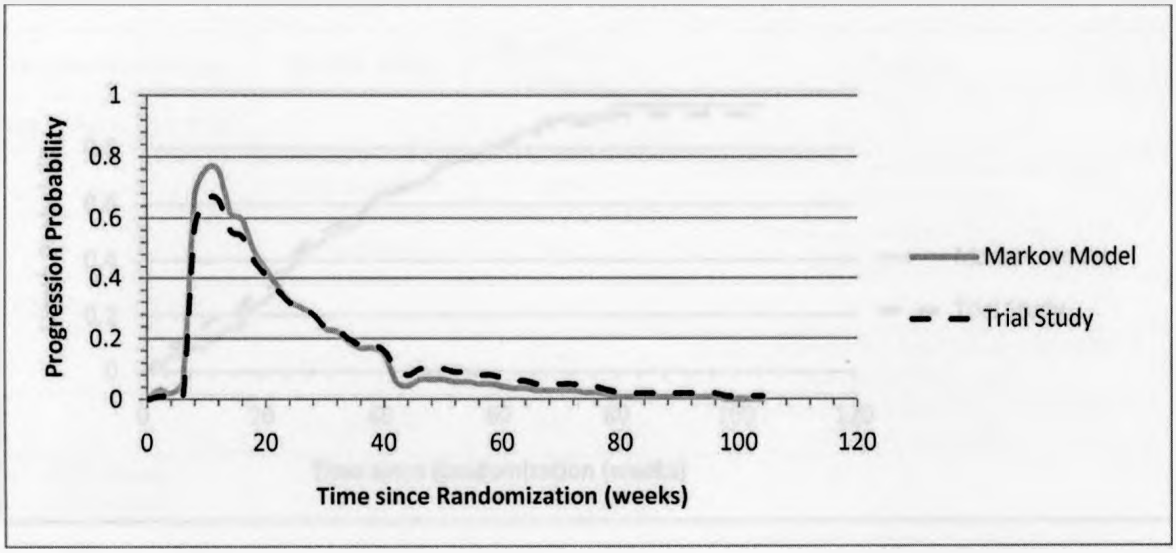


Figure 4.11. Comparison of progression-free survival (4.11a), death (4.11b) and progression (4.11c) probabilities Kaplan – Meier plots obtained from the Markov model output and from the trial study (Open Label phase III trial) for *panitumumab plus best supportive care (wild-type KRAS).*

Figure 4.11a

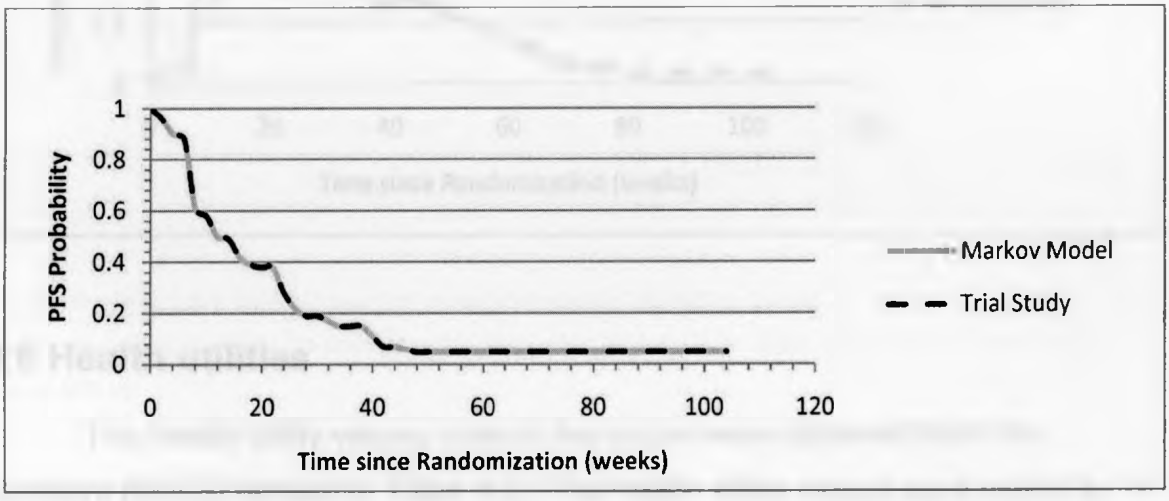


Figure 4.11b

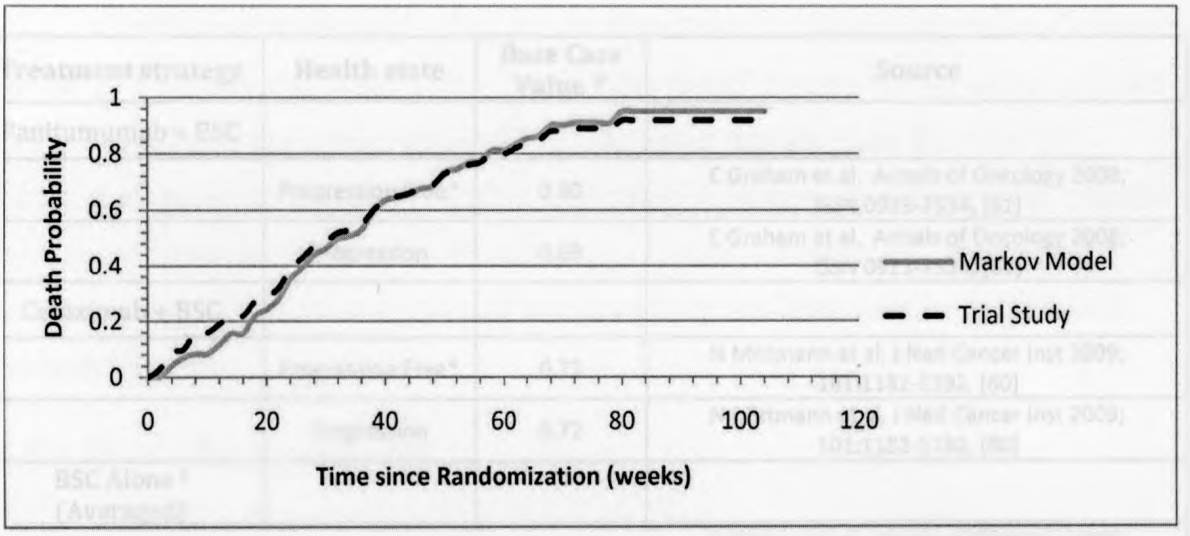
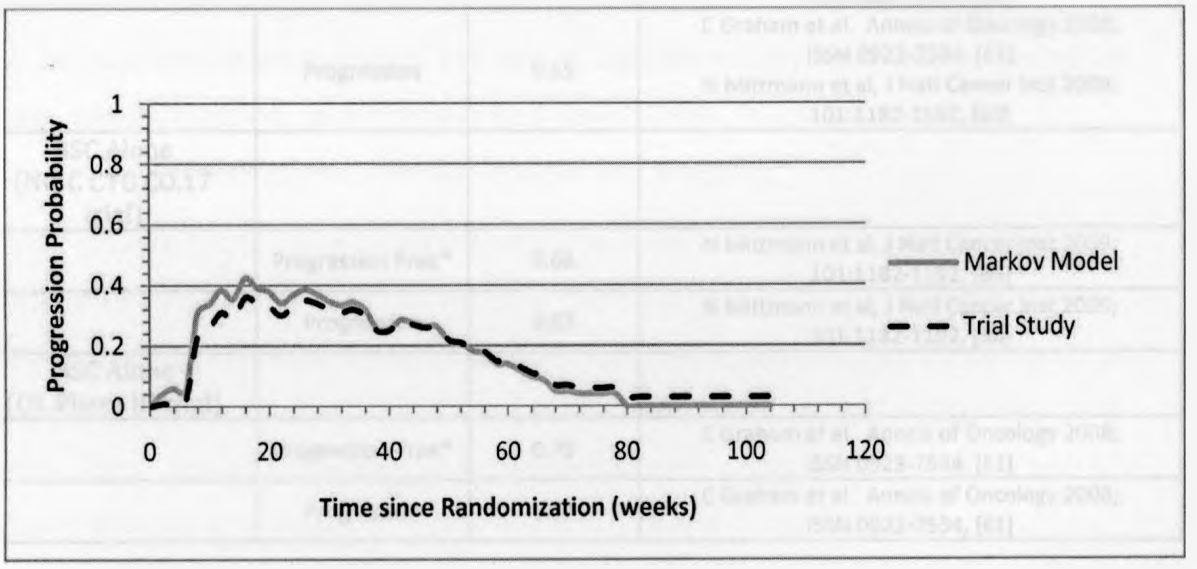


Figure 4.11c



4.6 Health utilities

The health utility values used in the model were obtained from the literature [60-63] (shown in Table 4.2). The health utility values were varied by +/- 20% of the original base case value for the purpose of various sensitivity analyses.

Table 4.2. Health utility values for different health states used in the Markov model

Treatment strategy	Health state	Base Case Value Ψ	Source
Panitumumab + BSC			
	Progression Free*	0.80	C Graham et al. Annals of Oncology 2008; ISSN 0923-7534, [61]
	Progression	0.69	C Graham et al. Annals of Oncology 2008; ISSN 0923-7534, [61]
Cetuximab + BSC			
	Progression Free*	0.73	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182-1192, [60]
	Progression	0.72	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182-1192, [60]
BSC Alone † (Averaged)			
	Progression Free*	0.715	C Graham et al. Annals of Oncology 2008; ISSN 0923-7534, [61] N Mittmann et al, J Natl Cancer Inst 2009; 101:1182-1192, [60]
	Progression	0.65	C Graham et al. Annals of Oncology 2008; ISSN 0923-7534, [61] N Mittmann et al, J Natl Cancer Inst 2009; 101:1182-1192, [60]
BSC Alone (NCIC CTG CO.17 trial)			
	Progression Free*	0.68	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182-1192, [60]
	Progression	0.63	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182-1192, [60]
BSC Alone (OL Phase III trial)			
	Progression Free*	0.75	C Graham et al. Annals of Oncology 2008; ISSN 0923-7534, [61]
	Progression	0.67	C Graham et al. Annals of Oncology 2008; ISSN 0923-7534, [61]

*Progression-free State includes patients with stable or partially responsive disease.

Ψ Base case values represent the average health utility value for a particular health state adjusted for treatment related toxicity.

† The base case values for best supportive care alone group represents the averaged health utility values for progression free and progression state obtained from both trial studies.

BSC = best supportive care, NCIC CTG = National Cancer Institute of Canada Clinical Trials Group.

OL Phase III = Open Label Phase III study

4.7 Costs

Costs were estimated using the perspective of a public payer (the Ontario Ministry of Health and Long-Term Care). Only direct medical costs were included in the model and are presented in 2010 Canadian dollars (Can $1 = US $1). Costs that were not available in 2010 Canadian dollars were adjusted for inflation by using consumer price index (Healthcare - Ontario) Statistics Canada [64]. Indirect medical costs were not estimated as they are irrelevant for the chosen perspective [60].

4.7.1 Direct Medical Costs

Direct medical costs used in the model include best supportive care costs, drug cost of anti-EGFR monoclonal antibodies (*cetuximab* and *panitumumab)*, cost of KRAS testing and cost of management of adverse events. Best supportive care costs includes the cost of outpatient physician visits, laboratory tests, hospitalization, emergency department visits, blood transfusions, concomitant medications, blood products and Imaging.

These costs were obtained from the literature [60] and adjusted for consumer price index (CPI -2010) [64]. I used a cost value of $452 per patient for KRAS testing [57]. Best supportive care costs were assumed to be same for both anti-EGFR therapies (*cetuximab* and *panitumumab)*. The best supportive care alone (BSC alone) costs and best supportive care costs in combination with anti-EGFR therapy are shown in Table 4.3 and Table 4.4 respectively.

Table 4.3. Best supportive care alone costs

Components	Base case value* (Bi-weekly)	Source
Outpatient Physician Visits	8.864	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Laboratory tests	0.701	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Hospitalization	75.04	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Concomitant Medications	2.694	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Blood Products	5.416	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Imaging	1.939	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Other costs ¥	9.026	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Total BSC alone cost†	103.682	

* Base case value represents cost per patient every 2 weeks and adjusted for consumer price index- 2010.

¥ Other costs include cost of emergency room visits and blood transfusions.

† Total BSC alone costs represent the total best supportive care alone cost per patient every two weeks used in the Markov model.

BSC = Best supportive care, All costs are presented in 2010 Canadian dollars.

Table 4.4. Best supportive care costs in combination with anti-EGFR therapy

Components	Base case value* (Bi-Weekly)	Source
Outpatient Physician Visits	12.044	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Laboratory tests	9.188	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Hospitalization	102.469	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Concomitant Medications	2.694	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Blood Products	4.392	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Imaging	8.137	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Other costs Ψ	10.562	N Mittmann et al, J Natl Cancer Inst 2009;101:1182–1192, [60]
Total BSC Costs†	149.487	

* Base case value represents cost per patient every 2 weeks and adjusted for consumer price index- 2010

Ψ other costs include cost of emergency room visits and blood transfusions.

† It represents total best supportive care (in combination with anti-EGFR therapy) cost per patient every two weeks used in the Markov model, BSC = Best supportive care, All costs are presented in 2010 Canadian dollars.

4.8 Drug costs

4.8.1 Drug cost of cetuximab

In the NCIC CTG (National Cancer Institute of Canada Clinical Trials Group) CO.17 trial study [9], the patients in cetuximab plus best supportive care group received an initial dose of cetuximab as 400 mg / m^2 (body surface area) given intravenously over a period of 120 minutes [9]. The initial dose was followed up by weekly maintenance dose of 250 mg /m^2 given intravenously over a period of 60 minutes [9]. The weekly maintenance dose was continued until disease progression [9].

A cost of $345 for 100 mg / 5ml single use vial of cetuximab was obtained from London Health Sciences Center (LHSC) drug formulary intranet. The cost estimation for total dose of cetuximab given to each patient is based on average healthy male with a body weight of 70 kg and body surface area of 1.7 m^2 [65, 66]. For the initial dose of cetuximab i.e. 400 mg / m^2, the estimated total dose is 680mg (400mg x 1.7 (body surface area) = 680mg) or 7 single-use vials of cetuximab. The estimated total cost for initial dose of cetuximab is $2,415 per patient. For the weekly maintenance dose of cetuximab i.e. 250 mg / m^2, the estimated total dose is 425mg (250mg x 1.7 (body surface area) = 425mg) or 5 single-use vials of cetuximab. The estimated total cost of weekly maintenance dose of cetuximab is $1,725 per patient (Table 4.5).

Table 4.5. Drug cost of cetuximab and source information

Variable	Cost (Can $)	Source
Cost of 100 mg/5ml single use vial	345	LHSC drug formulary intranet - 2010
Cost of Initial dose of 400 mg /m^2 (680mg - 7 Vials)†	2415	Calculated (see text)
Cost of weekly maintenance dose of 250 mg/m^2 (425mg - 5 Vials)†	1725	Calculated (see text)
Administration cost / hr (adjusted for CPI -2010)	108.91	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182–1192, [60]
Total Cost / patient for the first 2 weeks*	4466.72	Calculated (see text)
Total Cost / patient for every following 2 weeks*	3667.82	Calculated (see text)

† Based on average healthy male with a body weight of 70kg & body surface area of 1.7m^2 (initial dose= 400 x 1.7 = 680 mg, maintenance dose= 250 x 1.7 = 425mg)

*First 2 weeks includes the cost of initial dose (400 mg/m^2) plus the cost of weekly maintenance dose (250 mg/m^2) along with 3 hours of administration cost (2 hrs for initial dose plus 1 hr for maintenance dose)

*Every following 2 weeks includes cost of two maintenance doses along with 2 hrs of administration cost

CPI = consumer price index, LHSC = London Health Sciences Center, All costs are presented in 2010 Canadian dollars.

4.8.2 Drug cost of panitumumab

In the Open-Label Phase III trial study, the patients in panitumumab plus best supportive care group received a bi-weekly dose of panitumumab as 6mg / kg (body weight) given intravenously over a period of 60 minutes [8]. The bi-weekly maintenance dose was continued until disease progression [8]. A cost of $650 for 100 mg /5ml single use vial of panitumumab was obtained from London Health Sciences Center (LHSC) drug formulary intranet. The cost estimation for total dose of panitumumab given to each patient bi-weekly is based on average healthy male with a body weight of 70 kg [65, 66]. For bi-weekly dose of panitumumab i.e. 6mg / kg, the estimated total dose is 420mg (6mg x 70 (body weight) = 420mg) or 5 single-use vials of panitumumab. The estimated total cost for bi-weekly dose of panitumumab is $3,250 per patient (Table 4.6).

Table 4.6. Drug cost of panitumumab and source information

Variable	Cost (Can $)	Source
Cost of 100 mg/5ml single use vial	650	LHSC drug formulary intranet – 2010
Cost of Bi-Weekly dose of 6 mg /kg (420mg - 5 Vials)†	3250	Calculated (see text)
Administration cost / hr (adjusted for CPI -2010)	108.91	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182–1192, [60]
Total Cost / patient for every 2 weeks*	3358.91	

† Based on average healthy male with a body weight of 70kg (6 x 70 = 420mg or 5 single use vials)

*Every 2 weeks includes cost of Bi-weekly dose of 6mg/kg along with 1 hr (60 minutes) of administration cost

CPI = consumer price index, LHSC = London Health Sciences Center, All costs are presented in 2010 Canadian dollars.

4.9 Cost of Adverse Events

Only the costs for the management of grade 3 and 4 adverse events were included in the model because the costs for the management of less severe adverse events would not be associated with any substantial health-care resources consumption and economically not relevant [60, 61]. The cost estimation was done for grade 3 or 4 skin toxicity, infusion reaction, hypomagnesaemia, non-neutropenic infection and other pain (Table 4.7). These adverse events were significantly different among the treatment groups in both trial studies [8, 9]. Grade 3 or 4 toxicity profile for each treatment strategy is shown in Table 4.8. The other pain category excludes myalgia, earache, headache and abdominal, bone, chest, hepatic, neuropathic, pelvic, pleuritic, rectal, perirectal, and tumour pain [9, 60].

The cost estimation for management of toxicity was based on treatment protocols for each grade 3 or 4 adverse event obtained from existing literature [27-30] and expert opinion. The total cost per patient represents the costs for the management of an incident case of grade 3 or 4 adverse for entire model length (Table 4.7).

Table 4.7. Treatment cost of grade 3 and 4 adverse events

Type of Toxicity (only grade 3 and 4)	Cost (Can $)	Source
Skin Toxicity		
Cost per patient for the first month (Including physician visit)	199	London Regional cancer program- 2010
Cost per patient for every month afterwards	56	London Regional cancer program- 2010
Infusion reactions		
Average cost per stay for Infusion reaction	7263.09	The cost of acute care Hospital stays by Medical condition in Canada , 2004 – 2005, CIHI
Average cost per ER visit	268.38	The average cost of an ED visit in 2007–2008 , CIHI
Total cost per patient*	7531.47	
Hypomagnesaemia		
Magnesium sulfate 5 g / 10 ml Injection	0.75	LHSC drug formulary intranet - 2010
3-times weekly IV infusion of Magnesium sulfate at 10g per dose	4.5	
Non-neutropenic infection		
Total cost per patient*	2458.95	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182–1192, [60]
Pain†		
Total cost per patient*	28.37	N Mittmann et al, J Natl Cancer Inst 2009; 101:1182–1192, [60]

*Total cost per patient represent cost for treating one incident case of grade 3 or 4 adverse event and cost adjusted for consumer price index -2010, where applicable.

† It excludes arthralgia, myalgia, earache, headache and abdominal, bone, chest, hepatic, neuropathic, pelvic, pleuritic, rectal, perirectal, and tumour pain.

ER visit = Emergency room visit, IV infusion = Intravenous infusion, LHSC = London Health Sciences Center, CIHI = Canadian Institute for Health Information, All costs are presented in 2010 Canadian dollars.

Table 4.8. Grade 3 or 4 toxicity profile for each treatment strategy & source information

Type of Toxicity (Grade 3 or 4)	Patients with grade 3 or 4 adverse events	Source
Toxicity due to BSC Alone ¥		
Skin toxicity	0.40 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8; [16] Eric Van Cutsem et al. DOI:10.1200/JCO.2006.08.1620, [15]
Non-neutropenic infection	5.50 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8; [16] Eric Van Cutsem et al. DOI:10.1200/JCO.2006.08.1620, [15]
Pain	7.30 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8; [16] Eric Van Cutsem et al. DOI:10.1200/JCO.2006.08.1620, [15]
Toxicity due to Cetuximab †		
Skin toxicity	11.40 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8, [16]
Infusion reaction	4.50 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8, [16]
Hypomagnesaemia	5.80 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8, [16]
Non-neutropenic infection	7.30 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8, [16]
Pain	7.60 %	Derek J. Jonker et al.(2007), N Engl J Med 2007;357:2040-8, [16]
Toxicity due to Panitumumab Ψ		
Skin toxicity	11.60 %	Eric Van Cutsem et al. DOI:10.1200/JCO.2006.08.1620, [15]
Infusion reaction	0.43 %	Eric Van Cutsem et al. DOI:10.1200/JCO.2006.08.1620, [15]
Hypomagnesaemia	3.0 %	Eric Van Cutsem et al. DOI:10.1200/JCO.2006.08.1620, [15]

¥ Toxicity profile (grade 3 or 4 adverse events) for best supportive care alone (BSC alone) obtained from CO.17 trial and Open-Label phase III trial.

† Toxicity profile (grade 3 or 4 adverse events) for cetuximab only, after adjusting for toxicity due to best supportive care.

Ψ Toxicity profile (grade 3 or 4 adverse events) for panitumumab only, after adjusting for toxicity due to best supportive care.

AE = Adverse Events.

4.10 Discounting

In Canada a discount rate of 5% is used for economic analysis [67], therefore the incremental cost-utility ratios presented in my model were discounted at a rate of 5% using TreeAge Pro Suite 2009 (TreeAge Software Inc., Williamstown, MA). However, it is important to note that, given the median survival of less than a year for patients in both trial studies [8, 9], it is unlikely that discounting would have a large impact on model outcome.

4.11 Sensitivity analyses

I performed a series of deterministic and probabilistic sensitivity analyses using TreeAge Pro Suite 2009 (TreeAge Software Inc., Williamstown, MA) to test the robustness of the key model output (incremental cost-utility ratios), and to handle uncertainty in model parameters.

4.11.1 Deterministic sensitivity analyses

The one-way deterministic sensitivity analyses were carried out to estimate the effect of variation in all model parameters on model outcome. The parameter values above or below which each treatment strategy became cost-effective were recorded. An additional univariate sensitivity analysis was also conducted by changing the values of key model parameters such as best supportive care costs, drug costs, cost of toxicity, health utility values and cost of KRAS testing by + /- 20 % of the original base case values to determine which variables have the greatest influence on the results of the model. I also carried out one-way deterministic sensitivity analysis on sensitivity and specificity of KRAS testing. For sensitivity analysis purpose the sensitivity of KRAS testing was varied from 0.92 to 0.98 and specificity was varied from 0.95 to 1.0.

4.11.2 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis was performed with 1,000 Monte Carlo simulations using distributions for all key model parameters such as various model costs, state transition probabilities and health utility values. I used normal distributions for all types of costs in the Markov model with base case values serving as the mean and the standard deviations calculated from high and low ranges derived from +/- 20% change in base case values. The uniform distributions were used for health utility values with high and low values calculated from +/- 20% change in base case values. The uniform multiplier method was used to account for variability in state transition probabilities and the new distribution tables for state transition probabilities were directly input in the Markov model.

Chapter 5: Results

5.1 Cost-effectiveness of anti-EGFR therapies (No KRAS testing)

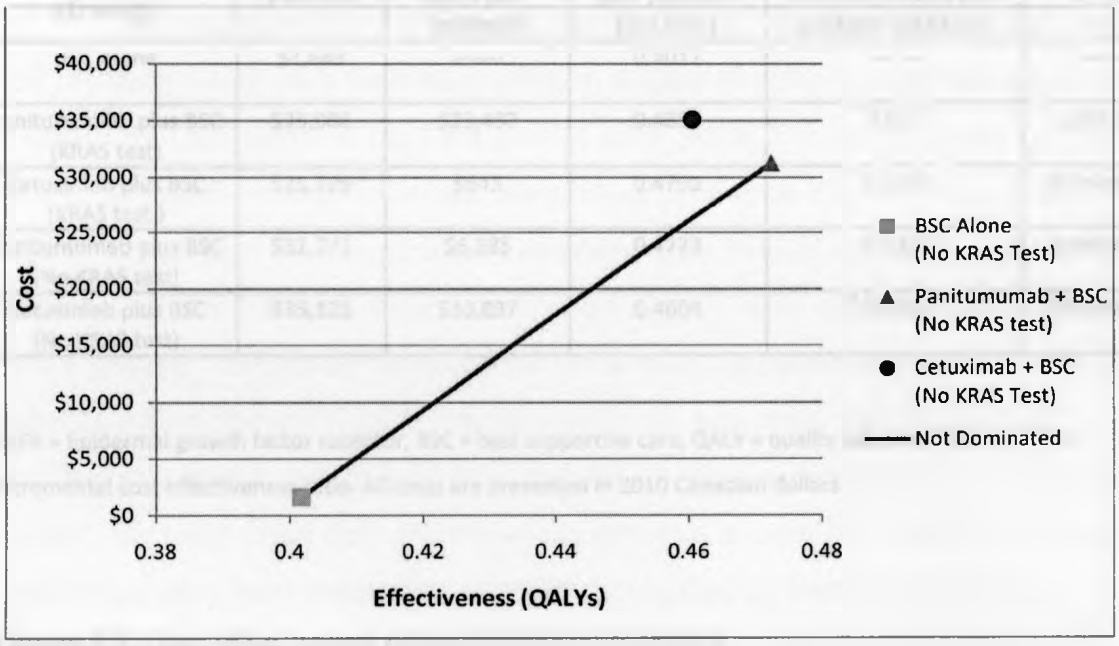
I first evaluated the incremental cost-effectiveness of both anti-EGFR therapies (cetuximab and panitumumab) plus best supportive care versus best supportive care alone without KRAS testing (Table 5.1). Compared to best supportive care alone, the incremental cost per patient for panitumumab plus best supportive is $29,622. The panitumumab plus best supportive care resulted in a mean gain of 0.07 QALYs, with a mean incremental cost utility ratio of $419,528 per QALY gained. Compared to cetuximab plus best supportive care, the panitumumab plus best supportive care resulted in a mean gain of 0.0118 QALYs with an incremental cost of - $3,852 per patient. My base case cost-effectiveness analysis showed that treatment strategy "cetuximab plus best supportive care" is dominated by treatment strategy "panitumumab plus best supportive care" (Figure 5.1).

Table 5.1. Incremental cost-effectiveness of anti-EGFR therapies (cetuximab and panitumumab) without KRAS testing (Markov model 1).

Treatment strategy	Cost per patient	Incremental cost per patient	Effectiveness per patient (QALYs)	Incremental effectiveness per patient (QALYs)	ICER
BSC Alone	$1,649	--------	0.4017	--------	-------
Panitumumab plus BSC	$31,271	$29,622	0.4723	0.0706	$419,528
Cetuximab plus BSC	$35,123	$3,852	0.4604	-0.0118	Dominated

EGFR = Epidermal growth factor receptor, BSC = best supportive care, QALY = quality adjusted life year, ICER = Incremental cost effectiveness ratio. All costs are presented in 2010 Canadian dollars.

Figure 5.1. Cost-effectiveness plane showing anti-EGFR therapies (panitumumab and cetuximab) plus best supportive care without KRAS testing.



5.2 Cost-effectiveness of KRAS testing

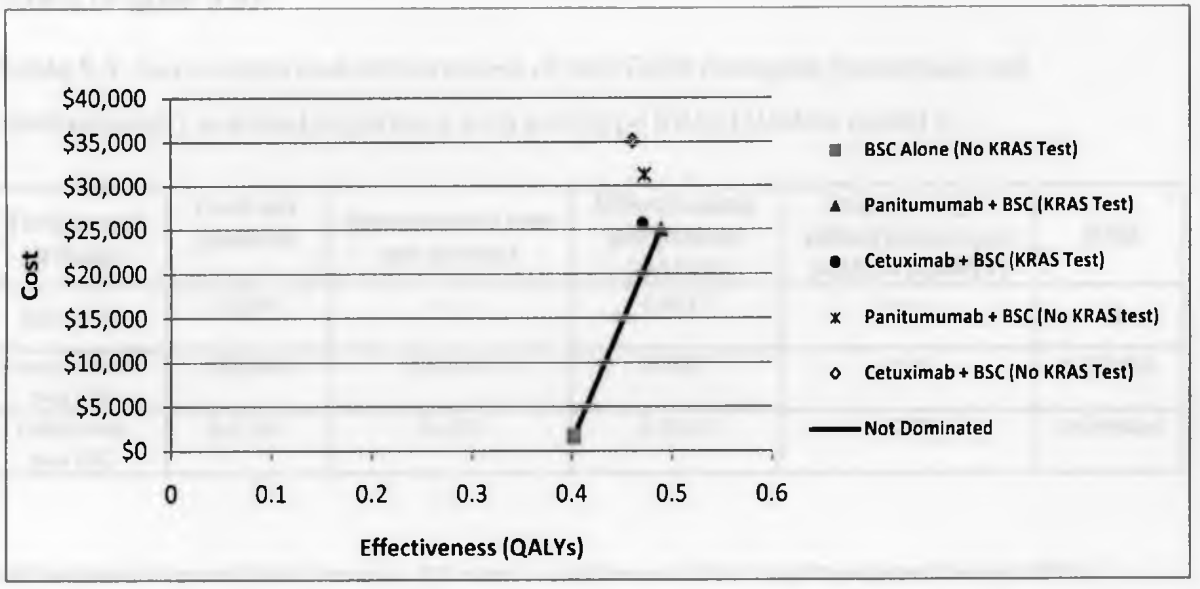
I next analyzed the cost-effectiveness of KRAS testing by comparing the costs and effectiveness of both anti-EGFR therapies (*cetuximab* and *panitumumab*) plus best supportive care with and without KRAS testing (Table 5.2). Compared to panitumumab plus best supportive care with no KRAS testing, panitumumab plus best supportive care with KRAS testing resulted in a mean gain of 0.0163 QALYs with an incremental cost of - $6,185 per patient. Compared to cetuximab plus best supportive care with no KRAS testing, panitumumab plus best supportive care with KRAS testing resulted in a mean gain of 0.0281 QALYs with an incremental cost of - $10,037 per patient. My base case analysis showed that the treatment strategy "panitumumab plus best supportive care with KRAS testing" dominates all other treatment strategies in the model (Figure 5.2). Compared to cetuximab plus best supportive care with no KRAS testing, the cetuximab plus best supportive care with KRAS testing resulted in a mean gain of 0.01 QALYs with an incremental cost of - $9,394 per patient.

Table 5.2. Cost-effectiveness of KRAS gene testing (Markov model 1 and 2)

Treatment strategy	Cost per patient	Incremental cost per patient	Effectiveness per patient (QALYs)	Incremental effectiveness per patient (QALYs)	ICER
BSC Alone	$1,649	-------	0.4017	-------	-------
Panitumumab plus BSC (KRAS test)	$25,086	$23,437	0.4886	0.087	$269,703
Cetuximab plus BSC (KRAS test)	$25,729	$643	0.4701	-0.0185	Dominated
Panitumumab plus BSC (No KRAS test)	$31,271	$6,185	0.4723	-0.0163	Dominated
Cetuximab plus BSC (No KRAS test)	$35,123	$10,037	0.4604	-0.0281	Dominated

EGFR = Epidermal growth factor receptor, BSC = best supportive care, QALY = quality adjusted life year, ICER = Incremental cost effectiveness ratio. All costs are presented in 2010 Canadian dollars.

Figure 5.2. Cost-effectiveness plane of KRAS gene testing.



5.3 Cost-effectiveness of anti-EGFR therapies (wild-type KRAS only)

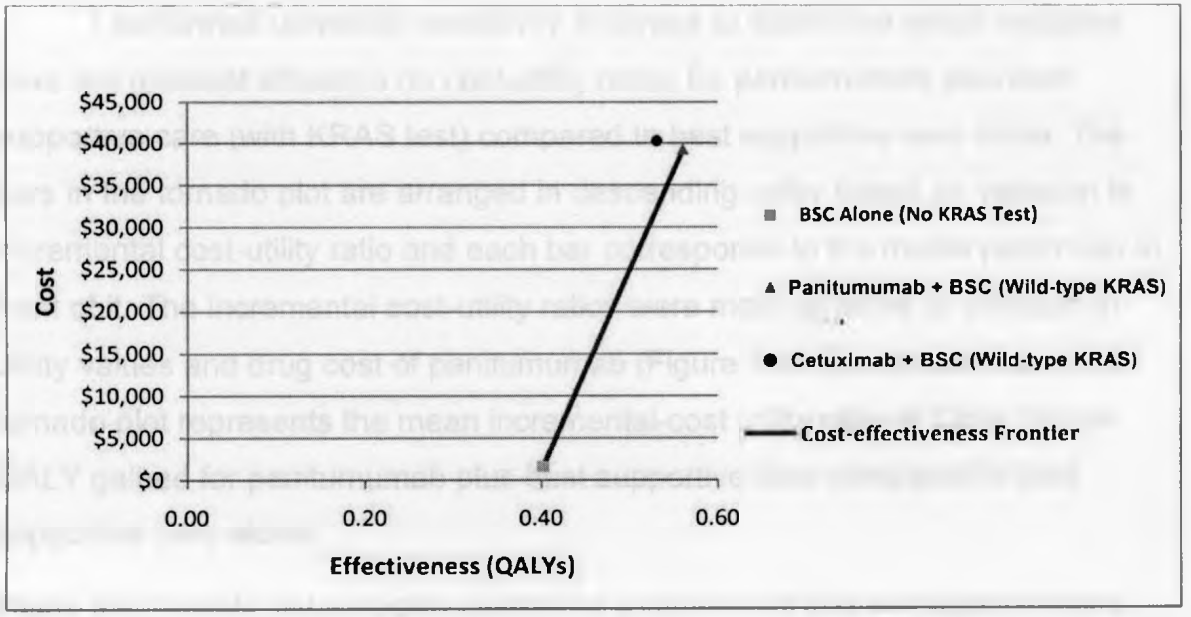
I also assessed the cost-effectiveness of anti-EGFR therapies (*cetuximab* and *panitumumab)* plus best supportive in subset of patients with wild-type KRAS (Table 5.3). Compared to best supportive care alone, the incremental cost per patient for panitumumab plus best supportive (wild-type KRAS) is $37,606. The panitumumab plus best supportive care (wild-type KRAS) resulted in a mean gain of 0.16 QALYs, with a mean incremental cost utility ratio of $236,469 per QALY gained. Compared to cetuximab plus best supportive care in subset of patients with wild-type KRAS, the panitumumab plus best supportive care resulted in a mean gain of 0.03 QALYs with an incremental cost of - $1,037 per patient. My base case cost-effectiveness analysis showed that treatment strategy "cetuximab plus best supportive care" is dominated by treatment strategy "panitumumab plus best supportive care" in subset of patients with wild-type KRAS (Figure 5.3).

Table 5.3. Incremental cost-effectiveness of anti-EGFR therapies (cetuximab and panitumumab) in subset of patients with wild-type KRAS (Markov model 3)

Treatment strategy	Cost per patient	Incremental cost per patient	Effectiveness per patient (QALYs)	Incremental effectiveness per patient (QALYs)	ICER
BSC Alone	$1,649	-------	0.4017	-------	-------
Panitumumab plus BSC	$39,255	$37,606	0.5607	0.16	$236,469
Cetuximab plus BSC	$40,292	$1,037	0.5309	-0.03	Dominated

EGFR = Epidermal growth factor receptor, BSC = best supportive care, QALY = quality adjusted life year, ICER = Incremental cost effectiveness ratio. All costs are presented in 2010 Canadian dollars.

Figure 5.3. Cost-effectiveness plane showing anti-EGFR therapies (panitumumab and cetuximab) in patients with wild-type KRAS.

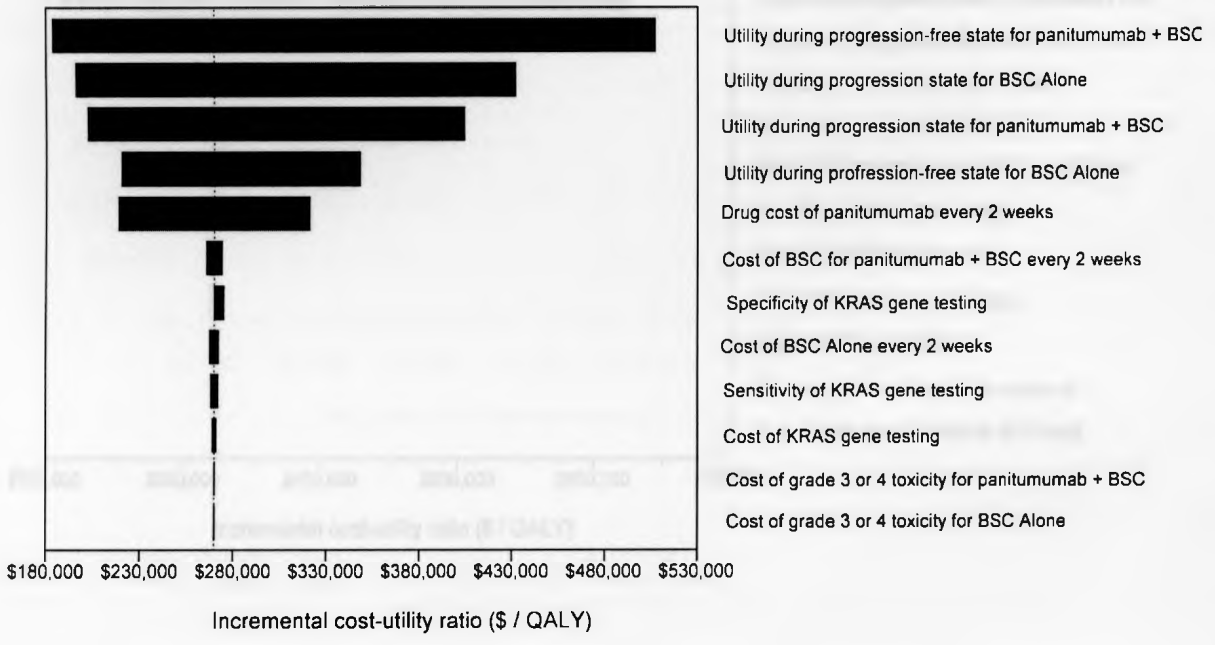


5.4 Deterministic sensitivity analysis

5.4.1 Tornado plot univariate sensitivity analyses for panitumumab plus best supportive care compared to best supportive care alone

I performed univariate sensitivity analyses to determine which variables have the greatest influence on cost-utility ratios for panitumumab plus best supportive care (with KRAS test) compared to best supportive care alone. The bars in the tornado plot are arranged in descending order based on variation in incremental cost-utility ratio and each bar corresponds to the model parameter in front of it. The incremental cost-utility ratios were most sensitive to variation in utility values and drug cost of panitumumab (Figure 5.4). The dotted line in the tornado plot represents the mean incremental-cost utility ratio of $269,703 per QALY gained for panitumumab plus best supportive care compared to best supportive care alone.

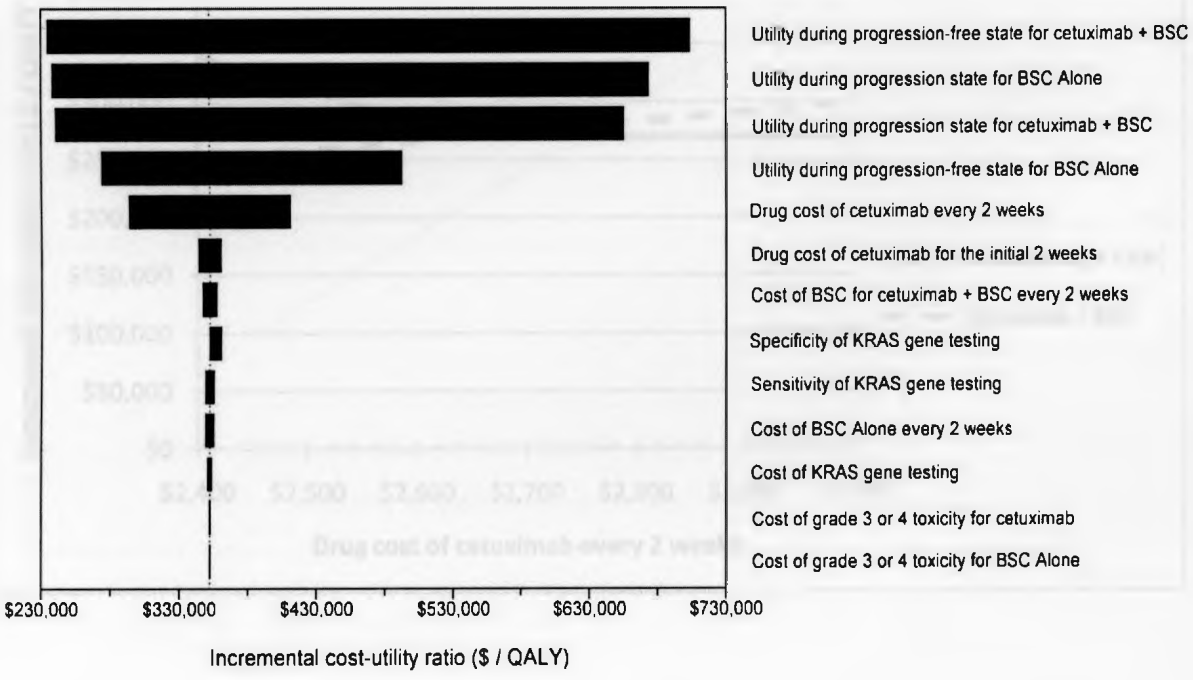
Figure 5.4. Tornado plot univariate analysis for panitumumab plus best supportive care compared to best supportive care alone.



5.4.2 Tornado plot univariate sensitivity analysis for cetuximab plus best supportive care compared to best supportive care alone

An additional univariate sensitivity analysis was carried out to determine which variables have greatest influence on cost-utility ratios for cetuximab plus best supportive care (with KRAS test) compared to best supportive care alone. The results were quiet similar to my previous sensitivity analysis for panitumumab plus best supportive care. The incremental cost-utility ratios were most sensitive to variation in utility values and drug cost of cetuximab (Figure 5.5). The dotted line in the tornado plot represents the mean incremental-cost utility ratio of $352,046 per QALY gained for cetuximab plus best supportive care compared to best supportive care alone.

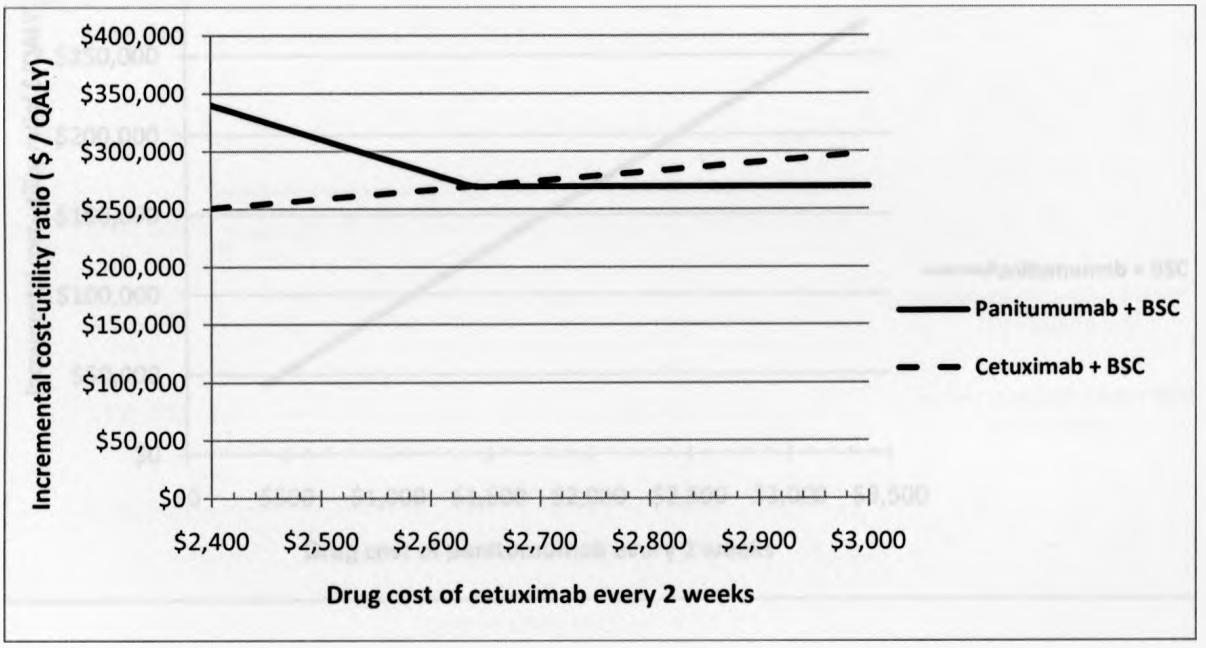
Figure 5.5. Tornado plot univariate analysis for cetuximab plus best supportive care compared to best supportive care alone.



5.4.3 Deterministic sensitivity analysis for cetuximab plus best supportive care compared to panitumumab plus best supportive care

A series of one-way deterministic sensitivity analyses were carried out on the drug cost of cetuximab. The drug cost of cetuximab was reduced from original base case value of $3,667 every 2 weeks and the parameter value at which "cetuximab plus best supportive care" became more cost-effective treatment strategy than "panitumumab plus best supportive care" was recorded. At a drug cost of $2,620 every 2 weeks for cetuximab, the treatment strategy "cetuximab plus best supportive care" became more cost-effective than "panitumumab plus best supportive care" (Figure 5.6).

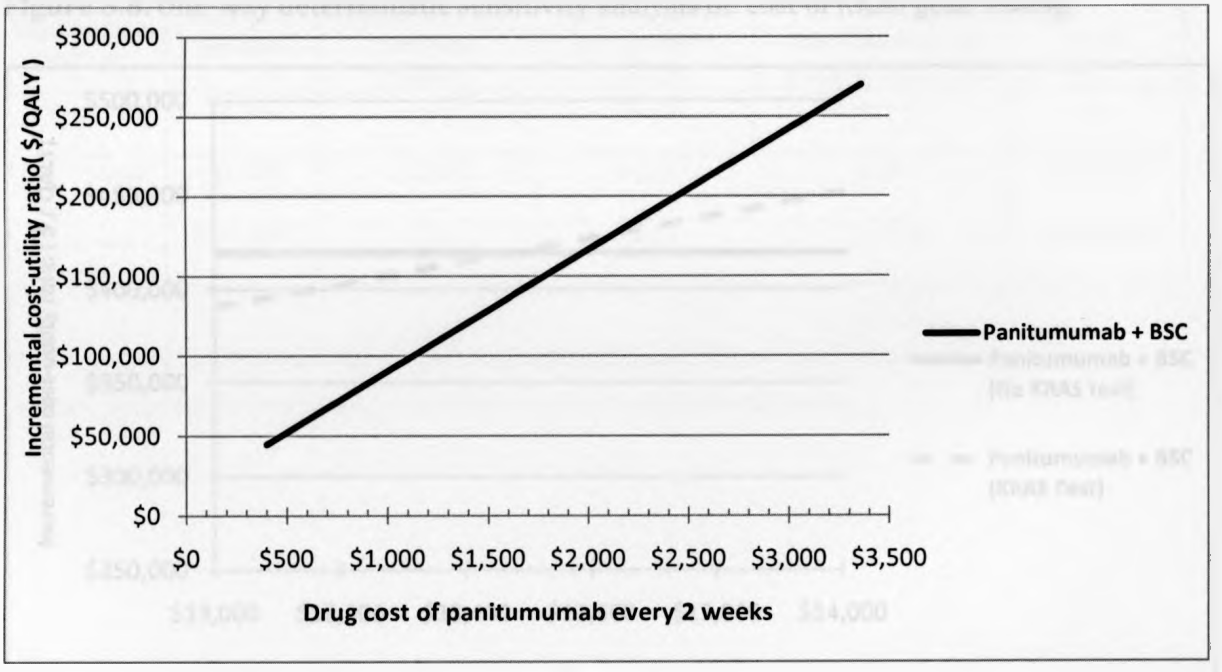
Figure 5.6. One-way deterministic sensitivity analysis on drug cost of cetuximab.



5.4.4 Deterministic sensitivity threshold analysis on the drug cost of panitumumab

I performed a one-way deterministic sensitivity analysis on the drug cost of panitumumab (every 2 weeks) until the willingness-to-pay threshold of $50,000 per QALY gained was reached. My analysis showed that by price reduction in drug cost of panitumumab from $3,359 to $460 every 2 weeks, the treatment strategy "panitumumab plus best supportive care" resulted in an incremental cost-utility ratio of $50,000 per QALY gained (Figure 5.7).

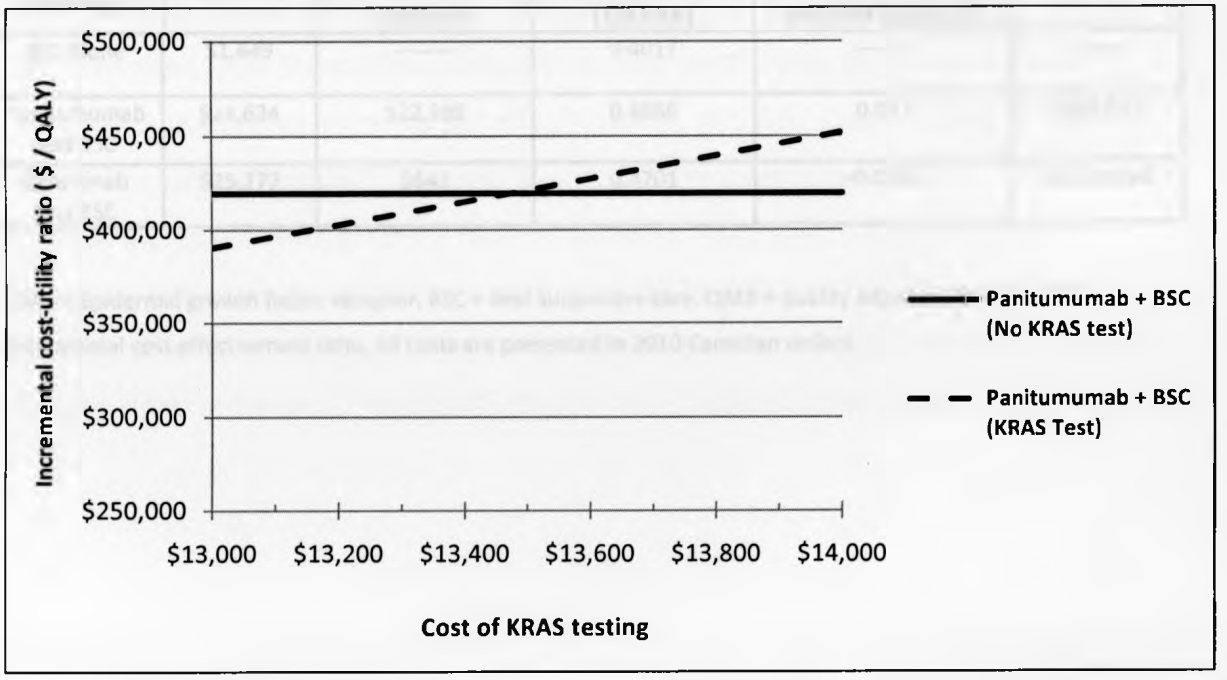
Figure 5.7. One-way deterministic threshold sensitivity analysis on drug cost of panitumumab every 2 weeks.



5.4.5 Deterministic sensitivity threshold analysis on the cost of KRAS testing

A series of one-way deterministic sensitivity analyses were performed to determine the cost value of KRAS testing at which the treatment strategy "panitumumab plus best supportive care with no KRAS test" becomes a better strategy than "panitumumab plus best supportive care with KRAS testing" in terms of cost-effectiveness. My analysis showed that at a KRAS testing cost of $13,500 per patient, the treatment strategy "panitumumab plus best supportive care with no KRAS test" becomes a better treatment strategy in terms of cost-effectiveness (Figure 5.8).

Figure 5.8. One-way deterministic sensitivity analysis on cost of KRAS gene testing.



I performed an additional cost-effectiveness analysis by keeping the price of KRAS testing as $0 to estimate the influence of the cost of KRAS testing in my economic model (Table 5.4). My analysis showed that the cost of KRAS testing has a very minimal impact on incremental cost-utility ratios. Compared to best supportive care alone, the incremental cost per patient for panitumumab plus best supportive (with KRAS test) is $22,985. The panitumumab plus best supportive care (with KRAS test) resulted in a mean gain of 0.087 QALYs, with a mean incremental cost utility ratio of $264,502 per QALY gained.

Table 5.4. Incremental cost-effectiveness of Anti-EGFR therapies (cetuximab and panitumumab) with KRAS testing cost as zero dollars

Treatment strategy	Cost per patient	Incremental cost per patient	Effectiveness per patient (QALYs)	Incremental effectiveness per patient (QALYs)	ICER
BSC Alone	$1,649	--------	0.4017	--------	-------
Panitumumab plus BSC	$24,634	$22,985	0.4886	0.087	$264,502
Cetuximab plus BSC	$25,277	$643	0.4701	-0.0185	Dominated

EGFR = Epidermal growth factor receptor, BSC = best supportive care, QALY = quality adjusted life year, ICER = Incremental cost effectiveness ratio. All costs are presented in 2010 Canadian dollars.

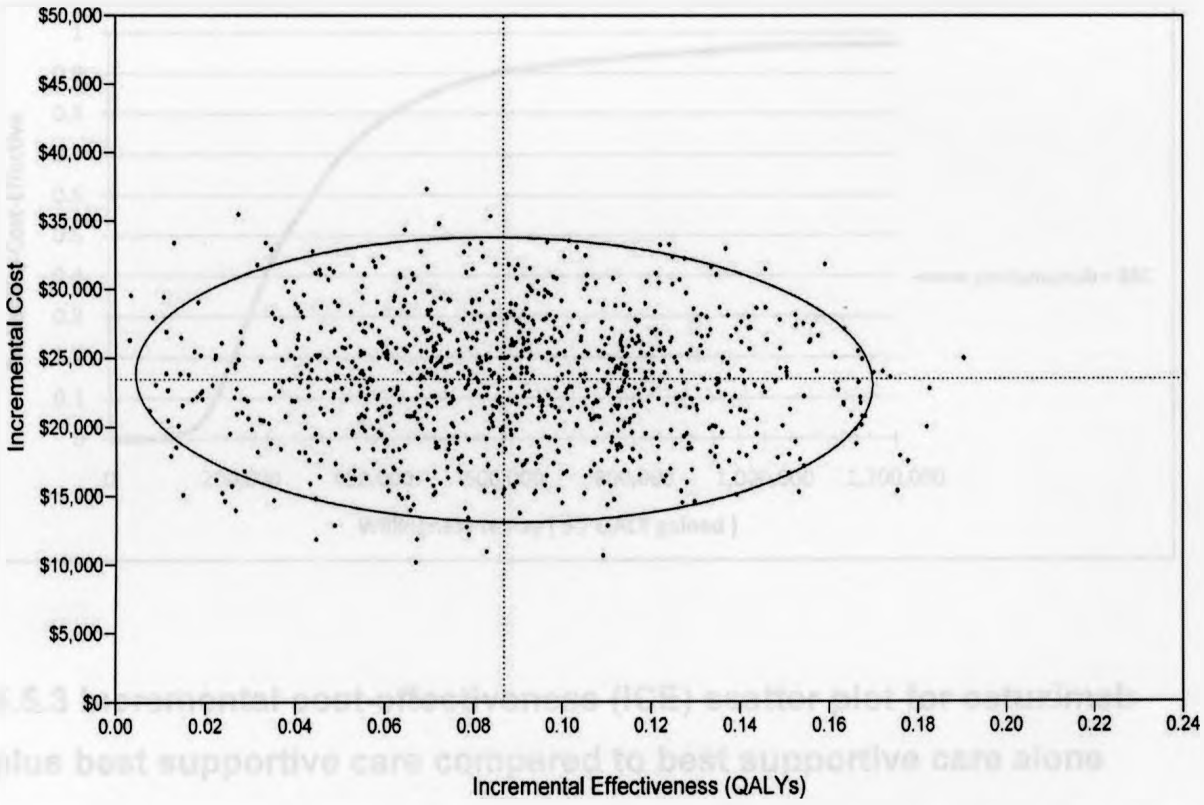
5.5 Probabilistic sensitivity analysis

5.5.1 Incremental cost-effectiveness (ICE) scatter plot for panitumumab plus best supportive care compared to best supportive care alone

The incremental cost-effectiveness scatter plot comparing panitumumab plus best supportive care (with KRAS test) to best supportive care alone is shown in Figure 5.9. The points in the scatter plot represent the comparator's (panitumumab plus best supportive care) incremental cost and incremental effectiveness relative to baseline (best supportive care alone).

The data from probabilistic sensitivity analysis was plotted onto 4 quadrants. The data plotted from probabilistic sensitivity analysis shows that 100% of the samples fell in quadrant I which represents the scenario where panitumumab plus best supportive care (with KRAS test) is more costly and more effective than best supportive care alone. The dotted line on horizontal axis represents the mean incremental effectiveness of 0.087 QALYs gained and the dotted line on vertical axis represents the mean incremental cost of $23,437 with a mean incremental cost-utility ratio of $269,703 per QALY gained (95% CI based on probabilistic sensitivity analysis = $135,432 to $766,072 per QALY gained). A 95% confidence ellipse was also drawn in the ICE scatter plot using TreeAge pro software (TreeAge Software Inc., Williamstown, MA).

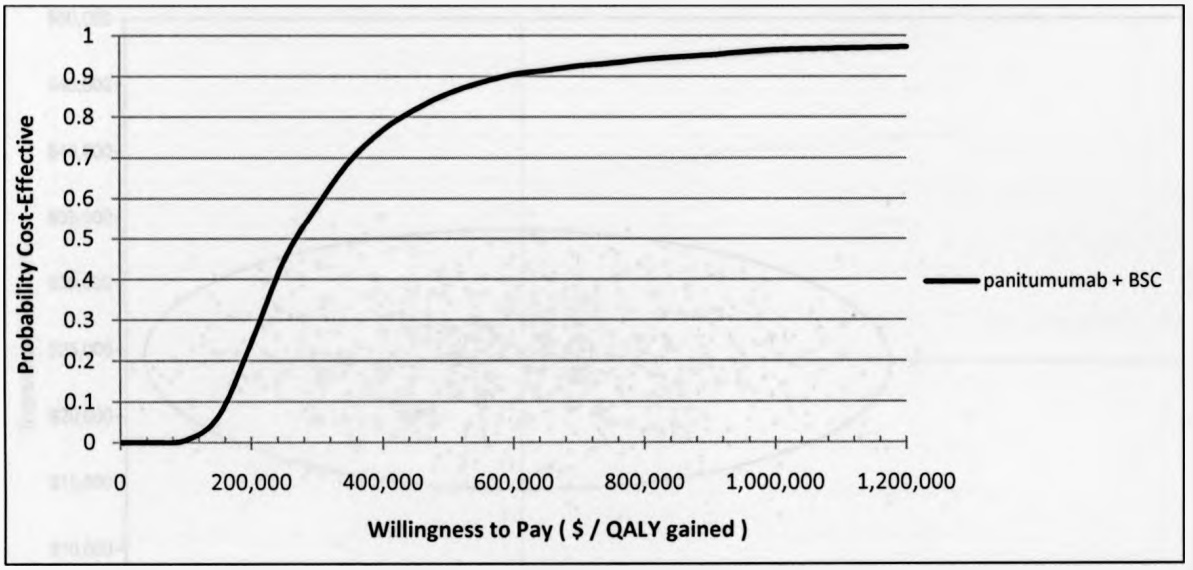
Figure 5.9. Incremental cost-effectiveness scatter plot comparing panitumumab plus best supportive care (with KRAS test) to best supportive care alone.



5.5.2 Willingness-to-pay threshold analysis for Panitumumab plus best supportive care compared to best supportive care alone

The cost-effectiveness acceptability threshold analysis for panitumumab plus best supportive care (with KRAS test) compared to best supportive care alone is shown in Figure 5.10. The acceptability curve shows the probability of panitumumab plus best supportive care for being considered cost-effective at various willingness-to-pay thresholds (ICER values i.e. $ per QALY gained). The probability of being considered cost-effective is 0% at a threshold of $50,000 per QALY gained; 0.6% at a threshold of $100,000 per QALY gained; 6.6% at a threshold of $150,000 per QALY gained; 24.7% at a threshold of $200,000 per QALY gained and 44.9% at a threshold of $250,000 per QALY gained.

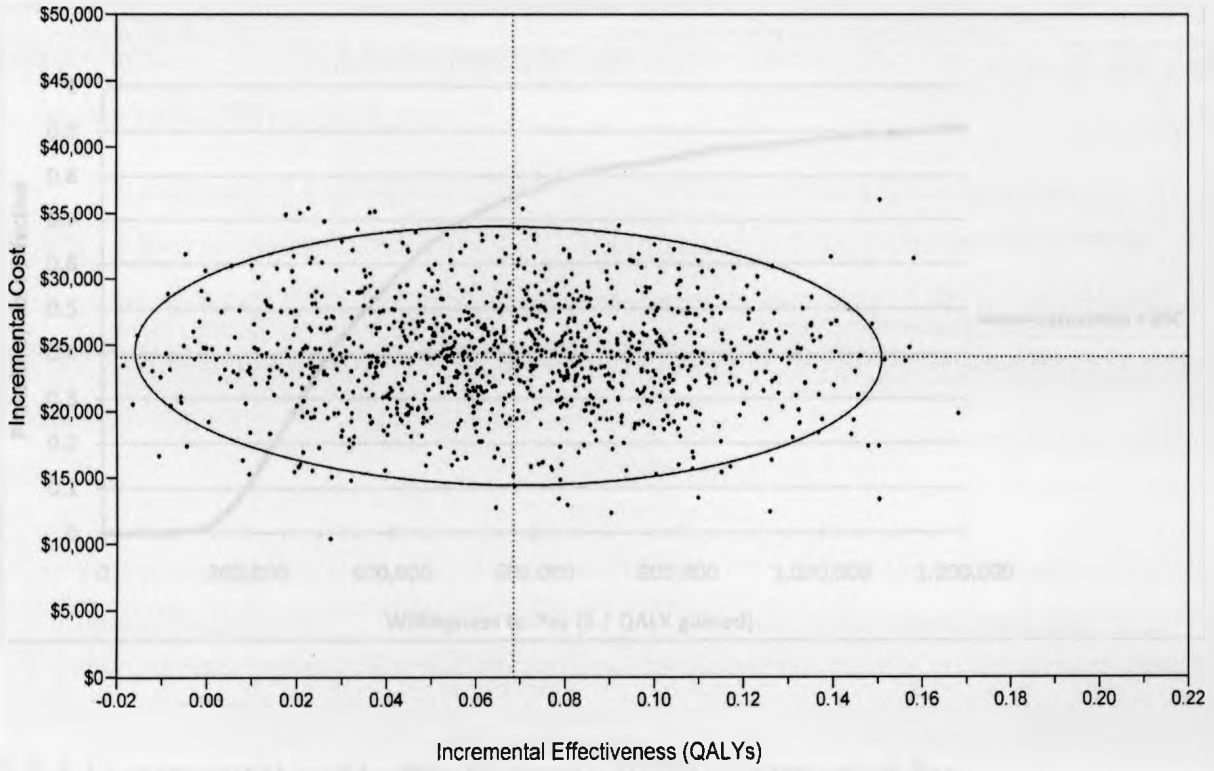
Figure 5.10. Cost-effectiveness acceptability threshold analysis for panitumumab plus best supportive care (with KRAS test) compared to best supportive care alone.



5.5.3 Incremental cost-effectiveness (ICE) scatter plot for cetuximab plus best supportive care compared to best supportive care alone

The incremental cost-effectiveness scatter plot comparing cetuximab plus best supportive care (with KRAS test) to best supportive care alone is shown in Figure 5.11. The data plotted from probabilistic sensitivity analysis shows that 98% of the samples fell in quadrant I which represents the scenario where cetuximab plus best supportive care is more costly and more effective than best supportive care alone; 2% of the samples fell in quadrant II which represents the scenario where cetuximab plus best supportive care is more costly but less effective than best supportive care alone. The dotted line on horizontal axis represents the mean incremental effectiveness of 0.068 QALYs gained and the dotted line on vertical axis represents the mean incremental cost of $24,080 with a mean incremental cost-utility ratio of $352,046 per QALY gained (95% CI based on probabilistic sensitivity analysis = $151,916 to $949,342 per QALY gained). A 95% confidence ellipse was also drawn in the ICE scatter plot using TreeAge pro software (TreeAge Software Inc., Williamstown, MA).

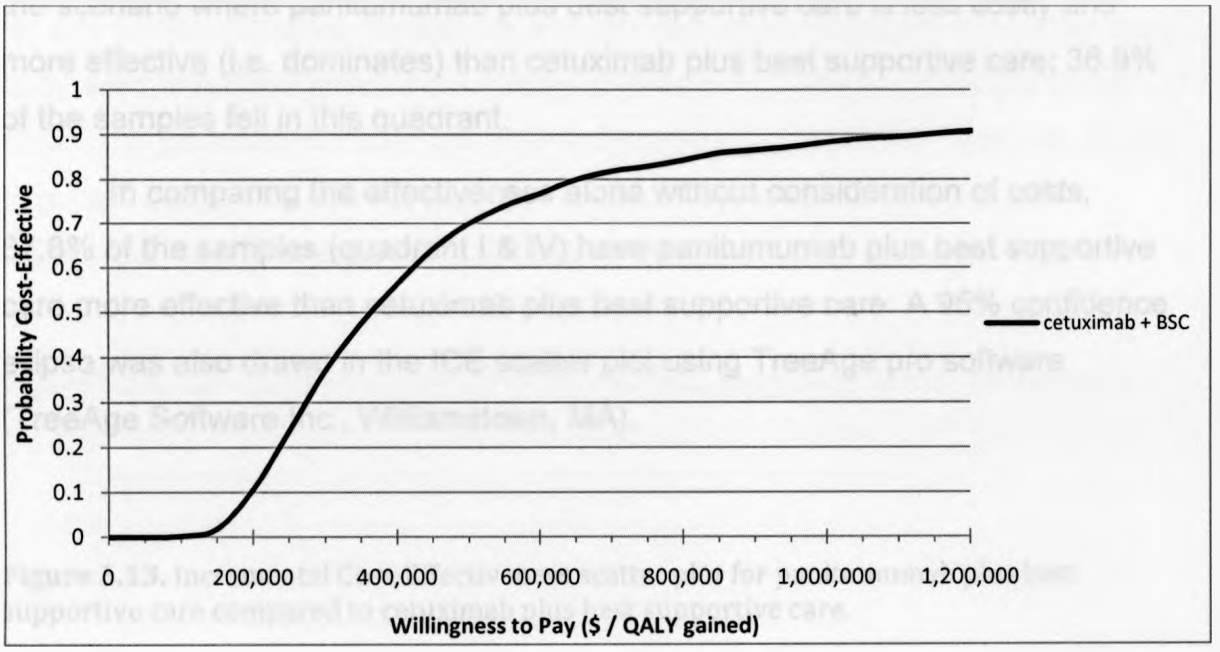
Figure 5.11: Incremental cost-effectiveness scatter plot comparing cetuximab plus best supportive care (with KRAS test) to best supportive care alone.



5.5.4 Willingness-to-pay threshold analysis for cetuximab plus best supportive care compared to best supportive care alone

The cost-effectiveness acceptability threshold analysis for cetuximab plus best supportive care (with KRAS test) compared to best supportive care alone is shown in Figure 5.12. The acceptability curve shows the probability of cetuximab plus best supportive care for being considered cost-effective at various willingness-to-pay thresholds (ICER values i.e. $ per QALY gained). The probability of being considered cost-effective is 0% at a threshold of $50,000 per QALY gained; 0.2% at a threshold of $100,000 per QALY gained; 1.8% at a threshold of $150,000 per QALY gained; 10.5% at a threshold of $200,000 per QALY gained and 23.5% at a threshold of $250,000 per QALY gained.

Figure 5.12. Cost-effectiveness acceptability threshold analysis for cetuximab plus best supportive care (with KRAS test) compared to best supportive care alone.



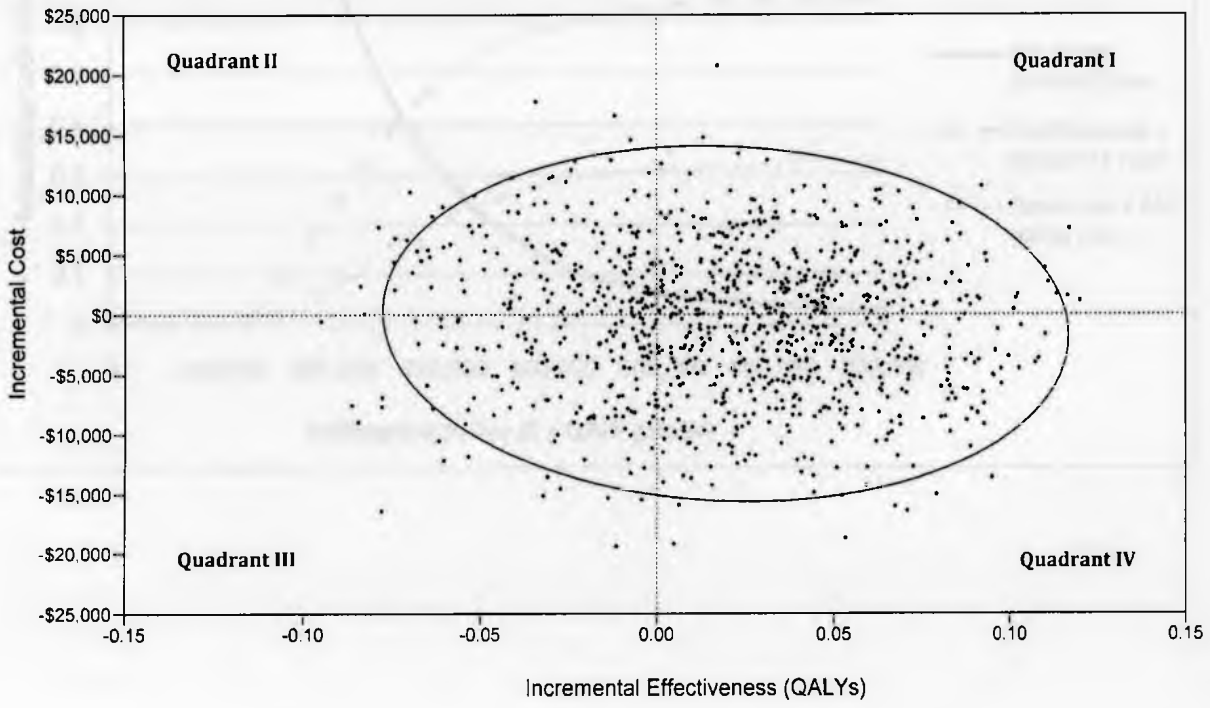
5.5.5 Incremental cost-effectiveness (ICE) scatter plot for panitumumab plus best supportive care compared to cetuximab plus best supportive care

The incremental cost-effectiveness scatter plot comparing panitumumab plus best supportive care (with KRAS test) to cetuximab plus best supportive care (with KRAS test) was produced using TreeAge Pro software (Figure 5.13). The points in the scatter plot represent the incremental cost and incremental effectiveness of panitumumab plus best supportive care relative to cetuximab plus best supportive care. The data from probabilistic sensitivity analysis was plotted onto 4 quadrants. Quadrant I represent the scenario where panitumumab plus best supportive care is more costly and more effective than cetuximab plus best supportive care; 30.9% of the samples fell in this quadrant. Quadrant II represents the scenario where panitumumab plus best supportive care is more costly and less effective (i.e. dominated); 13.2% of the samples fell in this quadrant. Quadrant III represents the scenario where panitumumab plus best

supportive care is less costly and less effective than cetuximab plus best supportive care; 19% of the samples fell in this quadrant. Quadrant IV represents the scenario where panitumumab plus best supportive care is less costly and more effective (i.e. dominates) than cetuximab plus best supportive care; 36.9% of the samples fell in this quadrant.

In comparing the effectiveness alone without consideration of costs, 67.8% of the samples (quadrant I & IV) have panitumumab plus best supportive care more effective than cetuximab plus best supportive care. A 95% confidence ellipse was also drawn in the ICE scatter plot using TreeAge pro software (TreeAge Software Inc., Williamstown, MA).

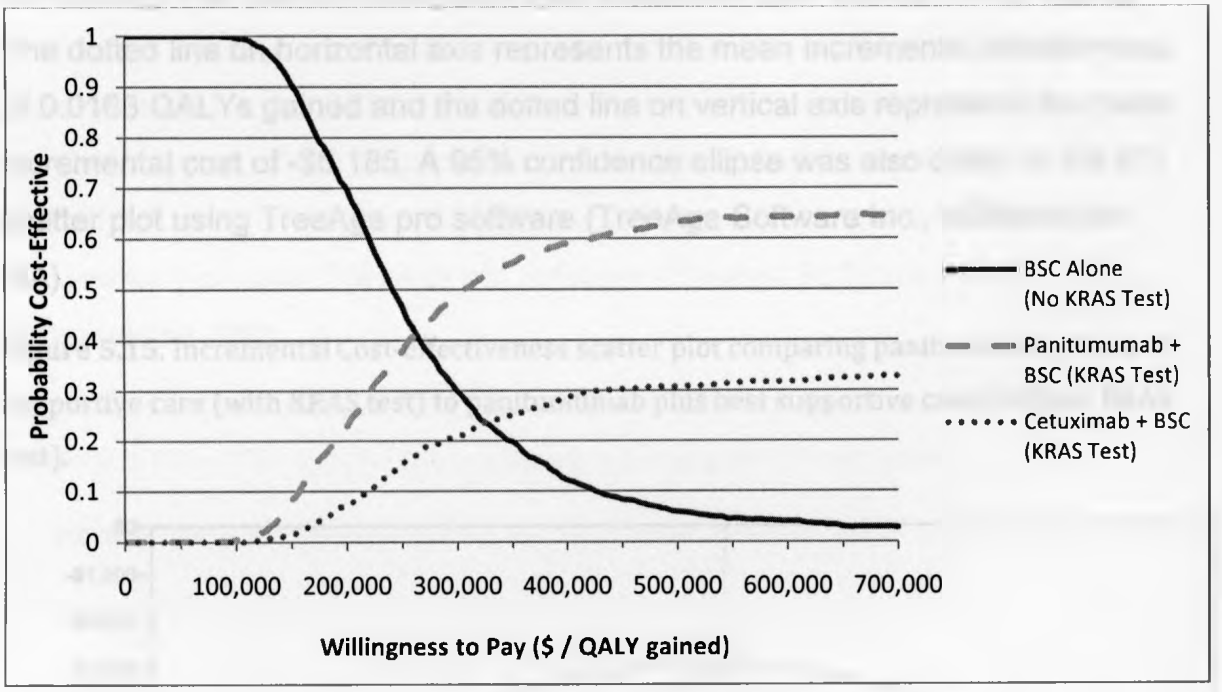
Figure 5.13. Incremental Cost-Effectiveness scatter plot for panitumumab plus best supportive care compared to cetuximab plus best supportive care.



5.5.6 Willingness-to-pay threshold analysis for anti-EGFR therapies

I performed a cost-effectiveness acceptability threshold analysis for anti-EFGR therapies (cetuximab and panitumumab) plus best supportive care compared to best supportive care alone (Figure 5.14). The acceptability curve shows the probability of both anti-EGFR therapies (panitumumab and cetuximab) plus best supportive care for being considered cost-effective at various willingness-to-pay thresholds (ICER values i.e. $ per QALY gained).

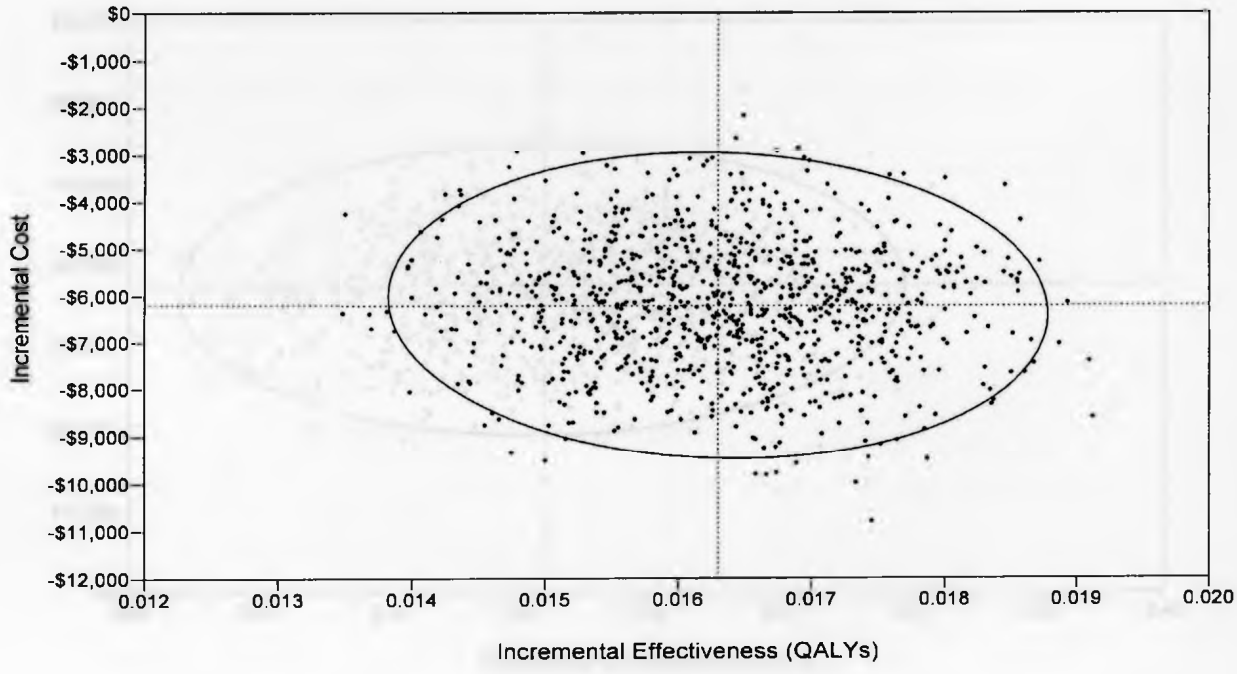
Figure 5.14. Cost–effectiveness acceptability threshold analysis for anti-EGFR therapies.



5.5.7 Incremental cost-effectiveness scatter plot for panitumumab plus best supportive care (with KRAS test) compared to panitumumab plus best supportive care (without KRAS test)

The incremental cost-effectiveness scatter plot comparing panitumumab plus best supportive care treatment with KRAS testing to panitumumab plus best supportive care treatment without KRAS testing is shown in Figure 5.15. The data plotted from probabilistic sensitivity analysis shows that 100% of the samples fell in quadrant IV which represents the scenario where panitumumab plus best supportive care with KRAS testing is less costly and more effective (i.e. dominates) than panitumumab plus best supportive care without KRAS testing. The dotted line on horizontal axis represents the mean incremental effectiveness of 0.0163 QALYs gained and the dotted line on vertical axis represents the mean incremental cost of -$6,185. A 95% confidence ellipse was also drawn in the ICE scatter plot using TreeAge pro software (TreeAge Software Inc., Williamstown, MA).

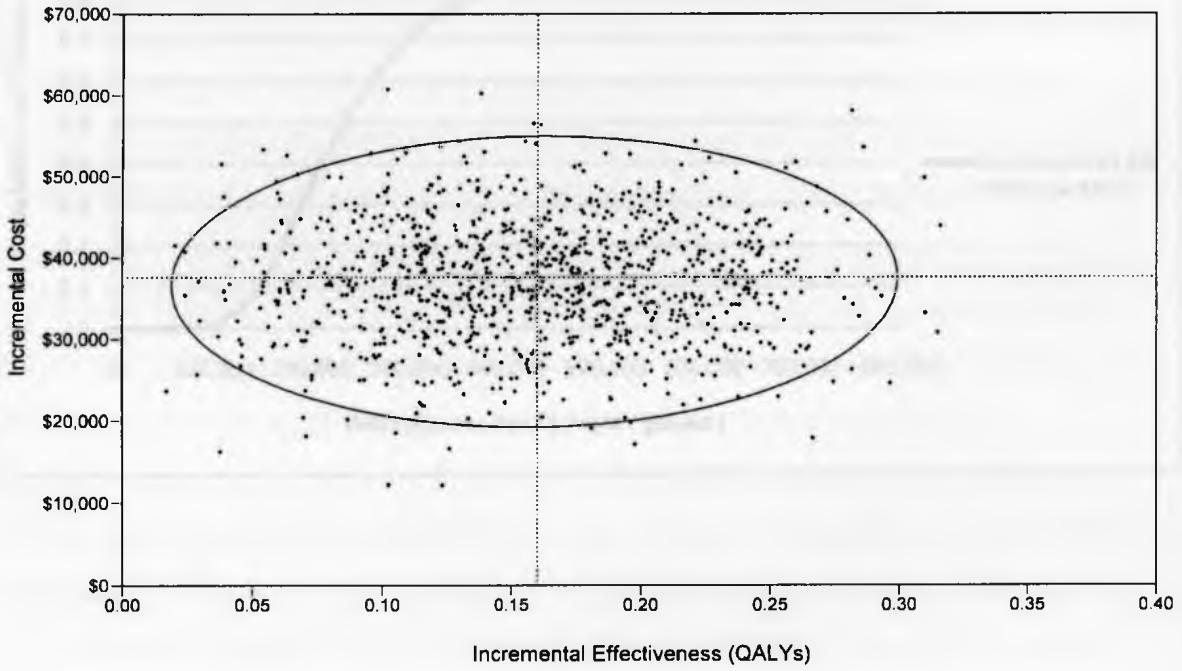
Figure 5.15. Incremental Cost-effectiveness scatter plot comparing panitumumab plus best supportive care (with KRAS test) to panitumumab plus best supportive care (without KRAS test).



5.5.8 Incremental cost-effectiveness scatter plot for panitumumab plus best supportive care (wild-type KRAS) compared to best supportive care alone

The incremental cost-effectiveness scatter plot comparing panitumumab plus best supportive care (in subset of patients with wild-type KRAS) to best supportive care alone is shown in Figure 5.16. The data plotted from probabilistic sensitivity analysis shows that 100% of the samples fell in quadrant I which represents the scenario where panitumumab plus best supportive care (wild-type KRAS) is more costly and more effective than best supportive care alone. The dotted line on horizontal axis represents the mean incremental effectiveness of 0.16 QALYs gained and the dotted line on vertical axis represents the mean incremental cost of $37,606 with a mean incremental cost-utility ratio of $236,469 per QALY gained (95% CI based on probabilistic sensitivity analysis = $125,259 to $557,750 per QALY gained). A 95% confidence ellipse was also drawn in the ICE scatter plot using TreeAge pro software (TreeAge Software Inc., Williamstown, MA).

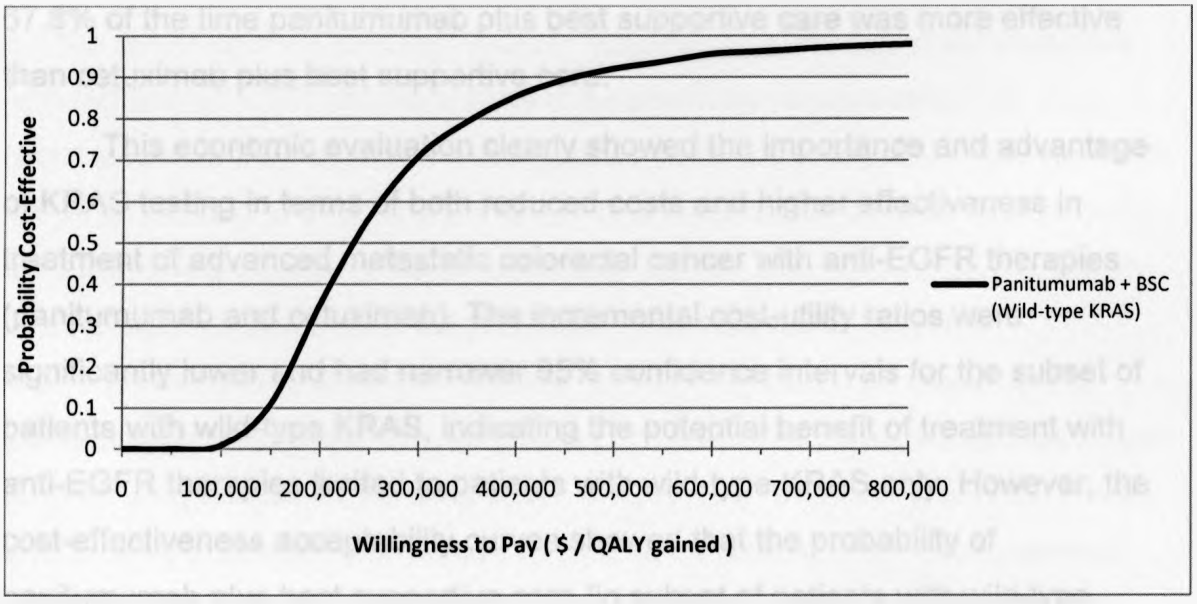
Figure 5.16. Incremental cost-effectiveness scatter plot for panitumumab plus best supportive care (Wild-type KRAS) compared to best supportive care alone.



5.5.9 Willingness-to-pay threshold analysis for panitumumab plus best supportive care (wild-type KRAS) compared to best supportive care alone

I constructed a cost-effectiveness acceptability threshold analysis for panitumumab plus best supportive care (wild-type KRAS only) compared to best supportive care alone is shown in Figure 5.17. The acceptability curve shows the probability of panitumumab plus best supportive care (in subset of patients with wild-type KRAS) for being considered cost-effective at various willingness-to-pay thresholds (ICER values i.e. $ per QALY gained). The probability of being considered cost-effective is 0% at a threshold of $50,000 per QALY gained; 0.9% at a threshold of $100,000 per QALY gained; 11.1% at a threshold of $150,000 per QALY gained; 33.5% at a threshold of $200,000 per QALY gained and 56.5% at a threshold of $250,000 per QALY gained.

Figure 5.17. Cost–effectiveness acceptability threshold analysis for panitumumab plus best supportive care (wild-type KRAS) compared to best supportive care alone.



Chapter 6: Discussion & Conclusions

6.1 Discussion

My economic analysis is the first to examine the cost-effectiveness of two anti-EGFR monoclonal antibodies (panitumumab and cetuximab) versus best supportive care alone in a single economic model. To my knowledge it is also the first economic analysis to analyze the cost-effectiveness of KRAS testing using the survival data from two phase III clinical trials.

In this economic analysis, panitumumab plus best supportive care and cetuximab plus best supportive care showed high incremental cost-utility ratios (ICER = $269,703 for panitumumab and $352,040 for cetuximab with KRAS testing) when compared with best supportive care alone. The base case and sensitivity analysis showed that among anti-EGFR therapies, panitumumab based therapy was much more cost effective than cetuximab based therapy for treatment of advanced metastatic colorectal cancer. The probabilistic analysis showed that, in comparing the effectiveness alone without consideration of costs, 67.8% of the time panitumumab plus best supportive care was more effective than cetuximab plus best supportive care.

This economic evaluation clearly showed the importance and advantage of KRAS testing in terms of both reduced costs and higher effectiveness in treatment of advanced metastatic colorectal cancer with anti-EGFR therapies (panitumumab and cetuximab). The incremental cost-utility ratios were significantly lower and had narrower 95% confidence intervals for the subset of patients with wild-type KRAS, indicating the potential benefit of treatment with anti-EGFR therapies limited to patients with wild-type KRAS only. However, the cost-effectiveness acceptability curves showed that the probability of panitumumab plus best supportive care (in subset of patients with wild-type KRAS) being considered cost-effective was 0% at a willingness-to-pay threshold value of $50,000 per QALY gained, 0.9% at a threshold value of $100,000 per QALY gained, and 56.5% at a threshold value of $250,000 per QALY gained.

The drug costs of both panitumumab and cetuximab were a major cost driver in my economic analysis. My sensitivity analysis showed that incremental cost-utility ratios were most sensitive to drug costs amongst all cost parameters in the analysis. The incremental cost-utility ratio for panitumumab plus best supportive care (with KRAS test) reached the willingness-to-pay threshold of $50,000 per QALY gained at a drug cost of $460 bi-weekly.

Economic evaluations are conducted to help provide the "value for money" information to decision and policy makers about resource allocation in a resource constrained environment [52]. Most countries such as Canada, the United Kingdom and Australia require a formal structured economic evidence for drug reimbursement [60, 68]. Cost-effectiveness analysis has been increasingly becoming the analytic method choice to help inform the reimbursement decisions for oncology medications by weighing the incremental costs and consequences of alternative treatment strategies being compared [60, 68]. Implicit incremental cost-effectiveness ratio (ICER) thresholds for drug reimbursement recommendations have been published in Australia and the United Kingdom [68].

In Canada, no such implicit economic thresholds have been published [68] but the evidence from existing literature suggests that the treatment strategies with "attractive" ICER are more likely to be positively recommended for drug reimbursement than treatment strategies with less attractive ICER [68]. An ICER range of $20,000 to $100,000 per QALY is considered as a reasonable boundary for determining whether a new medical intervention is cost-effective [68, 69]. In most Canadian territories (except Quebec), the drug reimbursement recommendations to Canadian publicly funded drug plans are made by the Canadian Common Drug Review (CDR) [70]. The CDR considers various factors such as drug effectiveness, drug costs, drug toxicity, ethical and societal issues, and existing pharmaco-economic evaluations for making drug reimbursement recommendations [70]. These recommendations are further reviewed by the Canadian Expert Drug Advisory Committee (CEDAC – a committee of 11 physicians, pharmacists and nurses) [70]. The CEDAC recommends one of three

possible options for drug reimbursement: fund the drug without restrictions; fund the drug with restrictions; and do not fund the drug [70].

The clinical evidence to support the benefit is stronger for oncology medications [68, 71] and they are usually adopted at the highest threshold of acceptability than non-oncology medications [68, 71]. Recent recommendations from Canadian Expert Drug Advisory committee (CEDAC) suggest that an ICER threshold of $75,000 per QALY may be considered acceptable for oncology medications [68]. A 2006 survey of medical oncologists inferred a willingness-to-pay threshold of up to $300,000 per QALY gained acceptable for oncology medications [72] but it is important to note that there is no empirical evidence to support such a threshold.

Table 6.1. Summary table

Model*	Treatment strategy	ICER
Markov model 1	Panitumumab plus BSC (No KRAS test)	$419,528
	Cetuximab plus BSC (No KRAS test)	dominated
Markov model 2	Panitumumab plus BSC (with KRAS test)	$269,703
	Cetuximab plus BSC (with KRAS test)	dominated
Markov model 3	Panitumumab plus BSC (wild-type KRAS only)	$236,469
	Cetuximab plus BSC (wild-type KRAS only)	dominated

*In the Markov model 1, 2 and 3, the baseline treatment strategy is best supportive care alone (No KRAS test).

ICER= Incremental cost-effectiveness ratio, BSC = best supportive care, All costs are presented in 2010 Canadian dollars.

6.2 Limitations

This economic analysis has several possible limitations. First, the utility weights used in the economic analysis were obtained from two different studies which used different health-related quality of life (HRQoL) instruments to measure utility values. The utility weights for cetuximab plus best supportive care were calculated using Health Utilities Index Mark 3 (HUI3) [60, 62] and utility weights for panitumumab plus best supportive care were calculated using Euroqol-5D (EQ-5D) [61, 63]. The use of different HRQoL instruments to assign quality of life scores (utilities) to health states may have some impact on overall effectiveness calculated in my model but I performed a series of deterministic and probabilistic sensitivity analyses to assess the robustness of the results.

Second, the economic analysis is based on survival and drug toxicity data obtained from clinical trials [8, 9]. Thus, results may not be generalizable to routine care of advanced metastatic colorectal cancer patients.

Third, the best supportive care costs were assumed to be the same for both panitumumab and cetuximab. However these costs may be different in routine care of advanced metastatic colorectal cancer patients with these drugs. My sensitivity analysis showed that best supportive care costs did not have a significant influence on the model outcome (incremental cost-utility ratios).

Fourth, the time horizon of 2 years for my economic analysis was based on maximum time of follow-up in both trial studies (1.58 years for NCIC CTG CO.17 trial and 2 years for Open-Label Phase III trial) [8, 9]. However, it is unlikely that there would be any statistically significant survival gain beyond time horizon of my economic model that could impact model outcome, as fewer than 10% of the patients were alive at the end of 2 years in both trials [8-9, 15-16].

Fifth, my economic analysis was based on multinational clinical trials which may be subject to geographical and jurisdictional differences in the patient population, health care costs, health care resources allocation and utilization [73, 74].

Sixth, In the open-label phase III trial, the treatment arm (panitumumab plus best supportive care) had 54% of the patients with ECOG performance status of 1 and 2 as compared to 66% in control arm (best supportive care alone) [8]. This difference is a potential limitation of the clinical trial as it could have impacted the overall survival and progression free survival among the treatment groups.

6.3 Conclusion

From a cost-effectiveness perspective, both anti-EFGR therapies (panitumumab and cetuximab) showed very high Incremental cost-utility ratios and were not cost-effective at a willingness-to-pay threshold of $100,000 per QALY. The cost-effectiveness of both anti-EGFR therapies (panitumumab and cetuximab) as compared to best supportive care alone with KRAS testing dominates the cost-effectiveness without KRAS testing and the incremental cost-utility ratios became more favourable. However, even with KRAS testing, both anti-EGFR therapies were not cost-effective at a willingness to pay threshold of $100,000 per QALY.

In most cases, among anti-EGFR therapies, the treatment option with panitumumab plus best supportive care dominates the treatment option with cetuximab plus best supportive care as third-line therapy for treatment of advanced metastatic colorectal cancer.

The cost-utility ratios for both anti-EGFR therapies (panitumumab and cetuximab) as compared to best supportive care alone were significantly lower and had narrower 95% confidence intervals in subset of patients with wild-type KRAS. This suggests that personalizing advanced metastatic colorectal cancer treatment based on KRAS mutation status could not only save health care system substantial sums but also spare thousands of patients with colorectal cancer from side effects of the anti-EGFR therapy that are unlikely to benefit from the treatment.

Appendix I (Release of information letter from AMGEN)

AMGEN

Medical Information

August 25, 2010

Dr. Muhammad Ali
157-1560 Adelaide St. North
London, ON N5X 2C1

Dear Dr. Ali:

Thank you for your request to Amgen Canada Inc. for information regarding the following topic(s), which was forwarded to our department on your behalf by Ben Ofori.

- Vectibix™ (panitumumab) - quality of life and cost

Please find enclosed the following references in response to your request.

•Siena S, Peeters M, VanCutsem E, et al. Association of progression-free survival with patient-reported outcomes and survival: results from a randomised phase 3 trial of panitumumab. Britis Journal of Cancer 2007;97:1469-1474.

•Peetrs M, PRice T, Hotko Y, et al. Randomized Phase 3 Study of Panitumumab with FOLFIRI vs FOLFIRI alone as 2nd-Line Treatment in Patients with Metastatic Colorectal Cancer (mCRC): Patient Reported Outcomes (PRO). Poster presented at

•Mancl E, Kolesar J, Vermeulen L. Clinical and economic value of screening for Kras mutations as predictors of response to epidermal growth factor receptor inhibitors. Am J Health-Syst Pharm 2009;66:e17-24.

•Bracco A, Farrimond BJ, Fitzgibbon JW, et al. A Model to Demonstrate the Comparative Costs Between Panitumumab and Cetuximab for Third-line Metastatic Colorectal Cancer Patients in Italy. Poster presented at ISPOR Annual European Congress Athens, Greece; November 8-11, 2008.

•Graham C, Borker R, Oppe M, et al Cost-effectiveness of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Chemorefractory Metastatic Colorectal Cancer Patients With Wild-Type KRAS Tumor Status in the Netherlands. ESMO, Stockholm, Sweden; September 12-16, 2008

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Tel: 1-866-502-6436 Fax: 1-866-472-6436 Email: medinfocanada@amgen.com

Please note that your contact information and request for information will be retained in our electronic database to facilitate delivery of the requested information and to comply with applicable laws. Please contact us should you have any questions or concerns about the retention of this information.

Should you have any additional questions, please contact our Medical Information Department at 1-866-502-6436 or via e-mail at medinfocanada@amgen.com.

Sincerely,

Diane Lord

Diane Lord, B.Pharm.
Medical Information Manager

1-793779111

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1. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2010. Toronto,ON, Canada: Canadian Society; 2010

2. Tumeh, J. W., Shenoy, P. J., Moore, S. G., Kauh, J., & Flowers, C. (2009). A markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal cancer. American Journal of Clinical Oncology, 32(1), 49-55. doi:10.1097/COC.0b013e31817c6a4d

3. Chau, I., & Cunningham, D. (2009). Treatment in advanced colorectal cancer: What, when and how? British Journal of Cancer, 100(11), 1704-1719. doi:10.1038/sj.bjc.6605061

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