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The Cost-Effectiveness of Combination Treatment Consisting of Either Cetuximab or Panitumumab plus FOLFIRI versus Treatment with Bevacizumab plus FOLFIRI as First-Line Treatment for KRAS Wild-Type Metastatic Colorectal Cancer Patients in Ontario

Emmanuel M.G. Ewara, *The University of Western Ontario*

Supervisor: Dr. Sisira Sarma, *The University of Western Ontario*
Joint Supervisor: Dr. Greg Zaric, *The University of Western Ontario*
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(Spine title: Cost-Effectiveness of First-Line Treatment for MCRC)

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Emmanuel Ewara

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London, Ontario, Canada

THE UNIVERSITY OF WESTERN ONTARIO
School of Graduate and Postdoctoral Studies

CERTIFICATE OF EXAMINATION

Supervisor

Dr. Sisira Sarma

Co-Supervisor

Dr. Greg Zaric

Supervisory Committee

Dr. Stephen Welch

Examiners

Dr. Eric Winquist

Dr. Bin Xie

Dr. Monali Malvankar

The thesis by

Emmanuel Mmodu Gerald Ewara

entitled:

The Cost-Effectiveness of Combination Treatment Consisting of Either Cetuximab or Panitumumab plus FOLFIRI versus Treatment with Bevacizumab plus FOLFIRI as First-Line Treatment for KRAS Wild-Type Metastatic Colorectal Cancer Patients in Ontario

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Abstract

I conducted a cost-effectiveness analysis of combination cetuximbab or panitumumab plus FOLFIRI as first-line treatment for patients with metastatic colorectal cancer (MCRC) from the perspective of the Ontario healthcare payer. I developed a Markov decision analytical model to simulate the lifetime costs and benefits of each treatment option. The model was parameterized using data collected from administrative databases in the province of Ontario and from published clinical trials. In the base case scenario, treatment consisting of bevacizumab plus FOLFIRI was found to dominate other treatment options. The ICER values were found to be sensitive to the efficacy of first-line treatment, cost of bevacizumab and cetuximab, and health utility values. In conclusion the use of bevacizumab plus FOLFIRI, the current standard of care, is the most cost-effective first-line treatment option for patients with metastatic colorectal cancer in Ontario..

Keywords

Cost-Effectiveness, Metastatic Colorectal Cancer, Cetuximab, Bevacizumab, Panitumumab, Ontario, Markov Model.

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Glossary of Terms

Adenocarcinoma: A cancer of the epithelium which originated in glandular tissue.

Angiogenesis: A physiological process in which new blood vessels are formed off of pre-existing ones

Anti-Apoptotic: Something that prevents the process of apoptosis.

Apoptosis: a programmed, multi-step cellular process in which biochemical events within cells which results in cellular death.

Chimeric: a substance or molecule which is composed of parts which are of different species origin.

Codon: a sequence of three adjacent nucleotides in a DNA or RNA molecule which encodes a specific amino acid to be incorporated in a protein chain.

Cytotoxicity: the degree of destructive or cell-killing ability a substance or agent has.

Epigenetic: changes in gene function which occur without changes in the DNA sequence of the gene.

Exon: the nucleotide sequence in mature messenger or non-coding RNA which refers to a specific sequence in the un-spliced RNA or DNA sequence and codes for a specific portion of a protein's peptide chain.

Extravasate: the movement of a substance/agent from the blood or lymphatic vessels into a tissue.

Immunohistochemistry: the process of detecting specific proteins within cells through the use of antibodies which bind to specific portions of the protein and which are visualized using antibody-specific stains or through the tagging of the antibody with a fluorophore.

Intravasate: the movement of a substance/agent into blood or lymphatic vessels.

Ligand: a substance which binds to a receptor to form a biological complex and initiates a biological response.

Monoclonal Antibody: identical antibodies which specifically target cellular surface antigens and are produced in large quantities by a clones of a single immune cell.

Neoplasm: a new and abnormal growth of tissue which serves no purpose and which may be benign or cancerous.

Phenotype: the observable characteristics of an organism that are produced through the interaction of the organism's genotype and their environment.

Proto-Oncogene: a gene which contributes to the development of cancer.

Vascularization: the abnormal or pathological formation of blood vessels.

List of Abbreviations

5-FU: 5-Fluorouracil

5-FU/LV: 5-Fluorouracil and Leucovorin

BSC: Best Supportive Care

CBA: Cost-Benefit Analysis

CCO: Cancer Care Ontario

CIHI: Canadian Institute for Health Information

CEA: Cost-Effectiveness Analysis

CUA: Cost-Utility Analysis

DAD: Discharge Abstract Database

EGFR: Epidermal Growth Factor Receptor

HCD: Home Care Database

ICER: Incremental Cost-Effectiveness Ratio

ICES: Institute of Clinical and Evaluative Sciences

IFL: Irinotecan plus 5-Fluorouracil and Leucovorin

ITT: Intention-to-Treat

KRAS: Kristen Rat Sarcoma Oncogene

KRAS-MT: KRAS Mutant

KRAS-WT: KRAS Wild-Type

LY: Life Year

MCRC: Metastatic Colorectal Cancer

NACRS: National Ambulatory Care Reporting System

NDFP: New Drug Funding Program

ORR: Overall Response Rate

ODB: Ontario Drug Benefit Program

OHIP: Ontario Health Insurance Plan

OS: Overall Survival

PFS: Progression Free Survival

QALY: Quality-Adjusted Life Year

RCT: Randomized Clinical Trial

TTP: Time-to-Progression

VGEF: Vascular Endothelial Growth Factor

Chapter 1

1 Introduction

Colorectal cancer is the third most common cancer in males and second most common cancer in females, with over 1.2 million new cases and 608,700 deaths estimated to have occurred worldwide in 2008 [1]. In Canada, colorectal cancer is the second most common cause of cancer deaths, with an estimated 22,000 new cases were diagnosed in 2011, of which 8,900 of those cases being fatal [2]. Of patients are diagnosed with colorectal cancer, approximately 15-25% will present with metastatic disease, and a further 40-50% will develop metastases in the course of their disease [3]. The majority of the cases of death in colorectal cancer patients are due to the formation of secondary neoplasms outside of the colon or rectum [4]. In the past, most cases of metastatic colorectal cancer (MCRC) have been incurable and only palliative treatment options were available. However, in the past decade, treatments for patients with MCRC have been subject to a number of advancements in the treatment of MCRC such as the introduction of new chemotherapeutic agents like oxaliplatin, and the development of targeted monoclonal antibodies such as bevacizumab (Avastin®), cetuximab (Erbitux®), and panitumumab (Vectibix®).

In particular, two fluorouracil containing chemotherapy regimens, FOLFOX which is comprised of oxaliplatin plus 5-fluorouracil (5-FU) and leucovorin, and FOLFIRI which is comprised of irinotecan plus 5-FU and leucovorin, have been widely accepted as the primary first-line treatments for patients with MCRC. Both of these chemotherapy regimens have been found to be equally as efficacious in terms of patients' overall response rate, time to progression, and overall survival [5, 6]. The two chemotherapy regimens differ in their toxicity profiles; patients taking FOLFOX experience neurotoxicity, while patients taking FOLFIRI experience gastrointestinal side effects [5, 6]. Unfortunately, the use of these chemotherapy regimens alone generally leads to an overall survival of less than 20 months [7, 8]. Thus, more effective treatments for patients with metastatic disease have been sought after.

Bevacizumab (Avastin®) is a humanized monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A) a key mediator in the angiogenesis of cancer cells[9] and was the first monocolonal antibody to be approved for use in the treatment of colorectal cancer by Health Canada [10]. Randomized clinical trials (RCT) investigating combination therapy with either FOLFIRI or FOLFOX plus bevacizumab demonstrated an increase in patients' overall response rate (ORR), overall survival (OS), and progression-free survival (PFS) when compared to those chemotherapy regimens alone in both first-line [7, 11] and second-line [12] settings. The combination of bevacizumab with FOLFIRI or FOLFOX was also shown to be both safe and efficacious when used in routine clinical practice settings in two large observational studies both showing an increase in overall survival of these patients of greater than 20 months [13, 14]. The results of these studies led to approval of the use of bevacizumab along with either FOLFIRI or FOLFOX chemotherapy regimens for use in first-line treatment for patients with MCRC by Health Canada in 2005 [10, 15].

After the introduction of bevacizumab, two other monoclonal antibodies, cetuximab and panitumumab, were introduced as potential treatment options for patients with metastatic colorectal cancer (MCRC). Both cetuximab (Erbitux®) and panitumumab (Vectibix®) are immunoglobulin G monoclonal antibodies that target the epidermal growth factor receptor (EGFR). The EGFR is a clinically validated anticancer molecular target which is highly expressed in the majority of colorectal cancers [16, 17]. Cetuximab is a chimeric (partially mouse and partially human) immunoglobulin which binds to EGFR with high affinity, competitively inhibiting EGFR downstream signaling, leading to cell cytotoxicity [18, 19]. Panitumumab is a fully human immunoglobulin G2 antibody that also binds the EGFR receptor with high affinity but whose binding prevents cancer cells TK autophosphorylation process, cell growth and metastasis [20].

Although EGFR receptors are highly expressed in colorectal cancer cells, it is the KRAS gene that plays an important role in determining whether anti-EGFR monoclonal antibody treatment is suitable for these patients [21-24]. Mutated KRAS genes are found in approximately 30-40% of patients with MCRC and KRAS mutation status acts as a predictive biomarker of resistance to treatment with both cetuximab and panitumumab [22,

[24-27]. KRAS is a signaling protein that works to activate a number of downstream protein targets which play an important role in cellular proliferation. The KRAS gene thus plays an important role in preventing further metastases while leading to cell death in those metastatic sites already present [24]. Genetic testing of the KRAS gene for patients with metastatic colorectal cancers is needed before patients can begin treatment with either cetuximab or panitumumab as both therapies are only indicated for patients having wild type KRAS [28, 29]. Clinical trials examining for cetuximab and panitumumab as monotherapies as well as their use in combination with fluorouracil containing chemotherapy regimens have shown that patients with mutated KRAS have worse outcomes than those patients with wild-type KRAS [13, 30-33]. Based on this observation, Health Canada has indicated cetuximab monotherapy for use in second or third-line treatment, or in combination with irinotecan as a third-line treatment, and panitumumab monotherapy as a third-line treatment for MCRC patients determined to have wild-type KRAS [28].

Given the positive results of the addition of bevacizumab to fluorouracil containing chemotherapy regimens as a first-line treatment for patients, different researchers have investigated whether the addition of cetuximab or panitumumab to these regimens in first-line settings in patients with wild type KRAS would be promising. Indeed, these aforementioned studies, the researchers have found statistically significant increases in progression free survival (PFS) as well as non-significant a trend toward improved in overall response rate (ORR) and overall survival (OS) in combination therapy when compared to the chemotherapy regimens alone for patients with wild type KRAS [13, 16, 20, 23, 30, 34-41].

This project aims to evaluate the cost-effectiveness of the use of combination cetuximab or panitumumab plus FOLFIRI chemotherapy compared to the current clinical practice of the use of combination bevacizumab plus FOLFIRI as first-line treatment for KRAS wild-type MCRC patients from the perspective of the Ontario healthcare payer. In this analysis, clinical outcome data were obtained from both patient level data in the province of Ontario as well as from phase III and IV RCTs which have investigated the addition of cetuximab, panitumumab, and bevacizumab to either FOLFOX or FOLFIRI

chemotherapy. The cost-effectiveness of each treatment regimen will be determined through the development of a decision analytic model consisting of Markov models capturing the full disease course for patients receiving either of the possible first-line treatment strategies. This information will assist decision makers to decide whether cetuximab or panitumumab should be adopted as first-line treatment options for this specific patient population.

Chapter 2

2 Literature Review

2.1 Metastatic Colorectal Cancer

Colorectal cancer develops as a consequence of the progressive accumulation of genetic and epigenetic changes within colonic epithelial cells which drive them to evolve to colon adenocarcinoma cells [42]. The multi-stage process in which these changes occur is believed to occur over a 10-15 year period in which the colonic epithelial cells pick up biological characteristics, often involving the activation of proto-oncogenes and the deactivation of tumor suppressor genes which, in turn, lead to the malignant phenotype [42]. The acquisition of these biological characteristics occurs through increased cellular genomic instability. Genomic instability occurs through a loss of the cell's DNA fidelity due to errors in DNA sequencing and repair mechanisms which allow the genetic and epigenetic changes to accumulate over time [42-44]. The mutations which drive the transformation from colonic epithelial cells to adenocarcioma cells provide a growth advantage which allows for adenocarcinoma cells' clonal expansion, eventually leading to the development of adenocarcinomic colonic polyps [4, 42].

Metastatic disease occurs when an adenocarcinoma cell(s) break off from the primary colonic tumors, travel to a secondary site, and proliferate into a secondary tumor. In order for a cancer to metastasize to a secondary site a number of sequential steps must successfully occur. To become a metastases cell(s) must first detach from the primary tumor and intravasate into the tumors blood or lymphatic vessels where it will travel through the individuals circulation system to reach secondary tumor sites [4]. If the cancer cell is not destroyed in the circulatory system and is able to reach a secondary site it must then initiate the process of forming a secondary tumor. The secondary site which the circulating cell has travelled to must have a microenvironment which is permissive for the incoming tumor cell to extravasate into, grow, and form metastases [4]. Due to different microenvironments being present in different organs, specific cancer cell types have organ preferences for which they tend to form metastases. In the case of colorectal

cancer, secondary tumors most often tend to develop in the liver and the lungs [4]. Once cells enter these sites their growth is regulated by cell-cell interactions with the cells present in their new environment [4]. Many cells will die via apoptosis in their new environments; however those cells which can develop anti-apoptotic mechanisms and initiate vascularization will gain the capability to colonize [4]. The metastatic process is not an easy one, as there are multiple obstacles a cell must pass in order for it to reach these secondary sites. Solitary cancer cells are very prone to death when in the circulation either through immune system mediated apoptosis or destruction via mechanical stresses [4, 42]. It has been seen in animal studies that only 0.01% of circulating cancer cells eventually become secondary metastases [4].

2.1.1 FOLFOX and FOLFIRI Chemotherapy Regimens

Chemotherapy has been the primary approach for the treatment of metastatic colorectal cancer for over 40 years, with the fluoropyrimidine 5-fluororuracil (5-FU) being the constant of the initial chemotherapy regimens designed to target MCRC [45]. The use of 5-FU as a monotherapy was initially proven to be mildly effective, with overall response rates of 10-15% and median overall survival (OS) of only 6-8 months[45]. The lack of efficacy of 5-FU monotherapy fuelled the search for more effective strategies for the treatment of MCRC. Over the last 20 years, significant advances have been made leading to an increase in median OS to 18-24+ months in recent years [6, 15, 20, 46-49]. These advancements are due to the development of chemotherapy drugs irinotecan, a topoisomerase I inhibitor, and oxaliplatin a third-generation platinum analog, as well as the development of the targeted monoclonal antibodies bevacizumab, cetuximab and panitumumab.

Conventional first-line treatment for patients with newly diagnosed, previously untreated MCRC is composed of a combination of chemotherapy drugs and certain targeted agents that either enhance the effectiveness of chemotherapy regimens, or have anti-cancer properties [45, 50]. Two chemotherapy regimens, FOLFIRI and FOLFOX have become the standard chemotherapy treatments for patients with MCRC [51]. Both regimens are

comprised of 5-FU and leucovorin. Leucovorin is a bio-modulating agent which enhances 5-FU's activity [45]. FOLFOX involves the addition of oxaliplatin to 5-FU and leucovorin. Oxaliplatin is a platinum based compound that acts as a cytotoxic agent by forming both intrastrand and interstrand DNA crosslinks in cellular DNA [45]. The typical FOLFIRI regimen involves the addition of irinotecan, a topoisomerase I inhibitor which forms a stable complex with cellular DNA and topoisomerase I, an enzyme involved in the unwinding of DNA in the DNA replication process [45]. Both of these treatment options lead to the prevention of cellular DNA replication and eventually resulting in the death of cancer cells [45].

Both FOLFOX and FOLFIRI regimens are administered intravenously on a 14 day cycle. Although multiple variations of the FOLFOX and FOLFIRI regimens are cited in the literature, the most commonly used versions in Ontario are as follows:

Modified FOLFOX6: oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2, followed by bolus FU 400 mg/m^2, followed by 46-hour infusion of FU 2400 mg/m^2.

FOLFIRI: irinotecan 180 mg/m^2 + leucovorin 400 mg/m^2, followed by bolus FU 400 mg/m^2, followed by 46-hour infusion of FU 2400 mg/m^2 [50].

Tournigand et al, conducted a randomized, multicentre, open-label, phase III clinical trial which compared a direct comparison of the FOLFIRI and FOLFOX chemotherapy regimens in both first and second-line settings for patients with metastatic colorectal cancer [5]. The investigators randomized patients to either FOLFOX6 or FOLFIRI as initial treatment, and then switched patients to the other regimen upon disease progression. FOLFOX and FOLFIRI were found be equally as efficacious, having almost identical overall response rates (ORR) (56% and 54%), median OS (20.4 months vs 21.5 months), and 2 year survival (45% and 41%) with FOLFIRI having a longer, but statistically insignificant, median time to progression (TTP) in the first-line setting [5]. Both regimens were equally well tolerated by patients; however, the type of adverse events patients experienced were different as with patients taking FOLFOX6 experienced neurotoxicity while patients given FOLFIRI experiencing gastrointestinal side effects [5]. Equivalency of

the two regimens in terms of TTP, duration of response, and OS were also seen in comparison of FOLFOX4 and FOLFIRI by Colucci et al [6].

One difference between the FOLFOX and FOLFIRI chemotherapy regimens is that FOLFOX has been shown to result in higher rates of surgical resection of liver metastases than FOLFIRI. In the Tournigand study, 21 of the 111 patients who received FOLFOX6 were able to undergo R0 surgical liver resections, with 62% of them having complete resections of their liver metastases. This was significant as only 8 of the 109 patients who received FOLFIRI underwent R0 surgical resection, with only 6% having complete resection [5]. This difference in resection rate has led to FOLFOX being more commonly administered as the first-line chemotherapy than FOLFIRI in the United States [51]. Hess et al found in a review of 304,654 metastatic colorectal patients from 19 states in the United States between 2004 to 2008 that FOLFIRI was administered as a first line treatment to 3.1% of patients while FOLFOX was administered to 40.5%, 14.3% receiving FOLFOX alone and 26.2% receiving combination therapy consisting of FOLFOX and bevacizumab [51]. By contrast, FOLFIRI is more commonly used than FOLFOX in the standard clinical practice in Ontario, mainly due to funding issues, as oxaliplatin is more expensive than irinotecan, making the FOLFOX regimen much more expensive than FOLFIRI [52, 53].

2.1.2 Anti-Epidermal Growth Factor Receptor (EGFR) and Anti-Vascular Growth Endothelial Factor (VEGF) Therapies

2.1.2.1 The EGFR and VEGF

The Epidermal Growth Factor Receptor (EGFR) which also goes by the name the HER-1 or c-erbB1 receptor is a trans-membrane glycoprotein that is a member of the erbB1 family of tyrosine kinase receptors [54]. The EGFR is a 170kDa glycoprotein that consists of an extracellular receptor domain, a trans-membrane region, and an intracellular domain that has tyrosine kinase activity [54]. The EGFR is a clinically validated anticancer molecular target which is highly expressed in the majority of colorectal cancers [17]. The function of the EGFR is to determine the behavior of epithelial cells, and its activation plays an important role in the behavior or tumors of epithelial cell origin such as MCRC

[54, 55]. The EGFR binds a number of substrate ligands such as epidermal growth factors (EGF), heparin-binding EGF, transforming growth factor α, amphiregulin, and betacelulin [55]. The binding of these ligands to the EGFR leads to autophorylation of the receptor, which initiates a number of signal transduction pathways involved in cellular proliferation, differentiation, angiogenesis, the inhibition of apoptosis, cellular motility, cellular adhesion, and metastasis, thus making the EGFR and important mediator in the transformation of normal cells to malignant ones [25, 54, 56-59].

EGFR over-expression has been characterized in breast, head-and-neck, non-small cell lung, renal, ovarian and colon cancers [54]. EGFR over-expression intensifies signaling through its downstream pathways and results in cells that have more aggressive growth and invasiveness characteristics [57]. EGFR expression has been associated with poorer patient prognosis and decreased survival as well as resistance to both chemotherapy and radiotherapy treatments [54]. Due to the role EGFR expression plays in the development and maintenance of cancer cells, it has become an important molecular target for cancer therapies. Anti-EGFR monoclonal antibodies such as cetuximab and panitumumab function by targeting the extracellular domains of the EGFR in cells over-expressing the receptor while not affecting normal cells [37]. Binding of these agents to the EGFR prevents receptor autophosphorylation and therefore prevents the activation of the downstream signal pathways [54].

Activation of the EGFR has been found to stimulate Vascular Endothelial Growth Factor (VEGF), another molecular target for which monoclonal antibody therapy has been developed for the treatment of patients with MCRC. VEGF is a family comprised of seven members VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-F, and P1GF, which are soluble diffusible glycoproteins all of which have a common VEGF homology domain [60]. Bevacizumab which is used in the treatment of patients with MCRC, specifically targets VEGF-A, a 32-43kDa protein which is released by cancer cells, hypoxic cells, as well as activated platelets and leukocytes, which play an important role in the angiogenic and neovascularisation processes [60, 61]. VEGF-A isoform binds to two VEGF tyrosine kinase receptors, the VEGFR1 and VEGFR2, both of which are downstream receptor proteins who share a similar structure [60, 62]. Binding of VGEF-A to either of these receptors results

in the activation of downstream signaling pathways which lead to endothelial cell proliferation and migration [60, 63]. This proliferation and migration results in the formation of new tubular structures which mediate the development of new blood vessels from pre-existing ones, providing cancer cells with oxygen and nutrients which promote tumor growth [60, 63]. Due to the strong relationship between VEGF and angiogensis, VEGF serum levels have often been used as a surrogate biomarker for angiogenic activity in cancer patients [61].

2.1.2.2 Bevacizumab and its Use with FOLFOX/FOLFIRI in First-Line Treatment

The development of bevacizumab (Avastin®) introduced a new, more targeted approach to treating MCRC. Bevacizumab is a humanized monoclonal antibody that binds and inhibits the action of all isoforms of the VEGF-A, a key mediator in the angiogenic process [7]. Angiogenesis plays a vital role in driving tumor progression through the formation of new and aberrant blood vessels [48]. In addition to preventing angiogenesis, bevacizumab prevents tumor growth through the normalization of tumor vasculature and the reduction of circulating endothelial and progenitor cancer cells [47, 48]. Bevacizumab has also found to be associated with improved delivery of chemotherapy to cancerous cells by reducing interstitial pressure within tumors, and its use was approved for use along with fluouropyrimidine-based chemotherapy for patients with MCRC by Health Canada in 2005 [10, 15].

The use of bevacizumab along with 5-FU-based chemotherapies a first line treatment for patients with MCRC has been investigated in a number of RCTs where the addition of bevacizumab has demonstrated increases in OS and PFS, as well as an increased risk of grade three of four adverse events when compared to treatment with chemotherapy alone [47]. Approval of the use of bevacizumab along with chemotherapy by the Federal Drug Administration (FDA) was mainly due to the favorable results of combination treatment (bevacizumab plus IFL) compared to IFL alone seen in a phase III AVF2107 RCT [64]. In this study combination treatment led to a 4.4 month increase in the PFS and a 4.7 month

increase in OS of patients with MCRC compared to patients who received IFL alone [64]. A subsequent phase IV clinical trial corroborated similar results and helped to establish the use of bevacizumab along with FOLFIRI as an effective treatment strategy in clinical practice [9].

The addition of bevacizumab to the FOLFOX has also been investigated in a number of clinical trials. One phase III study found that the addition of bevacizumab to FOLFOX resulted in a significant increase of 1.4 months in patient PFS and as well as a statistically insignificant an increase of 2.4 months in patients' OS [7]. Another retrospective study indicated that the addition of bevacizumab with first-line FOLFOX lead to favorable TTP and OS [46].

The BEAT study examined the safety and efficacy of the use of bevacizumab with both FOLFOX and FOLFIRI in MCRC patients who were followed for 43 months in routine clinical practice [65]. This study found almost identical TTP (11.9 months vs. 12 months), median PFS (11.6 months vs. 11.3 months), and a slight increase in the OS of patients who received combination treatment with FOLFOX compared to those who received combination treatment with FOLFIRI (25.9 months vs. 23.7 months) [65]. Similar to the Tournigand study, one key difference found by the researchers in the BEAT study was in the rate of R0 curative hepatic metastasectomy. Among patients who received each treatment, 10.4% patients who received bevacizumab and FOLFOX undergoing the procedure compared to only 6.4% of patients who received bevacizumab plus FOLFIRI [65].

2.1.2.3 Anti-EGFR Monoclonal Antibodies

Even with the advances made in the treatment of patients with MCRC, and the improvements seen in patients' prognoses when receiving combination therapy with bevacizumab and FOLFOX/FOLFIRI, treatment for the majority of patients is not curative. Disease progression is common among patients with MCRC and of all patients who receive first-line treatment with approximately 63-70% of patients going on to have

subsequent second and third-line treatments [40, 51]. After the introduction of bevacizumab, other molecular targets were sought after to develop similar therapies that would have the potential to further improvements in patient outcomes.

Both cetuximab and panitumumab are monoclonal antibodies directed towards the EGFR. The EGFR is a clinically validated anticancer molecular target which is highly expressed in the majority of colorectal cancers [16, 17] . EGFR activation plays an important role in the activation of a number of signaling pathways including the RAS/RAF/MAPK, and the PI3K/AKT pathways [21, 37, 49, 66] . Activation of these pathways are key to a number of processes which, when unregulated, are key to cancer cell growth and migration, such as cell proliferation, angiogenesis, inhibition of apoptosis, and metastases [21, 37, 66]. The EGFR is also known to play a role in resistance to both chemotherapy and radiotherapy in cancer patients, as well as an overall decrease in patients OS [58, 66]. Although cetuximab and panitumumab target the EGFR, EGFR status as determined by immunohistochemistry (IHC) has been shown to be an unreliable predictor of patient response to EGFR-targeted therapy, as responses to both cetuximab and panitumumab have been achieved in patients who did not express EGFR by IHC [25, 31, 35, 49].

2.1.2.4 The Kristen Rat Sarcoma Oncogene and its Importance in Anti-EGFR Therapy

The Kristen Rat Sarcoma Oncogene (KRAS) homolog has been found to play an important role in patients' response to anti-EGFR monoclonal antibodies [21, 24, 31, 32, 38, 39, 49, 67-71]. The KRAS gene encodes small guanosine tri-phosphate-binding protein which acts downstream of EGFR activation and plays an important role in the activation of RAF, ERK, and PI3K signaling, serving as an important mediator in the regulation of cellular proliferation [21, 37]. Multiple studies have found that the presence of a KRAS mutation negatively affects the potential efficacy of anti-EGFR therapies, when used as a monotherapy, or in combination with standard chemotherapy regimens [13, 23, 24, 33, 38]. Mutations in codons 12, 13, and 61 of exon 2 of the KRAS gene have been found to be associated with resistance to both cetuximab and panitumumab [21, 37]. These mutations are

present in 30-50% of patients with MCRC and lead to the constituent activation of the KRAS oncogene, resulting constant signaling through cell proliferation pathways even when the EGFR is blocked by agents such as cetuximab or panitumumab [21, 37]. Retrospective analysis of the phase II and III randomized clinical trials which examined the addition of cetuximab and pantiumumab to either FOLFOX or FOLFIRI as first-line treatments for patients with MCRC have confirmed that the benefit of the addition of the anti-EGFR monoclonal antibodies is restricted only to KRAS wild-type (KRAS-WT) patients [13, 22, 33, 37, 38].

A recent meta-analysis examined the real-effects of the use of cetuximab and panitumumab in first or second line treatment of KRAS WT patients using data from seven randomized clinical trials which contained KRAS subgroup analyses [37]. This study confirmed that cetuximab and panitumumab increased response rate and significantly reduced the risk of progression and death in KRAS WT patients [37]. In Ontario, the use of either cetuximab or panitumumab for patients with MCRC is restricted to only patients who are determined to by KRAS-WT[28, 29].

2.1.3 Cetuximab and its Use with FOLFOX/FOLFIRI in First-Line Treatment

Cetuximab (Erbitux®) is a chimeric (mouse/human) immunoglobulin G monoclonal antibody directed against the EGFR and is currently indicated for use for patients with MCRC as a monotherapy in second and third-line settings, and in combination with irinotecan as a third-line treatment in KRAS wild type patients in Ontario [29, 58].

2.1.3.1 Cetuximab and FOLFOX

Two critical RCTs have investigated the addition of cetuximab to FOLFOX in patients with MCRC. The “Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer (OPUS)” study was a phase II trial that compared the efficacy and safety of the addition of cetuximab to FOLFOX4 compared to FOLFOX4 alone in 344

patients with MCRC [33]. Within all patients enrolled in the trial the ORR was higher for patients who received combination therapy (46% vs 36%) leading to a 52% increase in the chance of having a response to treatment in patients receiving cetuximab plus FOLFOX4 compared to FOLFOX alone [33]. Amongst all patients enrolled there was also a doubling in the R0 resection rate for patients receiving combination therapy [33]. No significant difference was found in the median OS, with patients receiving combination therapy having a median OS of 18.3 compared to 18 months for those patients who received FOLFOX4 alone [32].

KRAS mutations were found to be present in 43% of the patients enrolled in this study, and when the results of the trail were stratified based upon KRAS mutational status the differential effects of combination treatment were made clear [32]. A clear trend between the treatment a patient received and their KRAS mutational status were displayed in patients ORR and PFS [32]. In KRAS-WT patients, the addition of cetuximab to FOLFOX4 led to increased ORR (57% vs 34%), with a 2.55 fold increase in the chance of having a response to treatment, a more than two-fold increase in the R0 resection rate, and a 43% reduction in the risk of disease progression when compared to those who FOLFOX4 alone [32]. PFS for patients receiving combination therapy was 8.3 months compared to 7.2 months for patients receiving FOLFOX4 alone [32]. A trend toward increased OS was also seen in patients who received combination therapy, however this increase was deemed to be statistically insignificant (22.8 months vs. 18.5 months) [32].

Contrary to the results for KRAS-WT patients, for those patients who carried mutations in their KRAS gene (KRAS-MT) the addition of cetuximab to FOLFOX4 resulted in a lower ORR (34% v 53%), no difference in the rates of R0 resection, and an increase in the risk of disease progression with a median PFS of 5.5 months for patients receiving combination therapy and 8.6 months for FOLFOX4 alone [32]. Overall survival was also greater KRAS-MT patients who received FOLFOX4 alone however the difference between the two treatments was not statistically significant (13.4 months vs. 17.5 months) [32].

A smaller phase II trial which aimed to evaluate the activity and safety of the addition of cetuximab to FOLFOX4 also reported high ORR to combination treatment (64%), a median TTP of 10 months, median OS of 22 months, and an observed disease control rate of 94% when compared to FOLFOX alone [6]. Increased ORR and PFS were also seen in KRAS-WT patients receiving cetuximab with FOLFOX6 [36].

The COIN clinical trial was the largest trial examining the addition of cetuximab to chemotherapy in the first-line treatment of patients with MCRC [35]. This clinical trial did not examine the effects of the addition of cetuximab to FOLFOX alone, however compared the addition of cetuximab to a number of different oxaliplatin containing chemotherapy regimens [35]. The investigators compared patients who had either received cetuximab along with oxaliplatin and capecitabine, or oxaliplatin with infused fluouroracil plus leucovorin (FOLFOX), to patients who received the either chemotherapy regimen alone [35]. KRAS mutations were present in 43% of patients enrolled in this trial, and the within this group of individuals the investigators saw no added benefit of the addition of cetuximab to chemotherapy compared to oxaliplatin based regimens alone [35]. Amongst this patient group there was no evidence of a median OS benefit (17.9 months without cetuximab vs 17.0 months with cetuximab), or decreased risk of disease progression (PFS 8.6 of months for both groups) [35]. The addition of cetuximab to oxaliplatin based chemotherapy however did significantly increase the ORR for KRAS-WT, with 64% of patients who received cetuximab having either a partial or complete response compared to only 57% of patients who received chemotherapy alone [35].

Due to the fact that patients in this clinical trial could have received cetuximab along with FOLFOX or oxaliplatin plus capecitabine, the results of this clinical trial do not fully capture the potential of combination therapy consisting of FOLFOX and cetuximab for KRAS-WT patients. Any potential gain in the addition of cetuximab to chemotherapy could be masked by the inherent differences in the outcomes of patients who receive the two different chemotherapy regimens. The effects of cetuximab combined with FOLFOX on OS and PFS could very well differ from those of cetuximab combined with oxaliplatin and capetcitabine. This combination of the results for patients who received the two

different chemotherapy regimens with or without cetuximab may have led to the apparent lack of advantage of the addition of cetuximab to first-line treatment which had been found in other clinical trials.

2.1.3.2 Cetuximab and FOLFIRI

The addition of cetuximab to FOLFIRI was investigated in the Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) multicentre phase III randomized clinical trial and found that combination therapy lead to significant reductions in the risk of disease progression [13]. In the intention to treat population (ITT) the difference median PFS was statistically insignificant with PFS for patients receiving combination therapy being 8.9 months compared to 8.0 months for patients receiving FOLFIRI alone [13, 30]. However in the ITT population, significant increases were found in both the ORR and OS of patients who received combination therapy, with an ORR of 46.9% and OS of 19.9 months for patients receiving combination therapy compared to ORR of 38.7% and OS of 18.6 months for those receiving FOLFIRI alone [30]. The chance of having a tumor response was 40% higher for patients who received combination treatment than that of patients receiving FOLFIRI alone [30]. The chances of having either R0 hepatatic metastctecomy surgery or complete R0 resection were nearly doubled in patients who received combination treatment [30].

KRAS mutations were present in 37% of the patients enrolled in the CRYSTAL study, and once again combination therapy was seen to be more effective in KRAS-WT patients. KRAS-WT patients who received combination therapy had a significantly reduction in the risk of disease progression (PFS 9.9 months vs. 8.4 months), significant increase in ORR (57.3% vs. 39.7%), and significantly improved OS (23.5 months vs. 20.0 months), as well as increase in the R0 resection rate compared to those patients who received FOLFIRI alone [30].

In patients who were KRAS-MT the addition of cetuximab to FOLFIRI resulted in no clinical benefit with OS, PFS, as well as resulted in the ORR being higher for patients who received FOLFIRI alone than those who received combination treatment [30].

2.1.4 Panitumumab and its Use with FOLFOX/FOLFIRI in First-Line Treatment

Panitumumab (Vectibix®) is a fully human immunoglobulin G2 monoclonal antibody which also targets the EGFR and whose binding inhibits TK auto-phosphorylation, tumor cell growth, and metastasis [20, 58]. Panitumumab differs from cetuximab in that it binds to the EGFR with higher affinity than cetuximab, resulting in fewer infusional related allergic reactions than cetuximab due to fully human characteristics [20, 58]. Panitumumab has shown to be effective as a monotherapy for chemo-refractory MCRC patients is currently indicated by Cancer Care Ontario for use as a third-line therapy for KRAS wild-type metastatic colorectal cancer patients [28]. As panitimumab is a fairly recent addition to the potential treatment options for patients with MCRC, its use in combination treatment with FOLFOX and FOLFIRI has not been as extensively investigated.

2.1.4.1 Panitumumab and FOLFOX

The "Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME)" study was an open-label, multi-centre, phase III RCT comparing the addition of panitumumab to FOLFOX4 versus FOLFOX4 alone [38]. KRAS mutations were detected in 40% of the 1183 patients enrolled in this trial and once again the effect of the addition of the anti-EGFR antibody to chemotherapy differed in wild-type and mutated patient populations [38]. In KRAS wild-type patients, combination therapy was seen to lead to a slight increase in ORR (55% vs. 48%) and R0 resection rate [38]. A favorable increase of 4.2 months was seen in the OS (23.9 months vs. 19.7 months) of patients receiving panitumumab with FOLFOX4 although this increase was not statistically significant [38]. A statistically significant improvement was seen in the patient PFS, with patients who received combination therapy having PFS of 9.6 months compared to 8.0 months for those who received FOLFOX4 alone [38].

The addition of panitumumab to FOLFOX4 demonstrated detrimental effects for those patients who were KRAS-MT present [38]. The addition of panitumumab to FOLFOX to

these patients resulted in a statistically significant decrease in patient PFS, as those patients' who received combination therapy had a median PFS of 7.3 months compared to 8.8 months for those patients' who received FOLFOX4 alone [38]. OS was also inferior for patients receiving combination therapy (15.5 months vs. 19.3 months), while ORR did not differ for the two treatment strategies for this patient group [38].

2.1.4.2 Panitumumab and FOLFIRI

The largest clinical trial examining the efficacy of panitumumab and FOLFIRI in a first-line setting was a single-arm, phase II multicentre trial which enrolled 154 patients with metastatic colorectal cancer [39]. In this trial 59% of the patients were found to be KRAS-WT and these patients were found to have higher rates of overall response (56% vs. 38%) resulting in an odds ratio of 2.1 when comparing KRAS-WT to KRAS-MT patients [39]. KRAS-WT patients also had increased TTP (11.2 months vs. 7.3 months), as well as PFS (8.9 months vs. 7.2 months) with a hazard ratio of 0.5 representing a lower event rate and longer time to progression or death for KRAS-WT patients compared to KRAS-MT patients [39]. There were two important findings in this study. Firstly, the overall response rate of 38% seen in KRAS-MT patients was very similar to the response rates found in two other studies for patients who received FOLFIRI alone, indicating that the addition of panitumumab to FOLFIRI may provide no benefit to KRAS-MT patients at all [39]. Secondly, was the fact that while the addition of panitumumab to FOLFIRI was shown to not benefit KRAS-MT patients, it also was shown not to negatively affect these patients, unlike what was seen with the combination of panitumumab and FOLFOX in the PRIME study [39].

Another smaller clinical trial also examined the addition of panitumumab to FOLFIRI in first-line treatment of patients with MCRC. This multicentre, open-label, phase II clinical trial was also only had one single-arm, only looking at patients who had received panitumumab plus FOLFIRI [20]. Twenty-four patients were enrolled in this trial and results were not stratified based upon KRAS status [20]. Of all of the patients enrolled 33% had an overall response, all of them being partial responses [20]. Stable disease occurred in 46% of patients receiving treatment, with median PFS being 10.9 months, and median OS

of 22.5 months [20]. Combination therapy was also found to be well tolerated by patients, with the most common adverse event being skin related toxicity [20].

The addition of panitumumab to FOLFIRI was also examined in an open-label, multicentre, randomized phase III clinical trial as a second-line treatment for patients who had initial treatment failure. KRAS mutations were found in 45% of the patients enrolled [40]. Similar to the study examining panitumumab to FOLFOX, significant increases were seen the differences in PFS between those patients who received combination therapy and those who received FOLFIRI alone, with an insignificant positive trend toward increased OS for KRAS-WT patients who received combination therapy, with the opposite being the case for KRAS-MT patients [40].

2.2 The Cost-Effectiveness of FOLFIRI/FOLFOX, Bevacizumab, Cetuximab, and Panitumumab in Colorectal Cancer Treatment

The cost effectiveness of the FOLFOX and FOLFIRI chemotherapy regimens as well as for bevacizumab, cetuximab, and panitumumab monoclonal antibodies in their use for colorectal cancer have been previously investigated in a number of studies in various treatment settings.

The cost-effectiveness of FOLFOX and FOLFIRI chemotherapy regimens for patients with unresectable metastatic colorectal cancer was investigated by Tumeh et al. using a Markov decision model to compare patients receiving either FOLFOX or FOLFIRI as first-line treatment. This study was based upon the phase III clinical trial by Collucci et al. in which patients were administered either FOLFOX or FOLFIRI as their first line treatment for eight, two week cycles [6]. The costs for hospital and physician services were estimated using Centres for Medicare and Medicaid services reimbursement data from the United States and utilities were derived from literature [72]. A Markov decision model was developed to compare patients receiving either FOLFOX or FOLFIRI as first-line treatment for patients with MCRC. The investigators then conducted univariate

sensitivity analyses on the number of cycles a patient received as well as on each probability of patients experiencing adverse events, utility, and costs [72].

In the base case analysis FOLFOX was found to provide 1.003 QALYs at a cost of $29,865 while FOLFIRI provided 0.921 QALYs at a cost of $24,551, resulting in an ICER of $65,170/QALY [72]. In their sensitivity analysis the investigators found the cost-effectiveness for FOLFOX compared to FOLFIRI varied from $34,772/QALY when patients only received 4 cycles, to $91,968/QALY when patients received 12 cycles. The investigators also found that the expected survival associated with the chemotherapy regimens, the probability of death following treatment, and the cost of the chemotherapy regimens themselves most greatly influenced the resultant ICER [72]. FOLFOX was found to be more cost effective when it was associated with an expected survival of 1.28 years or greater or when FOLFIRI was associated with less than 1.14 years[72]. FOLFOX also became more cost-effective than FOLFIRI when its cost was below $28,750 and the cost of FOLFIRI was less more than $26,040 [72]. An additional probabilistic Monte Carlo sensitivity analysis on 10,000 patients found that with a willingness-to-pay threshold of $50,000/QALY, FOLFOX was more effective and more costly 52.72% of the time and more costly and less effective 47.28% of the time, a result indicating that both regimens are very similar in terms of effectiveness and cost-effectiveness [72].

The cost-effectiveness of cetuximab monotherapy for patients with MCRC was investigated by Mittman et al. In this study the investigators used data from the National Cancer Institute of Canada's CO.17 study, an open-label, randomized phase III clinical trial where resource utilization and health utility data were collected prospectively alongside efficacy data for patients receiving either cetuximab monotherapy plus best supportive care, or best supportive care (BSC) alone[73]. This analysis was conducted in the perspective of the Canadian healthcare payer over the time horizon of 18-19 months which correlated to the duration of the CO.17 trial [73]. The cost of cetuximab was determined from the Patented Medicine Prices Review Board of Canada, outpatient as well as laboratory and diagnostic costs were determined using the Ontario Health Insurance Plan (OHIP) fee schedule, hospital costs were determined using data from the Sunnybrook Health Sciences Centre, and adverse event costs were determined using the

Ontario Case Costing Initiative and multiplied by the number of each event for each patient [73]. Sensitivity analyses were carried out on the cost of cetuximab to reflect changes in price in different countries, as well as around patient survival [73].

For the ITT population, patients who received cetuximab in addition to best supportive care were found to have a mean average cost of $28,202 per patient with an average of 0.64LYs and 0.40QALYs compared to an average mean cost of $4,233 with an average of 0.52LYs and 0.32QALYs resulting in ICERs of $199,742/LY ($125,973/LYs to $652,492/LY) and $299,613/QALY ($187,440/QALY to $898,201/QALY) [73]. The investigators then focused solely on those patients who were determined to be KRAS-WT. In this group patients receiving combination therapy had an average mean cost of $37,324 with average gains of 0.79LYs and 0.51 QALYs, while those who received BSC had an average cost of $3,707 with average gains of 0.51LYs and 0.33QALYs resulting in ICERs of $120,061/LY ($88,679/LY to $207,075/LY) and $186,761/QALY (130,326/QALY to $334,940/QALY) [73]. Cost-effectiveness acceptability curves showed a 0% probability of the cost-effectiveness of cetuximab falling below the standard threshold of $50,000/LY and $50,000/QALY, therefore concluding that cetuximab may not represent a cost-effective option over best supportive care alone [73].

The cost effectiveness of combination therapy consisting of cetuximab and irinotecan along with BSC compared to best supportive care was investigated by Starling et al. This analysis which was undertaken in the perspective of the National Health Service (NHS) in the United Kingdom used combined data from two clinical trials, one trial investigated the use of cetuximab plus BSC, and the other examined the addition irinotecan plus BSC in patients with MCRC [74]. Patient costs and consequences were determined over a lifetime time horizon and direct patient costs were determined from the NHS [74]. For patients receiving combination of cetuximab and irinotecan the average cost was determined to be £22,270 with a discounted life expectancy of 0.91LYs while patients receiving BSC had an average total cost of £3,368 and 0.472 discounted LYs [74].

Tappenden et al investigated the cost-effectiveness of the addition of bevacizumab to either irinotecan plus 5-FU and leucovorin (IFL) or 5-FU and leucovorin (5-FU/LV)

alone in first-line treatment of patients with MCRC in England and Wales. The investigators developed a decision-analytic model with three states where patients could either be alive and progression free, alive with progressive disease, or dead, with patient quality of life varying between the different states [75]. In this model all patients entered into the alive and progression free state where they would receive bevacizumab plus either IFL or 5-FU/LV alone [75]. The model was based on effectiveness data from two clinical trials; the AVF2107G phase III clinical trial which investigated bevacizumab + IFL versus IFL alone, and the phase II AVF2192G randomized clinical trial which compared bevacizumab plus 5-FU/LV versus 5-FU/LV alone [75]. Bevacizumab-specific quality-of-life data could not be found so researchers assumed a utility value of 0.8 for patients who did not have disease progression, 0.60 for patients who had progressive disease, and 0 for patients who were dead [75]. Drug unit costs used in the analysis were taken from the British National Formulary and other hospital, pharmacy, diagnostic, physician, and palliative care costs were found via literature review [75].

IFL treatment alone was found to have a mean cost of £23,779 with 1.57LYs and 1.13 QALYs gained while the addition of bevacizumab to IFL was found to have a mean total cost of £43,140 with a mean of 1.98 LYs and 1.44 QALYs gained, resulting in ICERs of £46,853/LY and £62,857/QALY [75]. 5-FU/LV treatment was found to have a cost of £21,459 with a mean gain of 1.41LYs and 1.01QALYs, while the addition of bevacizumab to 5-FU/LV resulted in a mean cost of £37,074 with average gains of 1.59LYs and 1.19QALYs resulting in ICERS of £84,396/LY and £88,436/QALY [75]. The investigators found that the key determinant of the cost-effectiveness of combination therapy with bevacizumab was acquisition cost of bevacizumab, however even with varying acquisition costs that combination therapy was unlikely to be below the standard threshold value of £60,000/QALY used by the NHS in the United Kingdom [75].

Asseburg et al. investigated the cost-effectiveness of combination therapy consisting of cetuximab and FOLFIRI to bevacizumab plus FOLFOX for KRAS -WT patients with initially unresectable metastases limited to the liver in a German setting. In this study the investigators carried out an indirect comparison using available clinical trial data and extrapolated them to a 10 year time horizon [76]. All patients in this model entered in the

metastatic colorectal carcinoma: monoclonal antibody state, from here patients could move to chemotherapy following progression or no chemotherapy after R0 resection states [76]. Patients who progressed to subsequent chemotherapy could then move to best supportive care and death while patients who had undergone successful R0 resection could then move to healed or death states. Efficacy data was collected from randomized controlled trials involving KRAS-WT patients with metastatic colorectal cancer who received cetuximab or bevacizumab with either chemotherapy regimen after which indirect meta analysis of survival outcome, discrete event simulations were carried out to combine data from the different sources [76]. This analysis was carried out in the perspective of the German statutory health insurance plan; costs for the active treatments were estimated from German Lauer-Taxe guidelines, ambulatory and physician service costs were calculated using the German Uniform Valuation Scheme; while inpatient costs for grade 3 and 4 adverse events were calculated using diagnosis related groups multiplied with the current German DRG value [76]. Sensitivity analyses were then carried out to account for uncertainty with estimates of OS, PFS, differing rates of R0 resection, and exploring how the cost-effectiveness of combination therapy with cetuximab compared to bevacizumab would differ if both FOLFOX and FOLFIRI were available at the same cost [76].

In the base cases analysis first line treatment with cetuximab was found to have an overall lifetime discounted cost of €99,134 with an expected total of 2.88 discounted LYs gained while treatment with bevacizumab was found to cost €91,563 with 2.38 discounted LYs gained, leading to an ICER of €15,020/LY [76]. Sensitivity analyses surrounding estimates of OS and PFS resulted in ICER values of between €3,806 - €24,660/LY. When the investigators conducted sensitivity analysis surrounding the proportion of patients successfully undergoing an R0 resection after treatment to 34% for patients receiving cetuximab and 15.4% for patients receiving bevacizumab the resultant ICER decreased to €9,170 [76]. When the investigators carried out the analysis with both FOLFOX and FOLFIRI having the same costs, treatment with cetuximab was found to have an ICER of €7,560/LY [76].

The cost-effectiveness of the use of cetuximab, panitumumab, and bevacizumab along with chemotherapy for KRAS-WT metastatic colorectal cancer patients has been investigated with the perspective of the UK NHS [77]. In this evaluation the investigators developed a semi-Markov model to simulate long-term patient outcomes for patients after receiving either combination as a first-line treatment. The model was parameterized using data from the CRYSTAL and PRIME clinical trials, with drug, physician cost, scans, hospitalizations and treatment of adverse event data compiled to determine patient resource utilization [77]. Sensitivity analyses were then carried out to determine the robustness of the results. In the base case the ICER for cetuximab and FOLFIRI versus FOLFIRI along was £30,665 QALY, £28,626/QALY when compared to bevacizumab plus FOLFOX, and £15,326 when compared to panitumumab to FOLFOX. From this analysis the investigators determined that the combination treatments fell within the commonly used willingness to pay threshold for cost-effectiveness in the UK and the main drivers of the ICER were the number of patients undergoing R0 resections as well as the acquisition costs of the monoclonal antibodies [77].

This study differs from the previously conducted cost-effectiveness analyses as it aims to determine the cost-effectiveness of the use of combination treatment consisting of either cetuximab or panitumumab with FOLFIRI within the Canadian health care system. In this study health care costs were found using patient-level data from administrative databases in the province of Ontario to capture the actual cost to the healthcare payer. In this study I use a semi-Markov model where the Markovian assumption is relaxed and the transition probabilities of progression from one state to another vary dependent upon a patients time in that state. This is able to capture the changes in the risk of progression over time. This study is also the first cost-effectiveness analysis to investigate the cost-effectiveness of the use of panitumumab plus FOLFIRI or FOLFOX when it is used as a first-line treatment.

2.3 Research Question

To determine whether treatment starting with first-line combination therapy consisting of either cetuximab or panitumumab plus FOLFIRI chemotherapy represent cost-effective treatment options compared to the current clinical practice of the use of combination bevacizumab plus FOLFIRI as first-line treatment for patients with Metastatic Colorectal Cancer from the perspective of the Ontario healthcare payer.

3 Chapter 3: Methods

3.1 Methods

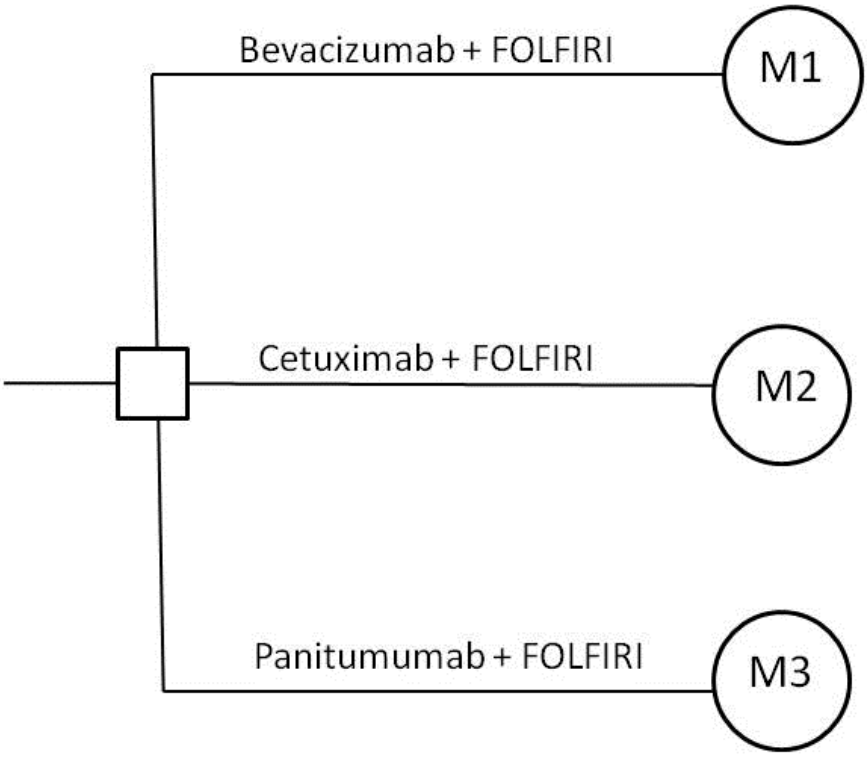
I developed a decision analytic model to project the lifetime clinical and economic consequences of patients receiving combination therapy in the first line. The combination therapy consists of either cetuximab or panitumumab plus FOLFIRI compared to the current standard of care of combination bevacizumab plus FOLFIRI for use in first-line treatment for patients with MCRC in the province of Ontario.

3.2 Model Overview

I developed decision tree analytic model to compare the projected lifetime clinical and economic consequences of MCRC patients receiving combination therapy in the first-line through the course of their disease. The decision tree consists of three different arms each representing one of the possible combination therapy regimens. At the end of each arm is a Markov model representing the treatment strategies used in current clinical practice for MCRC patients as their disease progresses. Model M1 represents the treatment strategy of patients receiving combination therapy consisting of bevacizumab and FOLFIRI, M2 the strategy for receiving cetuximab and FOLFIRI, and M3 the strategy for receiving panitumumab and FOLFIRI (Figure 3.1). Each model represents the potential treatment course a patient would receive over the course of their disease. In the case of patients receiving bevacizumab plus FOLFIRI model M1 represents the treatment course that is used in current clinical practice for patients with MCRC in Ontario. Models M2 and M3

represent the alternative treatment courses starting with first line cetuximab or panitumumab plus FOLFIRI. To date no RCT has investigated the effectiveness of these three treatment strategies head-to-head in this patient population. Therefore, analysis was conducted through indirect comparison using efficacy data from RCTs relevant to each treatment option used in these models. Each Markov model had a Markov termination condition and was run for a time horizon of 100 months. This Markov termination condition was selected to capture the entire expected lifetime for patients with MCRC. This decision analytic model was constructed using TreeAge Pro Suite 2009™.

Figure 3.1: Schematic of the Decision Analytic Model



3.3 Data Sources

I used data from both administrative databases from the province of Ontario as well as efficacy data from 5 randomized clinical trials. Patient level data for patients diagnosed with MCRC between January 1st 2008 and December 31st 2010 were compiled by the Institute of Clinical Evaluative Sciences (ICES) Ontario Cancer Data Linkage Program (cd-link). This program linked anonymized patient level data from the Ontario Cancer Registry (OCR), Ontario Health Insurance Plan (OHIP), Ontario Drug Benefit Claims (ODB), Canadian Institute for Health Information Discharge Abstract Database (CIHI – DAD), Canadian Institute for Health Information National Ambulatory Care Reporting System (NACRS), Home Care Database (HCD), and Cancer Care Ontario New Drug Funding Program (NDFP) databases.

Efficacy data were taken from four stage III and one stage IV randomized clinical trials which all examined the effectiveness of different therapies along the treatment course of patients with MCRC. The BEAT study was a phase IV RCT which compared the safety and efficacy of combination therapy consisting of bevacizumab with FOLFOX, FOLFIRI, or XELOX, which consists of capecitabine plus oxaliplatin, in first-line treatment for patients with MCRC [65]. The CRYSTAL study investigated the efficacy of the addition of cetuximab to FOLFIRI in first-line treatment of patients with MCRC [30]. The PRIME study examined the efficacy of the addition of panitumumab to FOLFOX as first line treatment [78]. The ECOG E3200 trail was used to determine the efficacy of the use of FOLFOX in second-line treatment for patients with MCRC [12] , while an open label phase III trial was used to determine the overall survival of patients receiving best supportive care alone in third-line treatment settings [41].

The model was parameterized using data collected from the selected phase III and IV randomized clinical trials as well as from data from administrative databases in the province of Ontario. Patient-level data were made available by the ICES Cd-link program which finds cases of cancer from the OCR and links these cases to cancer-relevant information from other health administrative databases. This enabled us to capture data from the OCR, NDFP, OHIP, ODB, NACRS, CIHI-DAD, and HCD databases.

3.3.1 Validation of Data Sources

The OHIP, CIHI-DAD, and OCR administrative databases have been shown to accurately represent the general population of patients diagnosed with a specific disease. The OHIP and CIHI-DAD databases have been shown to accurately identify those patients with hypertension from a population sample [79]. This was achieved through comparing the rates of hypertension determined through the use of multiple algorithms in the administrative databases and comparing them to patient charts reviewed from family practices in Ontario [79]. A validation of the OCR determined that the registry was effective in capturing cancer cases in the province of Ontario with 98% sensitivity, while another study which aimed to determine the accordance between cause of death data from the OCR compared to a cohort of patients followed in a prospective cohort study found very high levels in the abstraction techniques of the OCR, with the database having high sensitivity and specificity [80, 81].

The coding accuracy of these databases plays an important role in ensuring that the patient cohorts derived from these databases are truly reflective of the population of interest. The coding accuracy of the CIHI-DAD database has previously been studied for patients with cardiac diagnoses, and was found to have high specificities but quite variable sensitivities [82]. Austin et al. found that myocardial infarction which has clearly defined clinical criteria was found to have both high sensitivity and specificity, while those diseases which had less clearly defined clinical criteria and whose diagnoses could be affected by inter-observer variability tended to have lower specificities [82]. For a patient to be diagnosed with colorectal cancer their physician would have ordered blood tests, imaging studies, as well as biopsy to confirm the diagnoses, thus minimizing the chances of a patient having a false-positive diagnosis [83]. Given the clear diagnosis criteria for colorectal cancer we can assume that the CIHI-DAD would also have high specificity and sensitivity for capturing patients with MCRC.

3.3.2 Cohort of Interest

An initial data request was made to Cd-Link in October 2011 for all incident cases of colorectal cancer who had an ICD9 diagnosis code of 153.1-9, 154.0, or 154.1 who had been diagnosed between January 1st 2008 and December 31st 2010 as to capture a period when all three drugs of interest had been approved for funding by CCO. Ethics approval for the project was granted by the University of Western Ontario's Research Ethics Board in October 2011. The patient-level data provided from ICES were received in May 2012 and included data for 22,610 cases of colorectal cancer.

To conduct both survival and cost analyses on a patient cohort which was similar in both patient-level and clinical trials, patients of interest had to be selected from the initial 22,610 cases of colorectal cancer. From this cohort of patients I was interested in those patients who had MCRC and whose first-line treatment consisted of combination bevacizumab and FOLFIRI. I focused on patients receiving this bevacizumab plus FOLFIRI as first-line treatment. Treatment strategies consisting of either cetuximab plus FOLFIRI, or panitumumab plus FOLFIRI are not indicated or funded for use in the first-line by CCO and thus I expected to not find any cases of patients receiving either of these combination treatments. I was able to identify these patients specifically through the use of the NDFP database which provided both disease stage and treatment information. Patients were selected if for their unique subject identifier there was at least one record in their disease variable of "metastatic colorectal cancer-1st line". I then narrowed down this group to only include those patients who received both combination bevacizumab and irinotecan on the first day of treatment for metastatic colorectal cancer. This inclusion criterion resulted in 1,706 patients who received first-line bevacizumab plus FOLFIRI.

For this analysis only those patients who were diagnosed in the 2008 or 2009 were used to ensure that there would be at least two years of follow up data from the first date of treatment. This resulted in a final cohort consisting of 1216 patients. The KRAS status of the patients in the cohort of interest was not able to be determined from the CD-link data sources. To facilitate the comparison of the three treatment strategies the assumption was

made that all patients in the cohort were KRAS-WT. This assumption does not affect patient outcomes as patient's response to both bevacizumab and 5-fluorouracil containing chemotherapy regimens have previously been shown to be independent of patient KRAS status [64, 84-86]. Important characteristics of these patients are presented in Table 3.1.

Table 3.1: Cohort Patient Characteristics N=1216

Diagnosis Year	**%**
2008	50.40
2009	49.60
Sex	**%**
Female	39.94
Male	60.06
Age Category	**%**
Under 50	15.61
50-54	13.18
55-59	15.32
60-64	18.21
65-69	14.96
70-74	14.57
75+	8.14
Primary Site of Tumor	**%**
Colon	63.08
Rectum	27.22
Other	9.7
# of Metastatic Sites	**%**
1	79.40
>1	20.60
Height	169.0 cm ± 11.9
Weight	74.8 kg ±16.8
Drug Received	**%**
Bevacizumab	100
Irinotecan	100
Oxaliplatin	38.1

Panitumumab	8.4
Cetuximab	5.6

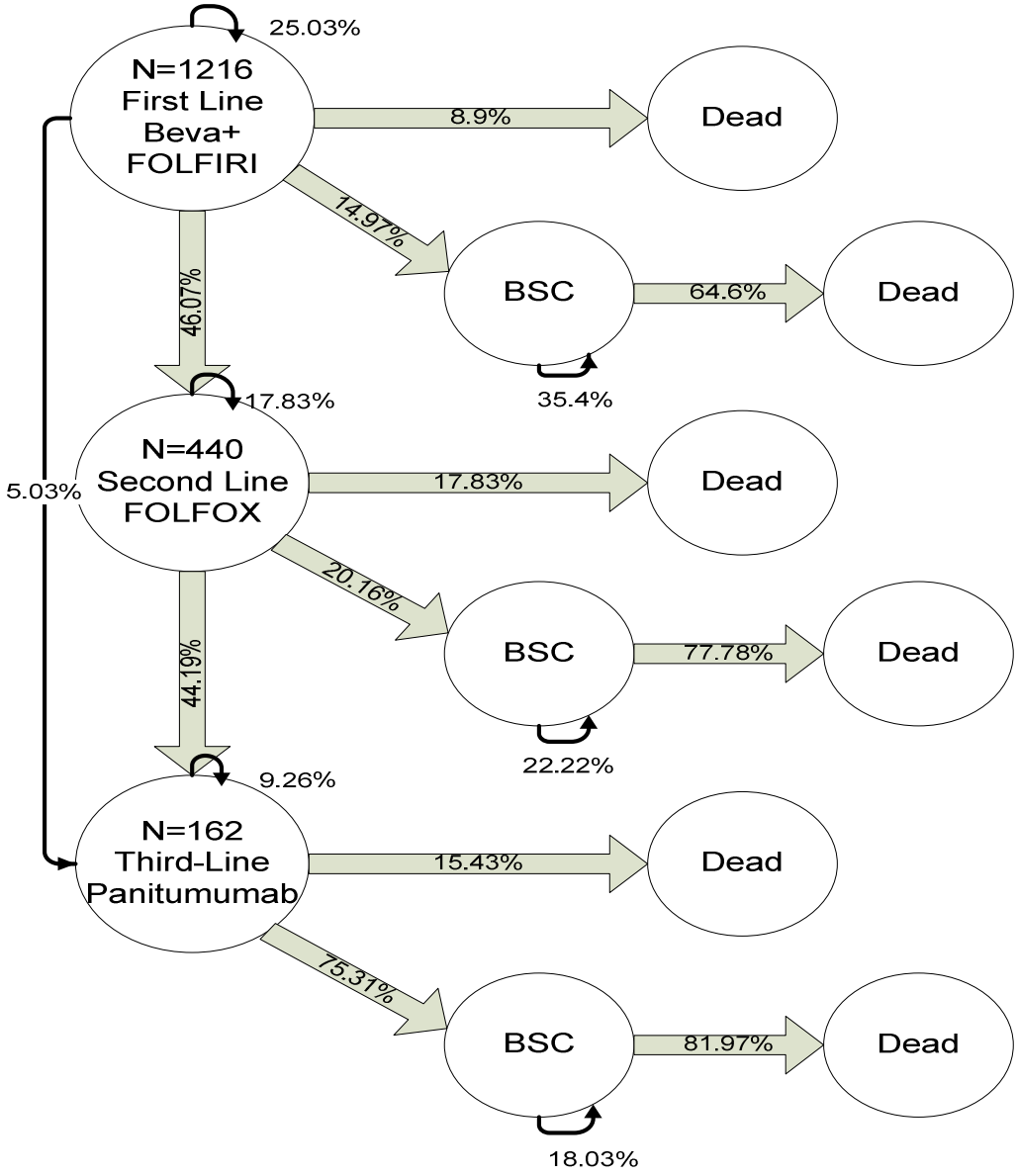
Once the cohort was identified I was able to track what treatments each patient received over the course of their disease. Of the 1216 patients who received first-line bevacizumab and FOLFIRI a total of 99 patients received all three lines of treatment within the two years of follow up. Of the patients who received first-line treatment, 25.03% remained receiving first-line treatment without progressing to receive subsequent lines of treatment while 8.9% died during the course of first line treatment. The majority of patients went on to receive later lines of treatment with 46.07% received second line treatment. Approximately 5% of patients went on to receive monotherapy panitumumab after their first line treatment, while 14.97% moved directly to receive BSC (Figure 3.2).

A total of 440 patients received second-line treatment with FOLFOX. Of these patients a total of 17.83% did not progress and remained receiving second-line treatment within two year s from the commencement of first-line treatment. An equal number of patients (17.83%) died during this line of treatment. Approximately 44% of patients moved on to receive third-line panitumumab monotherapy while 20% went directly to receive BSC (Figure 3.2).

One hundred and sixty two patients received third-line panitumumab. Of these patients 9.26% remained in third-line, 14.43% died while receiving treatment, and 75.31% moved on to receive BSC. For patients who received BSC, the proportion of patients who remained in state without dying and the number of patients who died varied depending on what line of treatment they entered in from. The percentage of patients who remained in BSC was highest for those patients who entered from first-line (35.4%). This value decreased to 22.22% for patients who entered from second-line and further fell to 18.3% for those individuals who entered from third-line. The percentage of patients who died increased as patients entered BSC from later stages in treatment. Approximately 65% of patients who entered BSC from first-line treatment died within the follow-up period. This value increased to approximately 78% for patients entering from second line and 82% for patients entering from third-line (Figure 3.2).

The time that each patient spent in each state was able to be determined from the disease and treatment date variables available in the NFP databse. Palliative care fee-codes were found in the Ontario physician schedule of benefits. The start of the best supportive care state was determined to be the first day that a palliative care fee-code was claimed in the OHIP database after the final date a patient had received their last treatment.

Figure 3.2: Schematic of the Treatment Courses Taken by Patients in the Cohort of Interest Over 24 Months.



3.3.3 The Economic Burden of Disease

The economic burden on the payer for patients with MCRC was found for the 1216 patients in the cohort of interest. Each patient's treatment course was determined using

the data provided in NDFP and OHIP databases and were then grouped according to the treatment courses they received. Each patient's clinic, homecare, hospital, OHIP, ODB, and NDFP drug costs were found from the date of diagnosis up until they died or until the end of data availability. The average cost for each database as well as total overall cost for each observed treatment course was then found.

3.3.4 Patient Characteristics from Randomized Control Studies

The demographic and baseline characteristics of the patients enrolled in the five RCTs used in this analysis are similar to those found in the cohort of interest. Median age, age range, and percentage of male and female patients were consistent across all five RCTs. Amongst the three first line trials, patient information on the primary site of tumor, as well as the number of metastases and sites of metastatic disease were consistent. To ensure that the results of these clinical trials could be used to model the progression of the patients of interest it was important that each clinical trial had similar enrollment criteria. The similarity of patients between the studies allowed for the use of the different trials to model the different treatment regimens used as patients disease progressed. In each of these trials enrollment was dependent upon patients being older than 18 years old, diagnosed with histologically confirmed MCRC, and were scheduled to receive fluoropyrimidine-based chemotherapy as the first-line treatment strategy [13, 30, 38, 65]. In all three trials patients were able to be included in the study if they had received previous chemotherapy for colorectal cancer but had not received any previous treatment for metastatic disease.

Another important similarity between the three first-line trials which was necessary to be able to compare the results of the three possible treatment options was that all three trials only included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. The ECOG was one of the first cooperative groups created to perform multi-centre randomized clinical trials of cancer therapies and introduced the ECOG performance status scale in [87]. The ECOG performance status or ECOG WHO is a scale ranging from 0 to 5; 0 indicates the best scenario where a patient

is fully active and is able to carry on all the activities he\she would be able to do before having the disease and 5 represents dead [87, 88]. This scale is widely used by clinicians in oncologic practice because it correlates patient survival duration, response to treatment, quality of life, and comorbidity [87, 88] and provide insight into how a patient's disease is progressing , how disease affects patients' daily living abilities, and to determine a patient's suitable treatment options [87, 88].

In the E3200 and Open Label Phase III the percentage of patients in each ECOG performance status starts to differ from those seen in the first line trials, however this is to be expected as these trials examine treatment options in patients who have had more progressive disease and thus we would expect to have greater percentages of patients in these higher ECOG states.

Table 3.2: Randomized Clinical Trial Demographics and Baseline Characteristics

Trial	**BEAT**		**CRYSTAL * KRAS WT Population**
Regimen	**Bevacizumab + FOLFIRI**	**Bevacizumab + FOLFOX**	**Cetuximab + FOLFIRI**
Line	1st	1st	1st
Age, Years			
Median	59	59	61
Range	25-82	21 – 85	24-79
Sex, %			
Male	61	60	62
Female	39	40	38
ECOG Performance Status, %			
0	65	69	57.9
1	35	31	38
2	n/a	n/a	4.1
Primary site of tumor, %			
Colon	65	61	55.2
Rectum	28	26	44.2

Colon and Rectum	7	13	0.6	
Site of Metastatic Disease %				
Liver	70	69	n/a	
Lung	31	28	n/a	
Other	29	25	n/a	
Number of metastatic sites, %				
1	61	63	* 87.7% had metastases at one or two sites	
>1	39	38		
Prior Adjuvant Chemotherapy %	44	36	23.3	

Trial	**PRIME *KRAS WT Population**	**ECOG E3200**	**Open Label III**	**CO. 17**
Regimen	**Panitumumab + FOLFOX**	**FOLFOX**	**Panitumumab + BSC**	**BSC**
Line	1st	2nd	3rd	BSC
Age, Years				
Median	62	60.8	62	63.6
Range	27-85	25-84	27-82	28.7 - 85.9
Sex, %				
Male	67	60.8	63	63.9
Female	33	39.2	37	36.1
ECOG Performance Status, %				
0	* 94% of patients were ECOG 0/1	51.2	46	22.5
1	* 94% of patients were ECOG 0/1	43	41	54
2	6	5.8	13	23.5
Primary site of tumor, %				
Colon	66	n/a	66	56.5
Rectum	34	n/a	34	24.6
Colon and Rectum	n/a	n/a	n/a	18.9

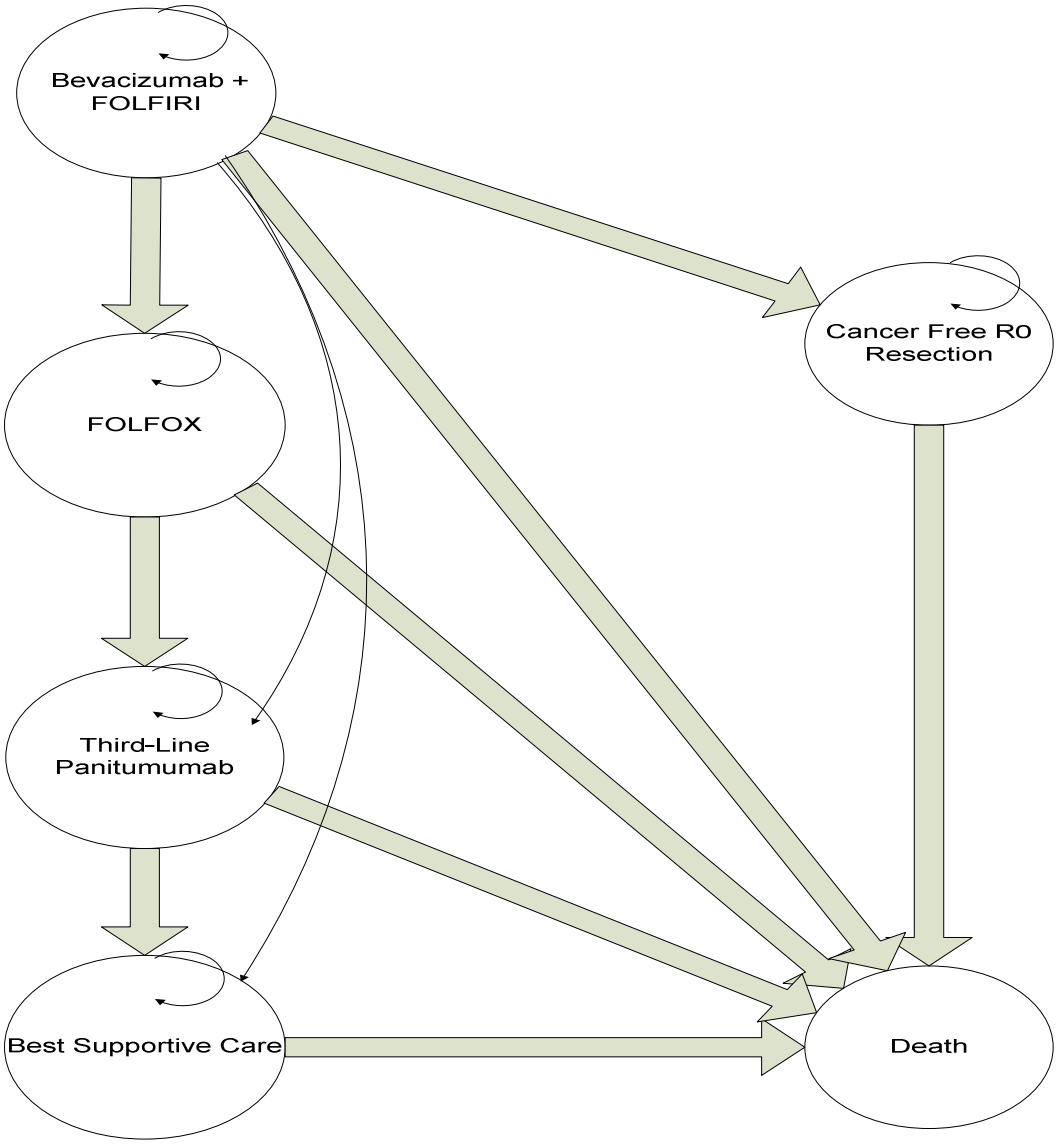
Site of Metastatic Disease				
Liver	69	75.9	n/a	81.8
Lung	n/a	51.2	n/a	63.2
Other	12	n/a	n/a	55.5
Number of metastatic sites, %				
1	21	n/a	n/a	18.6
>1	78	n/a	n/a	81.4
Prior Adjuvant Chemotherapy %	16		100	36.1

3.4 Detailed Description of Model

3.4.1 Model M1: Bevacizumab + FOLFIRI

Model M1 has six states: (1) first-line combination treatment with bevacizumab plus FOLFIRI, (2) a cancer-free state resulting from surgery for metastases (3) second-line treatment with FOLFOX (4) third-line treatment with monotherapy panitumumab, (5) best supportive care, and (6) death (Figure 3.3).

Figure 3.3: Schematic of Markov Model M1



In Model M1 patients receiving first-line bevacizumab can move to receive FOLFOX, panitumumab monotherapy, or best supportive care states based on transition probabilities from the PFS estimates derived from the patient level data and the observed treatment courses observed in the cohort of interest. Patients can transition to death using transition probabilities determined from age-dependent mortality estimates for patients aged 61, the average age of patients enrolled in all first line clinical trials. These mortality estimates were then weight-adjusted by sex by multiplying the percentage of patients of each sex by the sex-dependent mortality estimate for each year. It is also possible for

patients receiving first-line combination treatment to have a very good response to treatment which leads them to be able to have surgical resection of their metastases. The rate of surgical resections was provided over the course the clinical trial was published in the BEAT trial [65]. To determine the monthly probability of a patient undergoing surgical resection this rate was divided by the length of the trial. The resultant value was then used as the monthly probability of undergoing surgical resection and thus of moving to the cancer free state.

Patients who move to the cancer-free state can have a recurrence of their disease. It was assumed that those patients who had a recurrence of disease would move to have second-line treatment and this transition was determined from a retrospective review of patients who underwent resection conducted by Tomlinson et al. This transition occurred in a time dependent manner with more patients experiencing recurrence before 5 years survival than after 5 years of survival. Patients who did not have a recurrence of disease could then either remain in the healthy cancer-free state, or could transition to the death state via transition probabilities determined from OS estimates which were obtained in the same retrospective study [89].

For patients who move on to receive second line treatment, they can then transition to receive third line panitumumab monotherapy or best supportive care, using estimates of PFS or to death using time-dependent transition probabilities. The PFS estimate was used for second line treatment with FOLFOX [90]. Transitions from second-line chemotherapy to death occurred via age-dependent background mortality or due to death resulting from toxic adverse reaction to treatment [90].

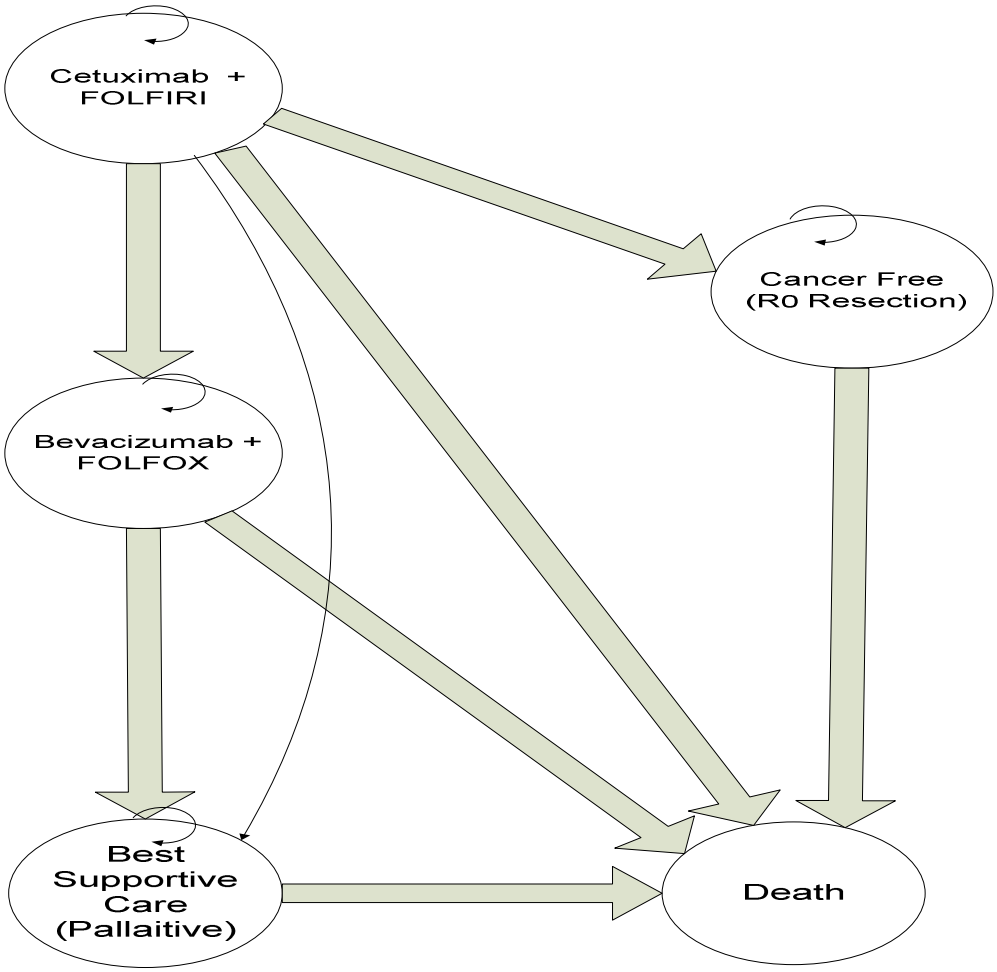
Patients receiving third line panitumumab can transition to the best supportive care or to death via disease-specific using transition probabilities determined from the PFS estimate for KRAS-WT patients from Van Cutsem et al. [38] or age dependent background mortality. Patients can enter the BSC state from either first, second, or third line stages and transition to the death state using transition probabilities determined from OS estimates for KRAS-WT patients derived from Jonker et al. [34].

In models M1, M2, and M3 the transition to death was determined from either mortality data provided in the randomized control trials or from age-dependent mortality estimates for patients aged 61 determined from the life table for Ontarians between years 2000 to 2002, as the mortality rate was unable to be determined from the patient-level data.

3.4.2 Model M2: Cetuximab + FOLFIRI

Model M2 has five states: (1) first-line combination treatment with cetuximab plus FOLFIRI, (2) a cancer-free state resulting from surgery for metastases (3) second line treatment consisting bevacizumab plus FOLFOX, (4) best supportive care, and (5) death (Figure 3.4).

Figure 3.4: Schematic of Markov Model M2

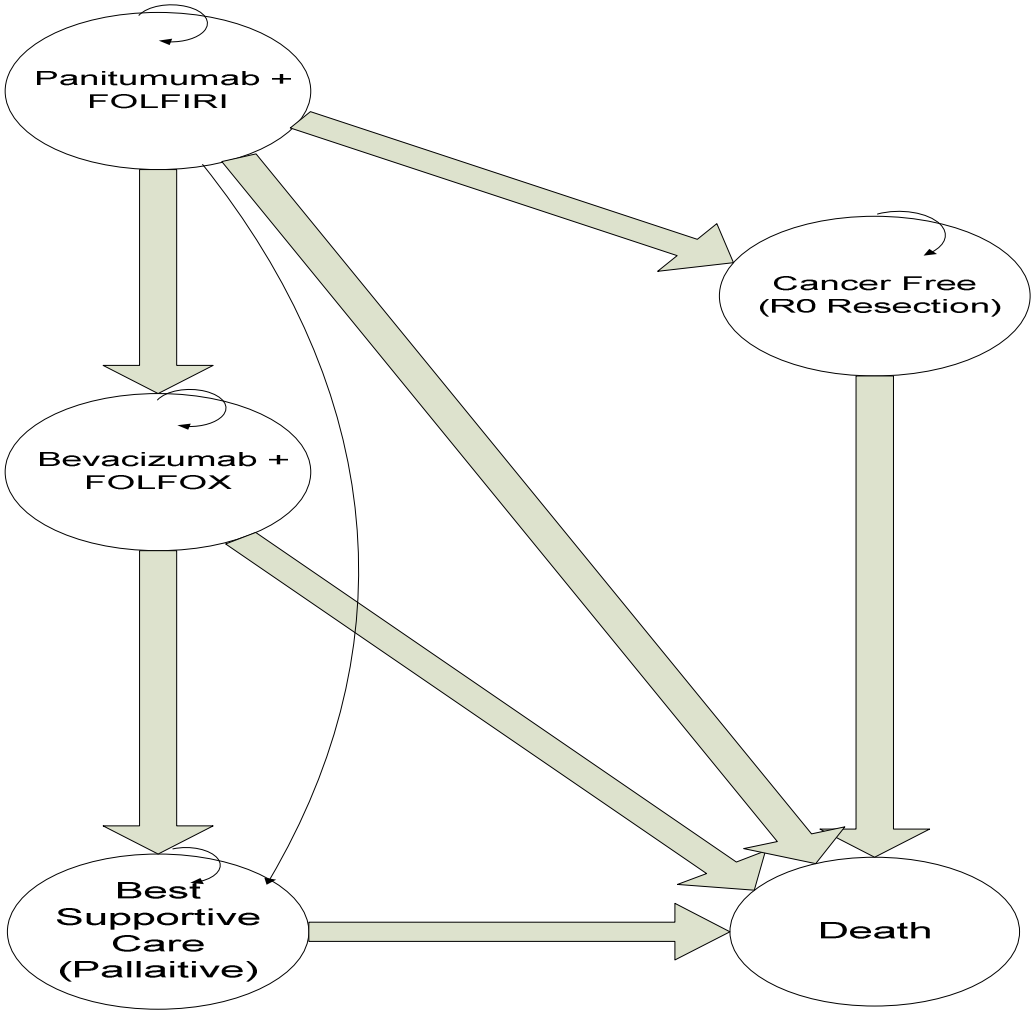


In model M2 patients receiving first-line cetuximab and FOLFIRI can transition to either second-line treatment, BSC, or cancer free based upon transition probabilities based data estimates from Van Cutsem et al. [30], or death via age-dependent background mortality determined from statistics Canada [91]. Patients who move to the cancer-free transition in the same manner as in model M1 and either have a recurrence of disease and move to have second-line bevacizumab and chemotherapy, remain cancer-free, or die via age-dependent mortality [92, 93]. Patients who transition to receive second line bevacizumab plus FOLFOX can then move on to receive BSC using time dependent transition probabilities derived from Giantonio et al. [90], or to death via a fatal toxicity related adverse event or via age-dependent background mortality. Those patients who are in the BSC state then transition to the death state using transition probabilities determined from OS estimates for KRAS-WT patients derived from Jonker et al.[34].

3.4.3 Model M3: Panitumumab + FOLIRI

Model M3 has five states: (1) first-line combination treatment with cetuximab plus FOLFIRI, (2) a cancer-free state resulting from surgery for metastases (3) second line treatment consisting bevacizumab plus FOLFOX, (4) best supportive care, and (5) death (Figure 3.5).

Figure 3.5: Schematic of Markov Model M3



Model M3 is much like model M2, the only difference being that patients receiving first-line panitumumab and FOLFIRI can transition to either second-line chemotherapy or BSC from transition probabilities based upon PFS estimates, or to the cancer-free state from data provided by Douillard et al. [38]. It was assumed that the progression of patients receiving pantiumumab plus FOLFIRI would be no different than that of patients receiving panitumumab plus FOLFOX given both regimens have been found to be equivalent in terms of their effects on patient PFS and OS [5, 6].

3.5 Survival Analysis & Transition Probabilities

The monthly transition probabilities used in the model to move patients between states were based upon PFS estimates of first-line treatment from determined from the patient level data, as well as estimates of PFS and OS from the published RCTs. The PFS estimate for patients receiving first-line bevacizumab and FOLFIRI was determined using data provided in the NDFP database. The assumption was made that a change in treatment would be indicative of disease progression. By determining the number of days from when the patient started first-line treatment to the commencement of their subsequent treatment line it was possible to determine whether a patient had progressed to either second, third, or best-supportive care or was continuing to receive first-line treatment. This was done for a two year window from the first day of treatment for each patient. If a patient was still receiving first line treatment at the end of the two year period they were considered censored. The Kaplan-Meier survival curve of patient PFS was then constructed from the patients in the cohort of interest (Figure 4.7). Weibull distributions were similarity fit to PFS estimates found from the NDFP data for patients receiving second-line FOLFOX/FOLFIRI, third-line treatment consisting of panitumumab monotherapy or combination cetuximab plus irinotecan, and for best supportive care to extrapolate survival outside of time period captured. These were then used to model the outcomes of patients receiving bevacizumab + FOLFIRI in the comparison of RCT versus patient-level data parameterized models.

Weibull distributions were also fit to Kaplan-Meier survival curves of patient PFS that were taken from the RCT's from patients receiving first-line cetuximab plus FOLFIRI and panitumumab plus FOLFIRI, second –line FOLFOX and FOLFOX plus bevacizumab, and third-line panitumumab montherapy, while a Kaplan-Meier survival curve for OS was taken from patients receiving best-supportive care alone[30, 38, 41, 90]. These estimates were used then in the base case model.

Data from the survival curve and the number of patients at risk at given monthly intervals allowed for Weibull distributions to be fit to each survival curve. In order to determine the number of events and censored cases the assumption had to be made that all progression, death, or censoring events would occur at the same time in the month. The

number of patients having disease progression or dying was able to be determined using the equation: Number of events = $[S_{(t)}-S_{(t+1)}]* N_t$. The number of patients who were censored in this time period could then be determined by using the equation: Number of Censored = $N_t-N_{events}-N_{t+1}$. With this information it was possible to develop a parametric regression model using Weibull distributions to each survival curve. The regression gave estimates of the Weibull scale (σ) and shape (β) parameters which were then used in the equation $S(t)=\exp\{-(\sigma/t)^{\beta}\}$ to model survival until there were no more patients in-state [94]. From this data the monthly transition probabilities were able to be determined.

The parametric Weibull model is often used to estimate survival at time points after the end of a RCT [94] and has previously been used to estimate survival in a CEA of oxaliplatin and capecitabine for patients with stage III colon cancer [95]. Gerdtham and Zethraeus looked at the use of different parametric survival models to predict survival outside of a clinical trial of patients who received enalapril versus placebo and compared these results with these patients observed true survival [96]. In this study the Weibull model was found to best predict survival of those individuals who received treatment with enalapril, with the exponential model being found to underestimate survival and the gamma and log-normal models found to overestimate survival [96]. To ensure that the Weibull model was an appropriate choice to model patient survival, I compared the model fit of the Weibull and exponential models to the PFS data for patients receiving first-line bevacizumab and FOLFIRI. The Weibull model was found to have a higher log-likelihood value as well as lower AIC and BIC values compared to the exponential model, thus indicative of the Weibull better fitting the survival data (Table 3.3).Also, the use of the Weibull distribution was a more attractive option to fit the survival data as it allows the hazard rate to increase or decrease over time, while the exponential model assumes constant hazard rate over time.

The monthly transition probabilities were then determined from the Kaplan-Meir curves constructed from the parametric models. Transition probabilities for a cycle of one month were determined using the formula:$transition\ probability = 1 - EXP(\frac{LN(1-(X\ Month\ Rate))}{X\ Months})$. The monthly percentage of patients` receiving surgery for the removal of metastases of R0 hepatic

metastectomy, as well as the occurrence of grade 3 or 4 adverse events was determined by first converting the probability of surgery over the course of the RCT to a monthly rate using the formula: $Rate = -1 * \frac{LN(1-(Trial\ Probability))}{\#\ Trial\ months}$ with trial months being the median follow-up. This value was then converted to a monthly transition probability of having that event using the formula: $transition\ probability = 1 - EXP(-Monthly\ Rate)$.

Table 3.3: Model Fit Statistics

Model	Log-Likelihood	AIC	BIC
Weibull	-1605.17	3214.35	3224.56
Exponential	-1656.32	3314.64	3319.74

For second-line PFS estimates for patients receiving FOLFOX and FOLFOX + bevaciuzmab, Weibull distributions were not able to be fit to the survival curves data on the number of patients at risk each month were not provided in the RCT [90]. Transition probabilities were derived directly from the PFS survival curves for the duration of the trial. For months where the monthly transition probability was found to be zero, the value of the previous month was used as these transition probabilities are an artifact of the clinical trial and it is not plausible to assume that no patients would progress during a certain month. Outside the time-horizon of the trial survival was extrapolated using the average of the transition probabilities in the last four months of the clinical trial.

3.6 Health State Utilities

Utilities for each state were found through a search of the relevant literature [73, 97-101]. The utility decrement of patients experiencing adverse events associated with each treatment option was assumed to be taken into account in these utility values. The utility values used in this analysis can be found in Table 3.4.

Table 3.4: Health State Utilities

Treatment	Range	Base Case Value	Sensitivity Analysis Range	Source
First-line Bevacizumab + FOLFIRI/FOLFOX (with adverse events)	0.80-0.77	0.77	± 0.20	99, 102
First-line Cetuximab + FOLFIRI/FOLFOX (with adverse events)	0.80-0.77	0.77	± 0.20	101, 103
First-line Panitumumab + FOLFIRI/FOLFOX (with adverse events)		0.778	± 0.20	97
Second-Line FOLFOX (with adverse events)		0.756	± 0.20	97
Third-Line Panitumumab (with adverse events)		0.72	± 0.20	98
Best Supportive Care		0.68	± 0.20	98
Cancer Free		0.84	± 0.20	100
Dead		0		

3.7 Costs

Costs used in this analysis were estimated from the perspective of the Ministry of Health and Long-Term Care (MOHLTC), the public health care payer in the province of Ontario. Only direct medical costs presented in 2012 Canadian dollars were included in the models. Costs prior to 2012 were adjusted for inflation to 2012 Canadian using the consumer price index for healthcare in Ontario [104]. Indirect medical costs were not included as they are not relevant given the perspective of this analysis.

3.7.1 Direct Medical Costs

The direct medical costs used in this analysis were determined through the analysis of data from administrative databases from the province of Ontario for those MCRC patients

who received bevacizumab and FOLFIRI as first-line treatment and also from the literature. Patient costs were determined using the, OHIP, ODB, NACRS, CIHI-DAD, and HCD databases. The direct medical costs used in this analysis included the cost of KRAS testing, cancer clinic visit costs determined using the NACRS, outpatient physician service, laboratory, and other health services costs determined from the OHIP database. Hospitalization and emergency department visit costs were determined using the CIHI-DAD database, drug costs accrued by those patients 65 and older from the ODB database, and home care services received using the HCD.

Monthly state-specific costs were able to be determined through the use of the NDFP database. This database contained information on the line of treatment as well as records of every date a patient received treatment. From this data I was able to determine the start date of each line of treatment a patient had received. The monthly costs accrued in each state were then able to be determined by compiling each date of service/hospitalization corresponding to the commencement of each line of treatment. This was conducted for all patients and the average of each state dependent monthly cost was estimated. This resulted in monthly cost estimates which varied quite differently over time. In order to smooth these costs over time, I fit a linear regression model to the monthly total average costs. In the BSC state total cost seemed to differ over time. In order to best smooth this cost data three separate equations for three separate time periods in which these costs seemed to differ were used to smooth the monthly costs. The resultant equation(s) were then used to determine the monthly costs that were then inputted into the model. For patients who moved into the cancer-free state, monthly costs were determined using the average health care utilization costs for patients in Ontario starting at age 61 to correspond with the average age of patients in the clinical trials used in this analysis [105] .

3.7.2 Hospitalization Costs

Hospitalization costs were determined using the CIHI-DAD database. In the 462 patients of interest there were a total of 779 hospitalizations, 491 occurred while patients were receiving first-line treatment, 166 during second-line, 22 during third-line, and 100 in BSC. The average monthly costs can be found in Table 9.2.

3.7.3 Physician Costs

Physician costs were determined using the OHIP database. In the 462 patients of interest there were a total of 101,045 OHIP claims. 63,255 of these claims occurred while patients were receiving first-line treatment, 23,237 during second-line, 2,856 during third-line, and 11,697 in BSC. The average monthly costs can be found in Table 9.2.

3.7.4 ODB Drug Costs

ODB drug costs were determined using the ODB database. In the 462 patients of interest there were a total of 27,693 ODB claims. 17,477 of these claims occurred while patients were receiving first-line treatment, 6,491 during second-line, 600 during third-line, and 3,125 in BSC. The average monthly costs can be found in Table 9.2.

3.7.5 Cancer Clinic Costs

Cancer clinic costs were determined using the NACRS database. In the 462 patients of interest there were a total of 10,303 cancer clinic visits. 6,984 of these claims occurred while patients were receiving first-line treatment, 2,744 during second-line, 394 during third-line, and 181 in BSC. The average monthly costs can be found in Table 9.2.

3.7.6 Home Care Costs

Home Care services costs were determined using the ODB database. In the 462 patients of interest there were a total of 30,797 home care visits provided. 18,928 of these claims occurred while patients were receiving first-line treatment, 7,406 during second-line, 1,092 during third-line, and 3,371 in BSC. The average monthly costs can be found in Table 9.2.

3.7.7 Drug Costs

The cost per milligram administered for patients receiving bevacizumab, cetuximab, and panitumumab were able to be obtained from the NDFP database, the London Health Science Centre (LHSC) drug formulary intranet, and from literature. The cost per 25mg/ml vial of bevacizumab was determined by using data available from the Patented Medicine Prices Review Board of Canada (PMPRB) [106]. Cost values for cetuximab,

panitumumab, irinotecan, and oxaliplatin were determined from the NDFP database by dividing each patients cost per dose by the dose they received of each drug. These values were then classified by what drug the patient received and an average value of cost per milligram was able to be determined. The cost of bevacizumab provided by the PMPRB was confirmed using this method. The cost per milligram values for fluorouracil and leucovorin used in FOLFIRI and FOLFOX regimens were determined using costs provided through the London Health Sciences Centre drug formulary intranet (Table 3.5)

The average cost per dose for patients who received each drug of interest was found using data provided in the NDFP database. In the clinical trials of interest each treatment was delivered in 14 day cycles [13, 34, 38, 41, 90]. To determine the monthly cost the assumption that a patient would receive each treatment twice a month was made. In addition to the cost of the drugs themselves, infusion time costs as well as pharmacy preparation costs were included each time a patient received treatment.

Table 3.5: Drug Costs

Drug	Cost/mg	Cost/Dose	Cost/Month	Source
Bevacizumab	$5.00	$1,879	$3,758	NDFP
Cetuximab - Initial Treatment	$3.39	$2,440	$4,880	NDFP
Cetuximab – All other Treatments		$1,620	$3,240	NDFP
Panitumumab	$6.00	$2,697	$5,394	NDFP
Irinotecan	$0.74	$185	$370	NDFP
Oxaliplatin	$10.00	$1,430	$2,860	NDFP
Fluorouracil + Leucovorin		$70	$140	LHSC
Infusion Time		$213	$426	LHSC
Pharmacy Prep		$47	$94	LHSC

3.7.8 Cost of Adverse Events

The costs associated with the treatment of grade 3 and grade 4 adverse events were captured in this analysis; the management of less severe adverse events would be very small to the healthcare payer and thus are negligible from this perspective [73]. All the adverse events selected to be important at each treatment line was based upon expert opinion. The monthly probability of each adverse event occurring were determined from the overall complication rates taken from each respective clinical trial (Table 3.6).

Table 3.6: Monthly Probability of Adverse Events

Treatment	Adverse Event	Monthly Probability	Source
Bevacizumab + FOLFIRI	Hypertension	0.0012	[65]
	Wound-healing complication	0.0005	[65]
	GI perforation	0.0005	[65]
	Diahorrea	0.0089	[65]
	Pain	0.0040	[65]
Cetuximab + FOLFIRI	Neutropenia	0.0151	[13]
	Leukopenia	0.0034	[13]
	Diarrhea	0.0074	[13]
	Vomiting	0.0017	[13]
	Rash	0.0072	[13]
	Infusion-related reactions	0.0011	[13]

Panitumumab + FOLFIRI	Neutropenia	0.0404	[38]
	Skin toxicity	0.0332	[38]
	Diarrhea	0.0149	[38]
	Hypokalemia	0.0080	[38]
	Infusion related	0.0080	[38]
FOLFOX	Hypertension	0.0045	[12]
Treatment	**Adverse Event**	**Monthly Probability**	**Source**
	Bleeding	0.0010	[12]
	Vomiting	0.0081	[12]
	Neuropathy (pain)	0.0238	[12]
FOLFOX + Bevacizumab	Hypertension	0.0023	[12]
	Bleeding	0.0012	[12]
	Vomiting	0.0038	[12]
	Neuropathy (pain)	0.0063	[12]
Panitumumab Monotherapy	Rash/Skin Toxicity	0.0053	[41]
	Vomiting	0.0015	[41]
	Diarrhea	0.0009	[41]

Cost estimation of treating these adverse events was determined from a search of the OHIP database for the fee codes associated with the treatment of each adverse event. For

those adverse events which did not have directly associated OHIP fee codes, costs were obtained from literature review, while the cost for hypokalemia and thromboembolism expert opinion [107, 108]. The cost of treating GI hemorrhage was used for bleeding events, the cost of treating non-neutropenic infection was used as the cost of treating both neutropenia and leucopenia, infusion-related reaction cost was determined by using the cost of treating poisoning by drugs, medications, and biological substances plus the average cost of an emergency room visit, while the average cost of an emergency department visit was used for the cost of wound complication. The cost of hypokalemia was determined using cost data from the LHSC drug formulary along with clinical guidelines for the cost of EGFR-induced hypomagnesiad [107]. The monthly cost of treating adverse events for each treatment line was determined by finding the sum total of each adverse events monthly probability by the cost of treating each event (Table 3.7).

Table 3.7: Cost of Treating Adverse Events

Adverse Event	Cost per event	Source
Hypertension	$42.63	OHIP Fee Codes
GI Hemorrhage	$3,388.33	CIHI patient cost estimator
Pain	$28.75	[73]
Diarrhea	$46.36	OHIP Fee Codes
Non-neutropenic infection (Neutropenia/Leukopenia)	$2,491.30	[73]
Rash/Skin toxicity	$37.10	OHIP Fee Codes
Hypokalemia	$6.23	LHSC drug formulary
Infusion related reaction	$6,613.72	[109]
ER Visit (Wound Healing Complication)	$153.59	[110]
Vomiting	$72.57	OHIP Fee Codes

	Thromboembolism	$1.75	LHSC drug formulary

Table 3.8: Model Parameters and Sources

	Variable	Base Case Value	Duration	Ranges Tested in Sensitivity	Probability Distribution	Reference
					Lognormal (μ,σ)	
Treatment Costs	Bevacizumab	$3,758	Treatment Course	±20%	8.01, 0.67	NDFP
	Cetuximab-Initial Dose	$4,880	Treatment Course	±20%	8.27,0.67	NDFP
	Cetuximab - Every Dose After	$3,240	Treatment Course	±20%	7.86,0.67	NDFP
	Panitumumab	$5,394	Treatment Course	±20%	8.37,0.67	NDFP
	FOLFIRI	$440	Treatment Course	±20%	5.86,0.67	NDFP, LHSC
	FOLFOX	$3230	Treatment Course	±20%	7.86, 0.67	NDFP. LHSC
	Infusion Time	$426.00	Treatment Course	±20%	5.83,0.47	LHSC
	Pharmacy Preparation	$94.00	Treatment Course	±20%	4.32,0.48	LHSC
Total First-Line Costs		Varying By Month	Treatment Course	±20%	Varying By Month	OHIP/ODB/HCD/NACRS/DAD
Cancer Free Costs		$359.40	First 48 Months	±20%	5.66, 0.67	CIHI
		$543.15	Following Months	±20%	6.07, 0.67	CIHI
Total Second-Line Costs		Varying By Month	Treatment Course	±20%	Varying By Month	OHIP/ODB/HCD/NACRS/DAD

	Variable	Base Case Value	Duration	Ranges Tested in Sensitivity	Probability Distribution	Reference
Total Third-Line Costs		Varying By Month	Treatment Course	±20%	Varying By Month	OHIP/ODB/HCD/NACRS/DAD
Total Best-Supportive Care Costs		Varying By Month	Treatment Course	±20%	Varying By Month	OHIP/ODB/HCD/NACRS/DAD
Adverse Event Costs	Bevacizumab + FOLFIRI	$2.24	Treatment Course	±20%	0.22, 0.76	65
	Cetuximab + FOLFIRI	$53.87	Treatment Course	±20%	3.81, 0.42	13
	Panitumumab + FOLFIRI	$155.27	Treatment Course	±20%	4.82, 0.47	38
	FOLFOX	$4.86	Treatment Course	±20%	1.32, 0.59	90
	FOLFOX + Bevacizumab	$4.74	Treatment Course	±20%	1.32, 0.48	90
	Panitumumab	$1.50	Treatment Course	±20%	0.18, 0.67	41
					Beta (α,β)	
Health State Utilities	Bevacizumab + FOLFIRI	0.77	Treatment Course	±20%	77, 100	99
	Cetuximab + FOLFIRI	0.77	Treatment Course	±20%	77, 100	101
	Panitumumab +FOLFIRI	0.778	Treatment Course	±20%	778, 1000	97

	Variable	Base Case Value	Duration	Ranges Tested in Sensitivity	Probability Distribution	Reference	
	FOLFOX	0.756			756, 1000	97	
	FOLFOX + Bevacizumab	0.756	Treatment Course	±20%	756, 1000	97	
	Panitumumab	0.72			72, 100	98	
	Best-Supportive Care	0.68	Treatment Course	±20%	68, 100	98	
	Cancer Free	0.84	Treatment Course	±20%	84, 100	100	
	Dead	0					
Transition Probabilities	Bevacizumab + FOLFIRI PFS	Varying By Month	Treatment Course	±20%	***Beta (α,β)*** Varying By Month		NDFP
	Cetuximab + FOLFIRI PFS	Varying By Month	Treatment Course	±20%	Varying By Month	13	
	Panitumumab + FOLFIRI PFS	Varying By Month	Treatment Course	±20%	Varying By Month	38	
	FOLFOX PFS	Varying By Month	Treatment Course	±20%	Varying By Month	90	
	FOLFOX + Bevacizumab PFS	Varying By Month	Treatment Course	±20%	Varying By Month	90	
	Panitumumab Monotherapy PFS	Varying By Month	Treatment Course	±20%	Varying By Month	41	
	Best-Supportive Care OS	Varying By Month	Treatment Course	±20%	Varying By Month	34	

	Variable	Base Case Value	Duration	Ranges Tested in Sensitivity	Probability Distribution	Reference
	Bevacizumab to Cancer Free	0.001536953	Treatment Course	±20%	15, 10000	65
	Cetuximab to Cancer Free	0.003423096	Treatment Course	±20%	34, 10000	13
	Panitumumab to Cancer Free	0.008284798	Treatment Course	±20%	83, 10000	13
	Cancer Recurrence	First 60 Months	0.012392865	±20%	124, 10000	89
		Following Months	0.003733782	±20%	37, 10000	89
	Background Mortality Rate	Varying By Month	Lifetime			91
Discount Rate			0.5	0-0.5%		

3.8 Discounting

All costs and QALYS were discounted at an annual rate of 5% to be consistent with standard practice of economic evaluations in Canada [111, 112]. The discounting of QALYs is a controversial topic in cost-effectiveness analyses as there are differing views as to whether individuals value QALY equally over time [113]. Although the discounting of QALYS goes against the theory of welfare economics which implies that individuals weigh health benefits by some measure of willingness to pay value, the US Panel on Cost-Effectiveness in Health and Medicine recommends the discounting of QALYS as to introduce a standard practice [113, 114].

3.9 Sensitivity Analyses

Both deterministic and probabilistic sensitivity analyses were carried out in TreeAge (TreeAge Software Inc., Williamstown, MA) to determine the robustness of the base-case result as well as to address any potential uncertainty in key model parameters. One-way deterministic sensitivity analyses were carried out in a +/- 20% range of each base case value for all costs, transition probabilities, and health utilities. Probabilistic sensitivity analysis was carried out in 10,000 Monte Carlo simulations where monthly transition probabilities, state dependent probabilities, and utility values were estimated using beta distributions, while costs were determined using log-normal distributions (Table 3.8).

3.10 Software

The decision analysis model was built using TreeAge Pro Suite 2009™ (TreeAge Software, Williamstown, MA, USA). All descriptive data analysis and survival data analysis were conducted using SAS software™ (SAS Institute Inc., Cary, NC, USA).

4 Chapter 4: Results

4.1 Cohort Data Analysis

4.1.1 Estimated Average Cost of Disease

The total cost to the payer over for patients treated with first-line bevacizumab plus FOLFIRI was found on average to be $121,750 over the course of their disease. The average total costs for patients receiving each potential treatment course can be found in Table 4.1

Table 4.1: The Average Cost of Treatment for Patients Receiving First-Line Bevacizumab Plus FOLFIRI.

Treatment Courses Received	N	Clinic	Home care	Hospital	ODB	OHIP	NDFP	Total
1	237	$16,405	$4,567	$22,872	$8,099	$14,707	$39,069	$105,720
12	49	$21,283	$5,975	$21,251	$9,742	$14,194	$49,716	$122,162
13	2	$36,541	$1,425	$14,590	$0	$16,351	$94,621	$163,528
14	145	$17,305	$434	$24,996	$8,893	$15,262	$37,544	$104,435
15	87	$8,957	$4,404	$34,552	$5,116	$9,694	$18,404	$81,128
123	13	$24,583	$4,672	$17,091	$4,291	$12,410	$92,353	$155,400
124	49	$25,216	$8,262	$23,217	$12,705	$14,575	$52,032	$136,008
125	50	$16,376	$5,786	$36,490	$6,960	$9,840	$29,642	$105,094
134	36	$22,963	$5,122	$30,435	$7,931	$14,389	$46,371	$127,211
135	10	$21,250	$5,969	$42,075	$7,419	$12,562	$41,173	$130,449
145	259	$12,568	$4,900	$36,660	$6,281	$12,358	$20,728	$93,495
1234	18	$22,909	$4,473	$21,489	$10,050	$13,597	$65,045	$137,564
1235	15	$19,509	$4,900	$20,824	$12,571	$7,848	$46,657	$112,308

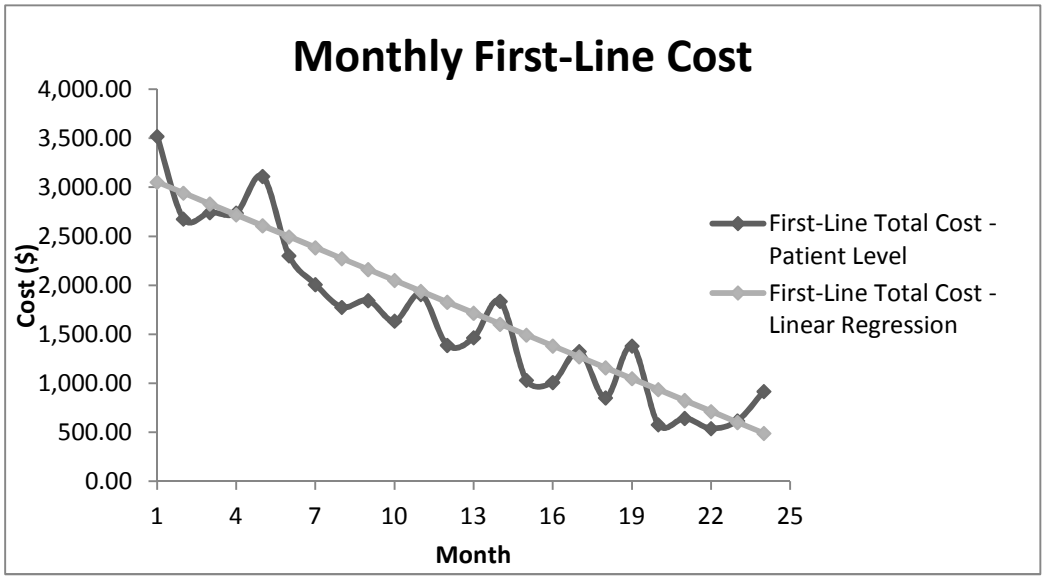
Treatment Courses Received	N	Clinic	Home care	Hospital	ODB	OHIP	NDFP	Total
1245	178	$21,302	$6,066	$26,215	$7,705	$12,056	$39,663	$113,006
12345	68	$26,371	$7,154	$25,969	$8,652	$13,623	$56,961	$138,729

*Note that the numbers in column 1 represent the following sequence of events: 1= First-line bevacizumab + FOLFIRI, 2= Second-line FOLFOX, 3= Third-line Panitumumab, 4=Best Supportive Care, and 5=Death

4.1.2 Monthly Costs

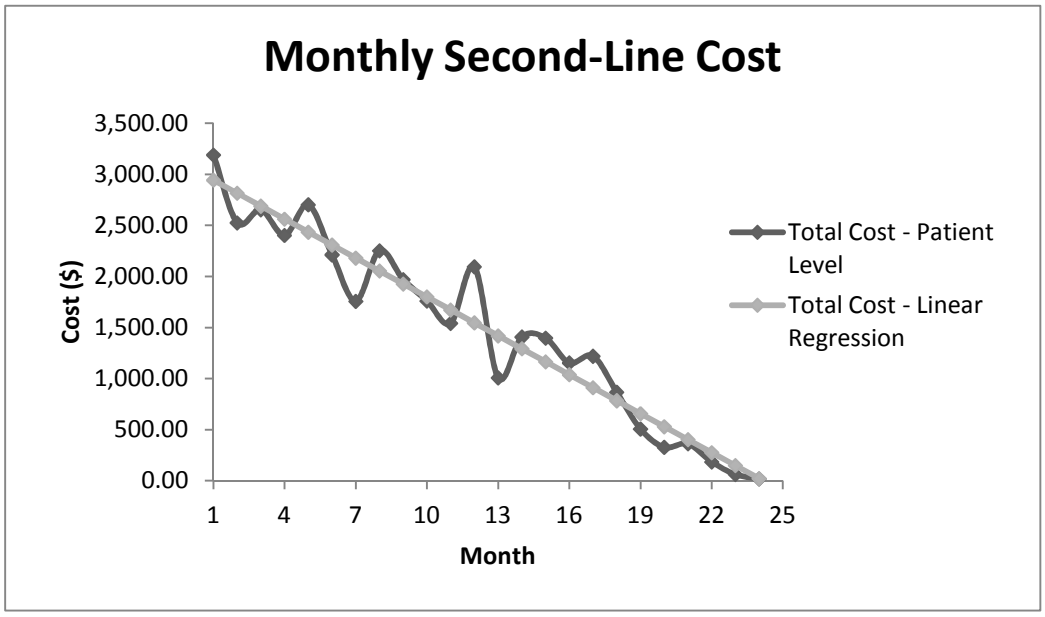
Monthly state-specific costs were determined from the 1216 patients of interest. The total monthly costs found from the patient level data and the smoothed costs used in the linear regression can be are reported in Table 9.1. The component costs from each respective database are presented in Table 9.2 . For patients who received first-line treatment the average monthly cancer clinic costs was $479.19, home care cost was $134.47, hospital cost was $523.50, ODB drug cost was $223.86, and outpatient physician cost was $270.54. The average monthly total healthcare cost over the course of first-line treatment was $1660.86. A graph of the total monthly first-line costs can is presented in Figure 4.1 .

Figure 4.1: Total Monthly First-Line Costs



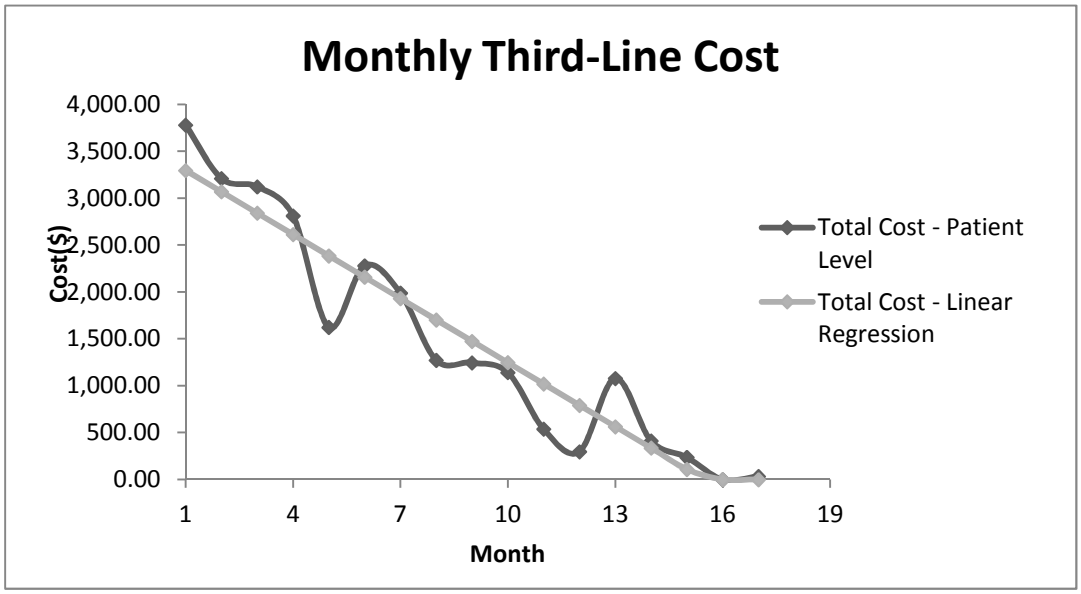
For patients who received second-line treatment the average monthly clinic cost was $483.65, home care cost was $142.54, hospital cost was $391.92, ODB drug cost was $227.00, and outpatient physician costs were $238.62. The average monthly total healthcare cost over the course of second-line treatment was $1483.73. A graph of the total monthly second- line costs is depicted in Figure 4.2.

Figure 4.2: Total Monthly Second-Line Costs



For patients who received third-line treatment the average monthly clinic cost was $441.29, home care cost was $161.02, hospital cost was $403.23, ODB drug cost was $184.31, and outpatient physician costs were $284.94. The average monthly total healthcare expenditure over the course of third-line treatment was $1474.78. A graph of the total monthly third-line costs is presented in Figure 4.3.

Figure 4.3: Total Monthly Third-line Costs



For patients who received best-supportive care the average monthly clinic cost was $16.49, home care cost was $87.36, hospital cost was $369.04, ODB drug cost was $104.98, and outpatient physician costs were $197.36. The average monthly total healthcare expenditure over the course of best-supportive care was $775.23. A graph of the monthly BSC costs can be found in Figure 4.4-4.6.

Figure 4.4: Total Monthly Costs in Months 1 to 7 of Best Supportive Care

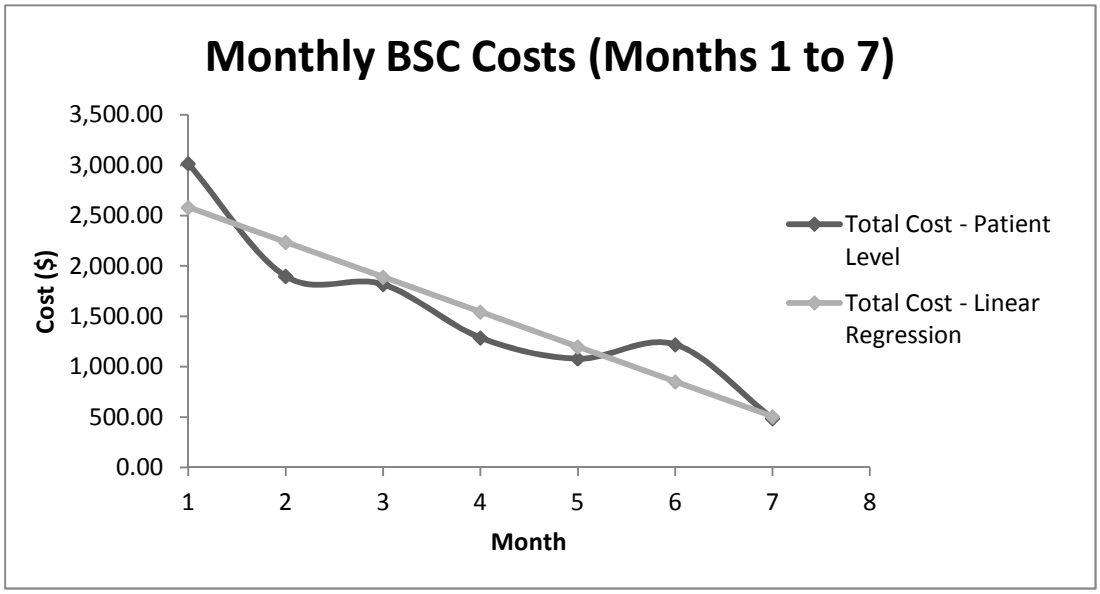


Figure 4.5: Total Monthly Costs in Months 8 to 15 of Best Supportive Care

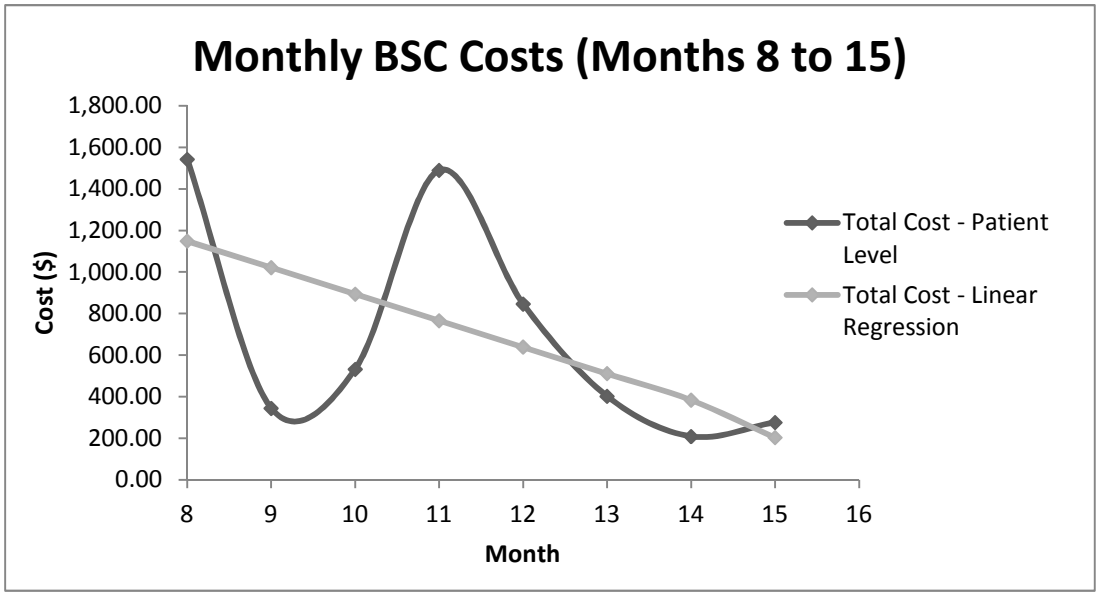
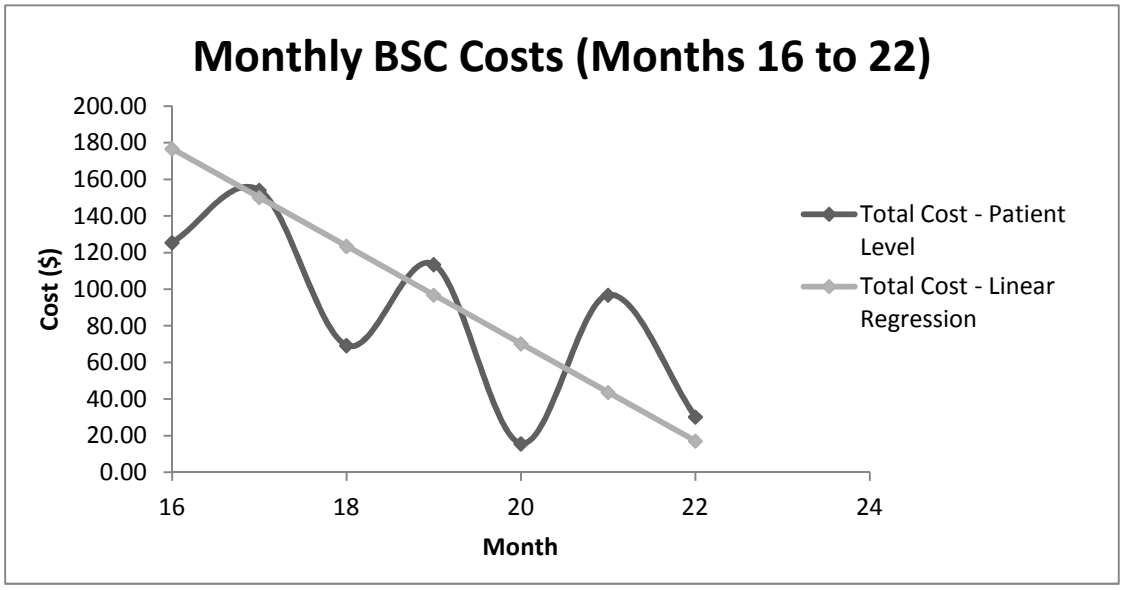


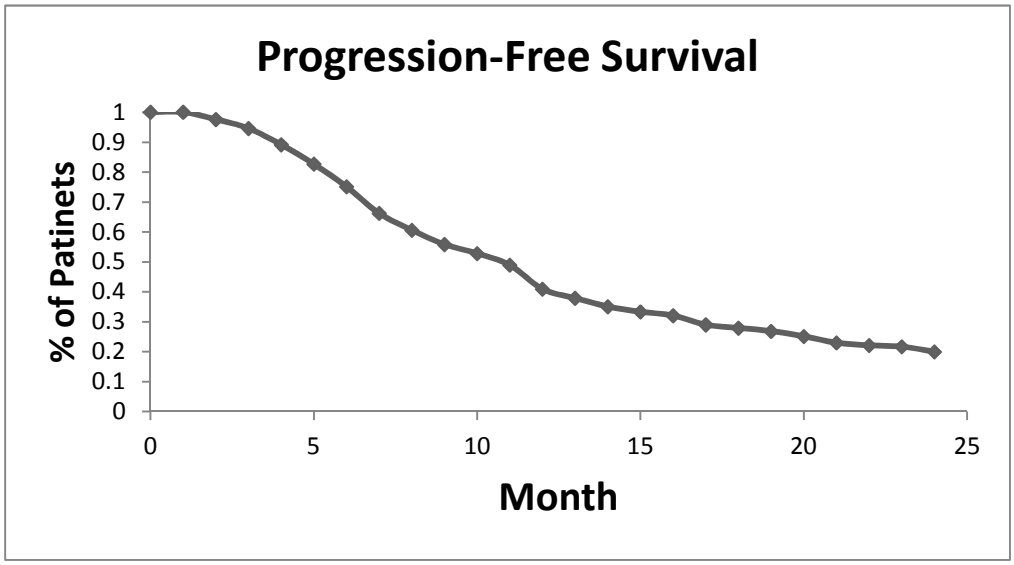
Figure 4.6: Total Monthly Costs in Months 16 to 22 of Best Supportive Care



4.1.3 Survival Analyses

The progression-free survival estimate for patients receiving first-line bevacizumab and FOLFIRI was determined from the analysis of the patient-level data. In this cohort the median PFS was found to be approximately 10.5 months (see Figure 4.7). The monthly transition probabilities derived from this PFS data can be found in Table 9.3.

Figure 4.7: Progression-Free Survival of the 1216 Patients Receiving First-Line Bevacizumab + FOLFIRI



Parametric regression was used to fit Weibull distributions to the PFS and OS curves determined from the patient level data and respective clinical trials. The estimated Weibull shape and scale parameters are reported in Table 4.2. Using the scale and shape parameters found from the regression PFS and OS were extrapolated until there were no more patients in each state. The Weibull distributions which were fit to the Kaplan-Meier curves for the PFS estimates for patients receiving first-line panitumumab plus FOLFIRI, and the OS estimate for patients receiving best supportive care, did not fit the data as closely as the distributions for Kaplan-Meier curves for the other treatment options. This lack of fit may be due to the high number of censored cases in these two trials. The two Weibull distributions were used to determine the monthly transition probabilities as they facilitated the hazard rate of progressing to differ over time. Graphs comparing the in-trial and Weibull-estimated survival curves estimates were then constructed (Figure 4.8-4.13).

Table 4.2: Shape and Scale Parameters Determined from Weibull Regression

Treatment	Weibull Shape (β)	Weibull Scale (σ)
Bevacizumab + FOLFIRI	1.3426	16.4469
Cetuximab + FOLFIRI	1.5963	16.4864
Panitumumab + FOLFIRI	1.563	15.8595
Third Line Panitumumab	1.4249	22.6985
Best Supportive Care	1.2827	10.8512

Figure 4.8: Comparison of Observed and Weibull Fitted PFS Estimates for Patients Receiving First-Line Bevacizumab + FOLFIRI

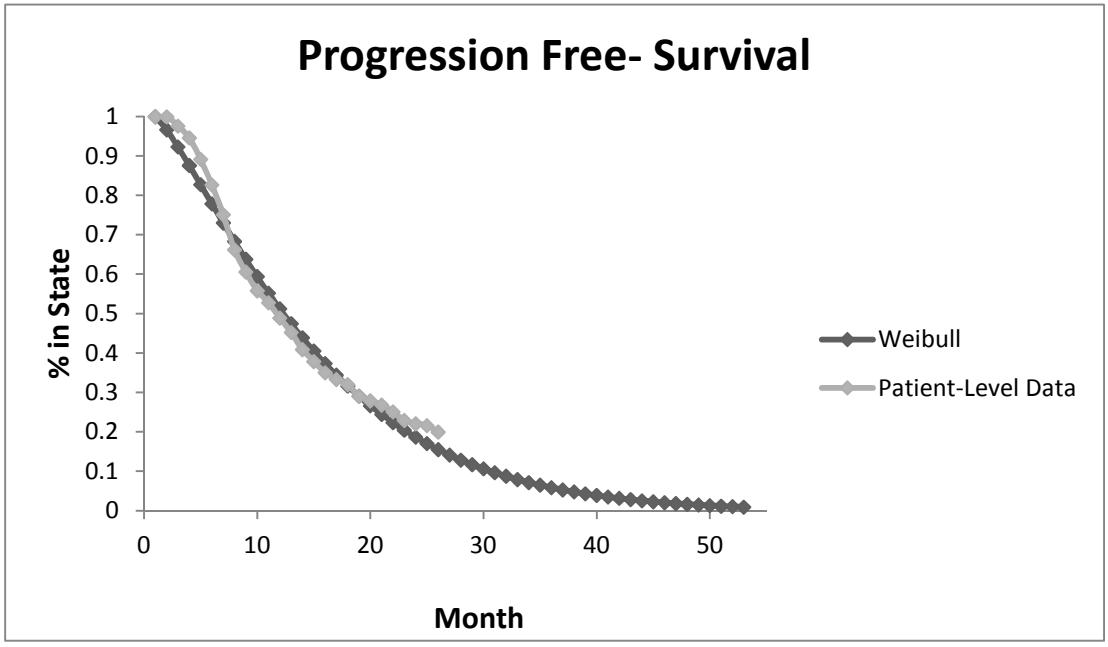


Figure 4.9: Comparison of Reported Clinical Trial and Weibull Fitted PFS Estimates for Patients Receiving First-Line Cetuximab + FOLFIRI

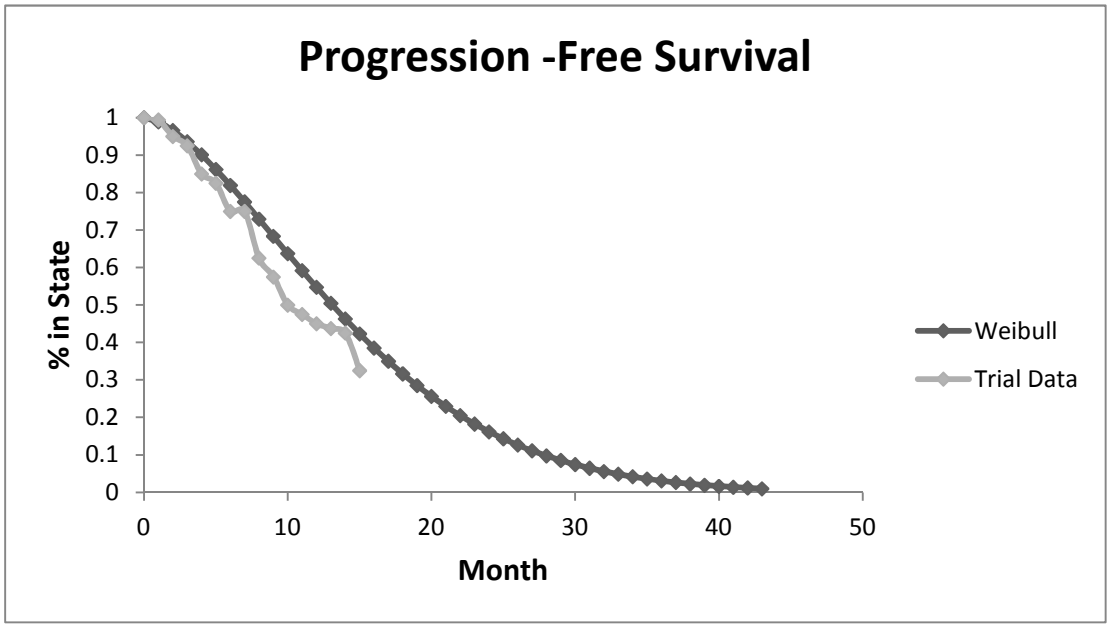


Figure 4.10: Comparison of PFS Estimates for Patients Receiving First-Line Panitumumab + FOLFIRI

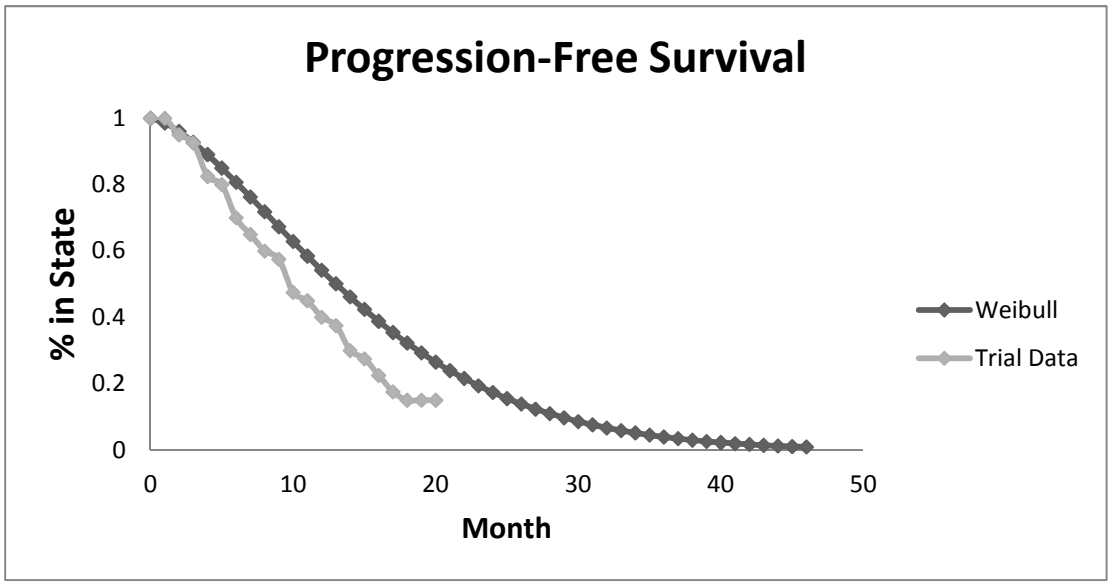


Figure 4.11: Comparison of PFS Estimates for Patients Receiving Second-Line FOLFOX

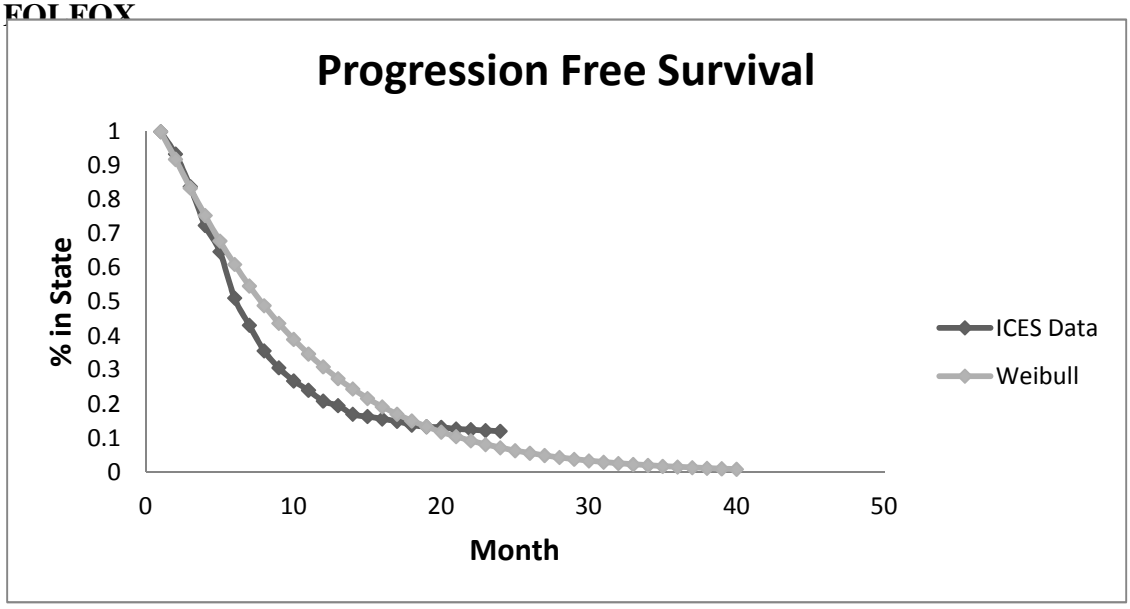


Figure 4.12: Comparison of PFS Estimates for Patients Receiving Third-Line Panitumumab

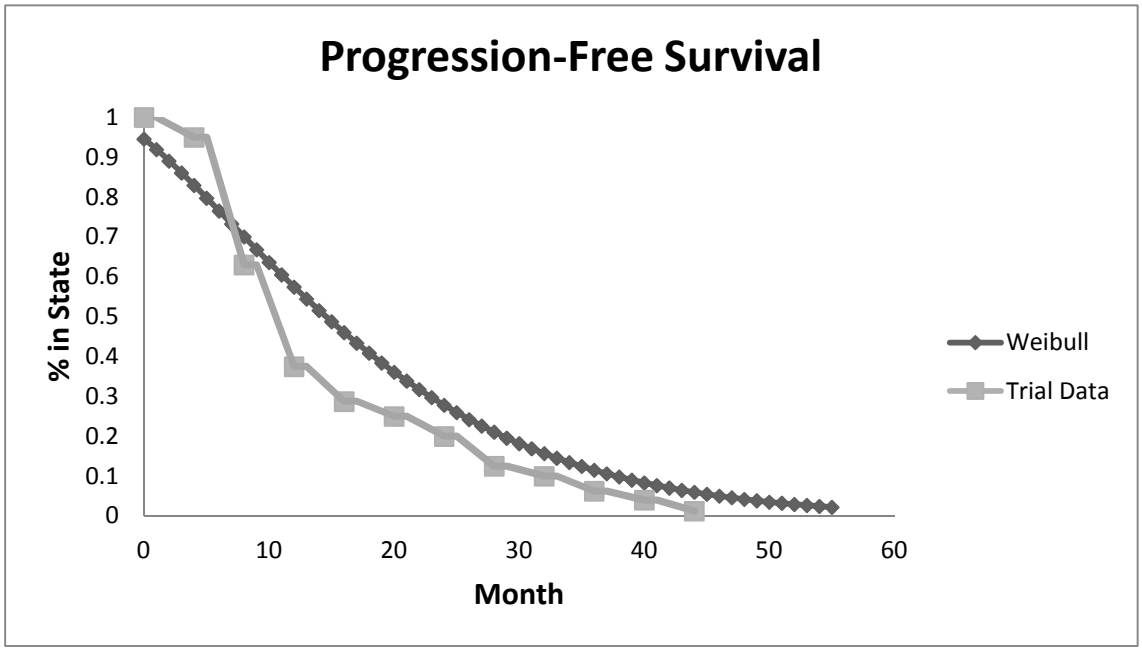
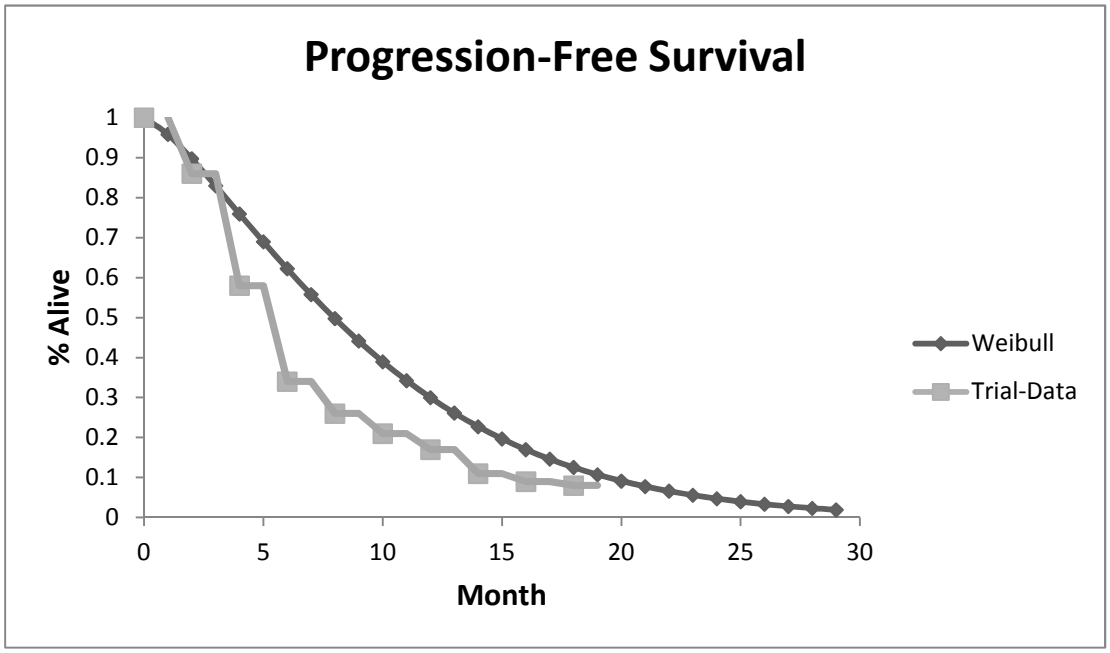


Figure 4.13: Comparison of OS Estimates for Patients Receiving Best-Supportive Care



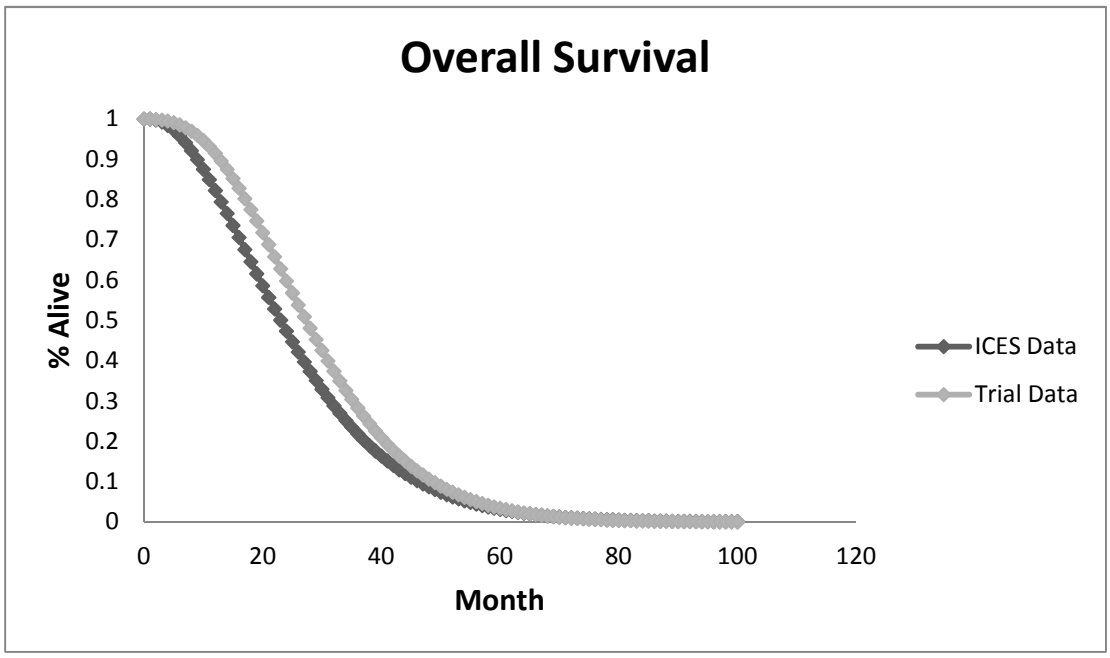
4.2 The Comparison of Patient-Level Data and Clinical Trial Data Parameterized Models

I compared the results of the Markov cohort simulation results for Model M1 when it was parameterized with transition probabilities from the patient-level data. When the PFS and OS estimates from the 1216 patients in the cohort of interest were used to determine the monthly transition probabilities, it resulted in a median overall survival of 23 months, with 1.56 QALYs at a cost of $148,528 for patients receiving first-line bevacizumab plus FOLFIRI.

These results were compared to the results found in the model which was used in the cost-effectiveness analyses where the monthly transition probabilities for first-line treatment were determined from the patient-level data, and the probabilities for all subsequent lines of treatment were determined from the PFS and OS estimates published in the clinical trials. When the model was parameterized with data from the ICES data as well as RCT's, the median overall survival was 27 months with the average patients surviving of 1.75 QALYs on average at a cost of $150,573. A graph of the overall

survival curves generated by the patient-level data and the clinical trial data in parameterized models are presented in Figure 4.14.

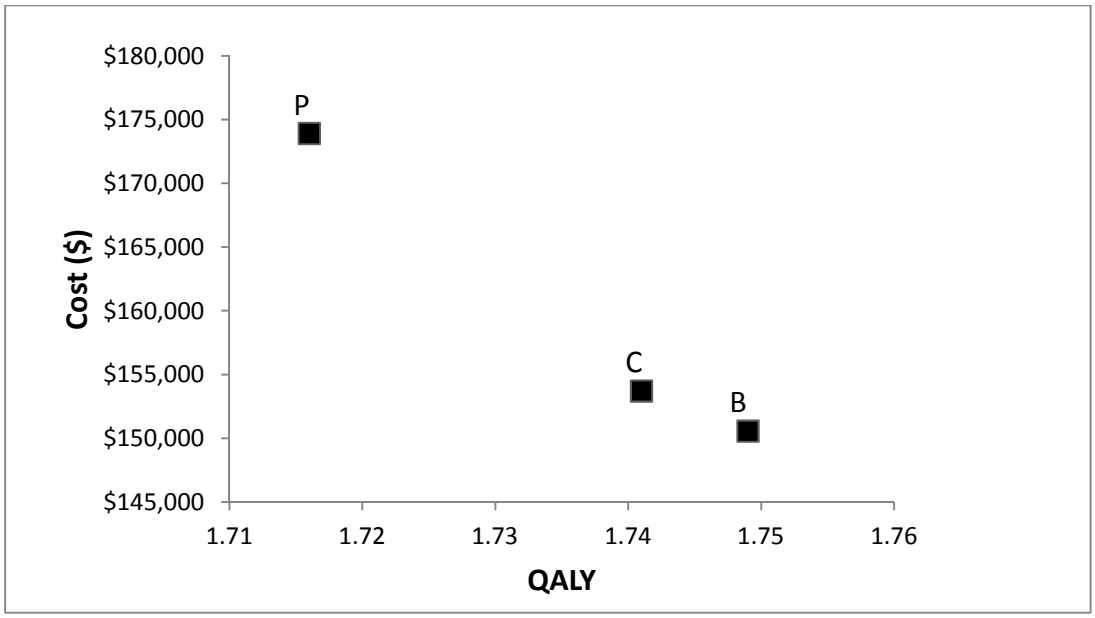
Figure 4.14: Comparison of the Overall Survival Curves Generated When Model M1 Was Parameterized With Patient-Level and Randomized Clinical Trial Data.



4.3 Base Case

In the base case, treatment consisting of bevacizumab plus FOLFIRI dominated treatment consisting of cetuximab plus FOLFIRI and treatment consisting of panitumumab plus FOLFIRI. Treatment with panitumumab plus FOLFIRI resulted in an incremental deficit of 0.034QALYs at an incremental cost of $23,359 when compared to treatment with bevacizumab plus FOLFIRI, while treatment consisting of cetuximab and FOLFIRI resulted in an incremental deficit of 0.008QALYs at an incremental cost of $3,159 when compared to treatment with bevacizumab and FOLFIRI.

Figure 4.15: The Results Displayed on the Cost-Effectiveness Plane



*Note B= Bevacizumab + FOLFIRI, C= Cetuximab + FOLFIRI, P=Panitumumab + FOLFIRI

Table 4.3: Results of the Base Case Analysis

Treatment	Cost	QALY	ICER
Bevacizumab + FOLFIRI	$150,572.08	1.749	
Cetuximab + FOLFIRI	$153,730.63	1.741	Dominated
Panitumumab + FOLFIRI	$173,930.64	1.716	Dominated

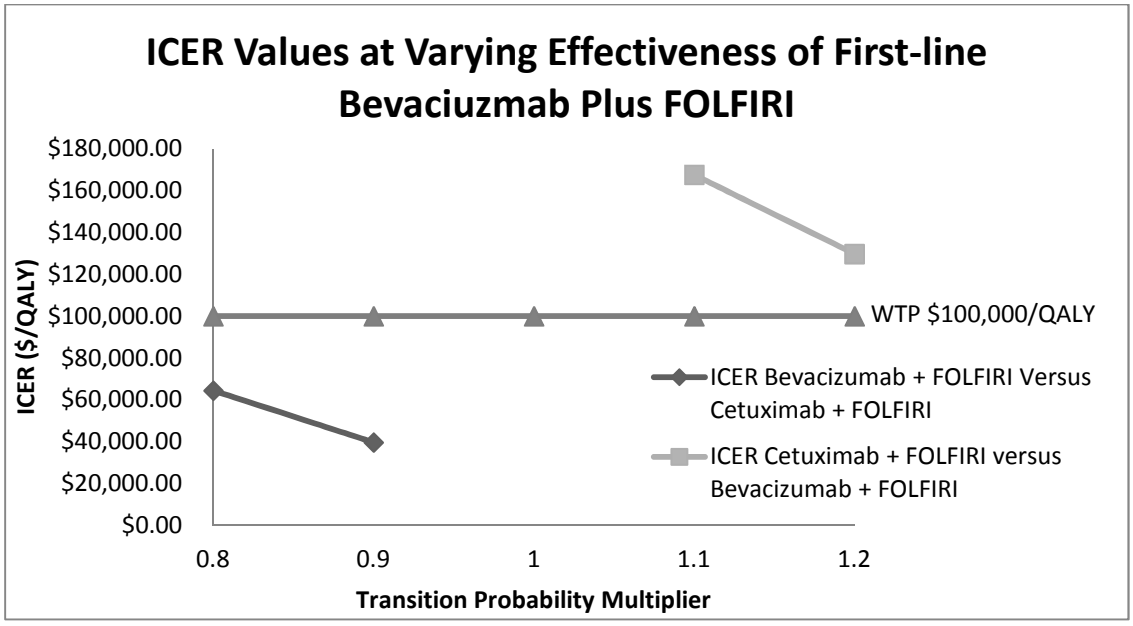
4.4 Deterministic Sensitivity Analysis

I conducted one-way deterministic sensitivity analyses on the majority of the parameters using a range of ±20% to examine their effect on the resultant ICERs. From these analyses it was seen that the results are sensitive to changes in the transition probabilities, the cost of bevacizumab and monthly cetuximab, and health utility values.

Changes to the monthly transition probabilities for patients receiving first-line bevacizumab, cetuximab, and panitumumab resulted in some dramatic changes to the final ICER values. When the monthly transition probabilities for patients receiving

bevacizumab plus FOLFIRI were decreased (i.e. treatment was more effective), treatment with bevacizumab and FOLFIRI became more costly and more effective than treatment with cetuximab plus FOLFIRI. Decreases of 10% and 20% resulted in ICER values of $39,539/QALY and 64,343/QALY respectively when compared to treatment with cetuximab and FOLFIRI (Figure 4.16). Ten and twenty percent increases in the transition probabilities (treatment being less effective) of treatment with bevacizumab and FOLFIRI resulted in treatment with cetuximab and FOLFIRI being the most effective treatment strategy. However, in these scenarios the ICER values of treatment with cetuximab plus FOLFIRI were both found to be greater than $100,000/QALY when compared to bevacizumab and FOLFIRI (Figure 4.16).

Figure 4.16: The Results of the Deterministic Sensitivity Analysis on the Effectiveness of Treatment with First-Line Bevacizumab Plus FOLFIRI

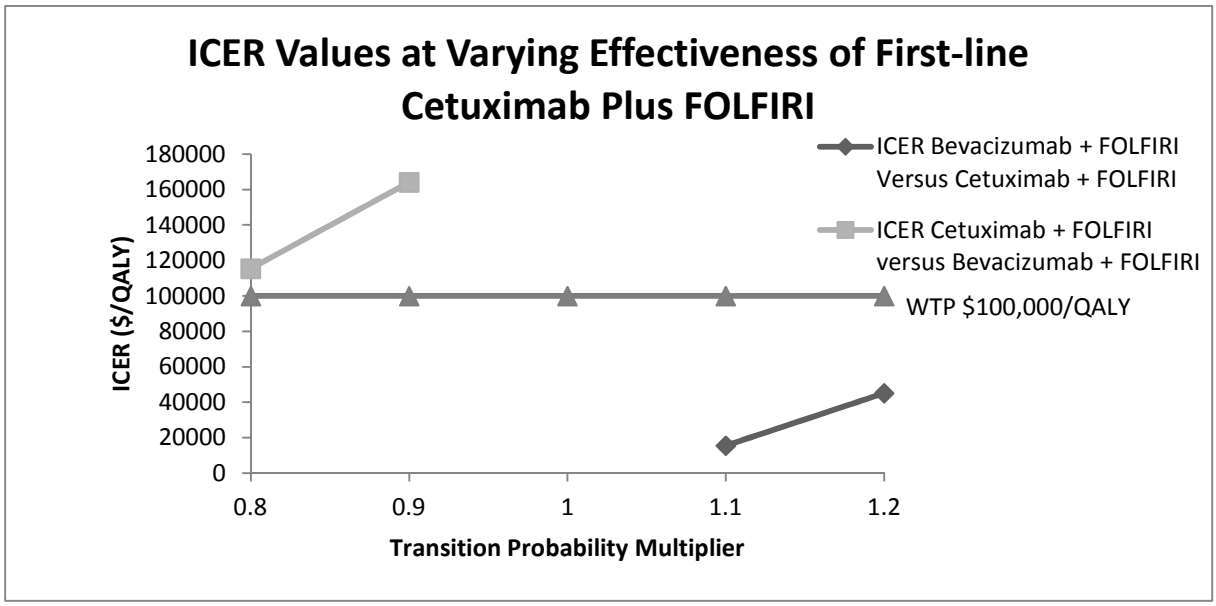


*Note: There are no ICER values for treatment the ICER generated for bevacizumab plus FOLFIRI versus cetuximab plus FOLFIRI for transition probability multipliers greater than 0.9 as past this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.
* Note: There are no ICER values for treatment the ICER generated for cetuximab plus FOLFIRI versus cetuximab plus FOLFIRI for transition probability multipliers less than 1.1 as before this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.

A similar pattern occurred when the monthly transition probabilities of first-line treatment with cetuximab plus FOLFIRI were altered. When the transition probabilities

were decreased, treatment with cetuximab and FOLFIRI became more costly and more effective than treatment with first-line bevacizumab plus FOLFIRI, however this resulted in ICER values of greater than $100,000/QALY. A decrease in the monthly transition probabilities of 10% resulted in an incremental gain of 0.048 QALYS at an incremental cost of $7,797 resulting in an ICER value of $164,127/QALY while a decrease of 20% resulted in an incremental gain of 0.11 QALYS at an incremental cost of $13,200 for an ICER value $115,449/QALY (Figure 4.17).

Figure 4.17: The Results of the Deterministic Sensitivity Analysis on the Effectiveness of Treatment with First-Line Cetuximab Plus FOLFIRI

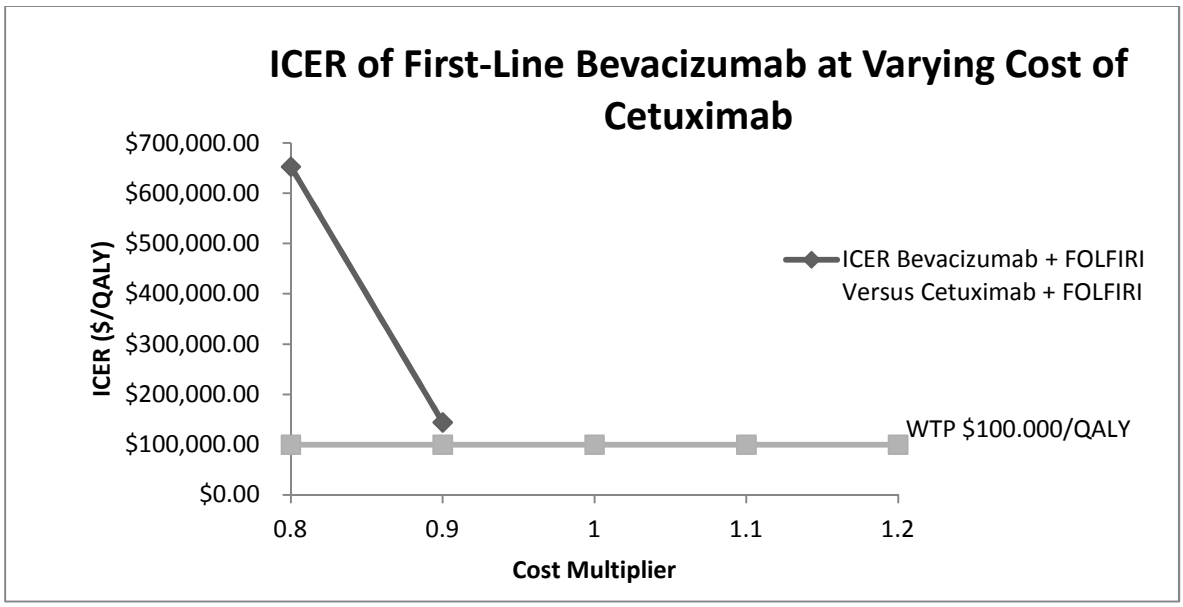


*Note: There are no ICER values for treatment the ICER generated for bevacizumab plus FOLFIRI versus cetuximab plus FOLFIRI for transition probability multipliers less than 1.1 as before this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.
* Note: There are no ICER values for treatment the ICER generated for cetuximab plus FOLFIRI versus cetuximab plus FOLFIRI for transition probability multipliers greater than 0.9 as beyond this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.

Decreases in the transition probabilities of patients receiving first-line panitumumab plus FOLFIRI resulted in this treatment option being the most costly and most effective treatment strategy of all three options, however it resulted in ICER values that were well over $100,000/QALY when compared to treatment with bevacizumab plus FOLFIRI.

The cost of cetuximab had dramatic effects on the final ICER values. As the cost of cetuximab increased treatment with bevacizumab plus FOLFIRI retained its dominance, however as this cost of cetuximab decreased it became the most cost-effective option, becoming less costly than treatment with bevacizumab plus FOLFIRI. When the cost of cetuximab was decreased by 10% it resulted in bevacizumab and FOLFIRI having an ICER value of $144,204/QALY when compared to treatment with cetuximab and FOLFIRI. This ICER value then increased to $652,855/QALY when the cost of cetuximab decreased 20% (Figure 4.18).

Figure 4.18: The Results of the Deterministic Sensitivity Analysis on the Cost of Cetuximab.

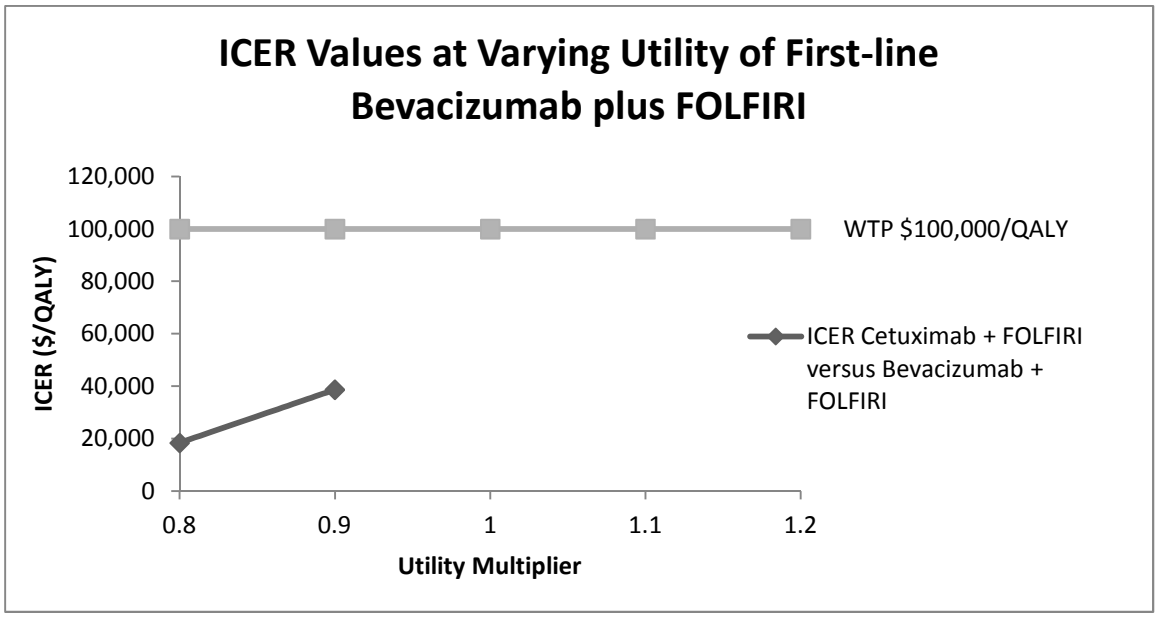


*Note: There are no ICER values for treatment the ICER generated for bevacizumab plus FOLFIRI versus cetuximab plus FOLFIRI for transition probability multipliers greater than 0.9 as past this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.

Changes in the health utility values of patients receiving first line bevacizumab or cetuximab plus FOLFIRI also had an effect on the resultant ICER values. When the utility value for patients receiving bevacizumab and FOLFIRI were decreased it resulted in treatment with cetuximab and FOLFIRI becoming a cost-effective treatment option. When the quality-of-life value was decreased by 10% it resulted in cetuximab having an

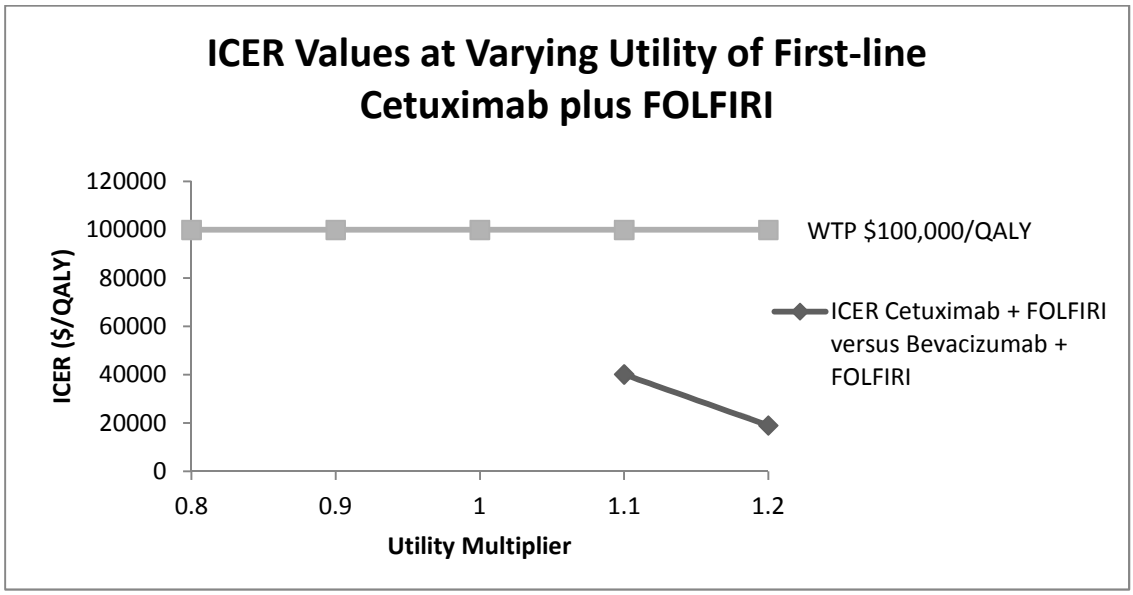
incremental gain of 0.082 QALYS resulting in an ICER $38,677/QALY. When this value was decreased by 20% the incremental effect of cetuximab and FOLFIRI increased to 0.172 QALY, resulting in the ICER value dropping to $18,373/QALY (Figure 4.19). Increases in the utility value of patients receiving cetuximab plus FOLFIRI had a similar result, with an increase in utility by 10% resulting in an incremental gain of 0.079 QALY resulting in and ICER of $40,194/QALY, and an increase of 20% resulting in an incremental gain of 0.166 QALY and an ICER of $19.037/QALY (Figure 4.20).

Figure 4.19: The Results of the Deterministic Sensitivity Analysis on the Utility of First-Line Bevacizumab Plus FOLFIRI.



*Note: There are no ICER values for treatment the ICER generated for cetuximab plus FOLFIRI versus bevacizumab plus FOLFIRI for transition probability multipliers greater than 0.9 as past this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.

Figure 4.20: The Results of the Deterministic Sensitivity Analysis on the Utility of First-Line Cetuximab Plus FOLFIRI.



*Note: There are no ICER values for treatment the ICER generated for cetuximab plus FOLFIRI versus bevacizumab plus FOLFIRI for transition probability multipliers less than 1.1 as before this point treatment bevacizumab plus FOLFIRI is the dominant treatment option.

I conducted two-way sensitivity analyses on the effectiveness and the monthly cost of cetuximab and panitumumab. Treatment consisting of cetuximab plus FOLFIRI became the dominant treatment option when the monthly transition probabilities were decreased by 5% and the monthly cost was reduced by 15%. The ICER for treatment with cetuximab plus FOLFIRI fell below the $100,000/QALY willingness-to-pay threshold when the monthly transition probabilities were decreased by 5% and monthly cost were reduced by 10% (Figure 4.21). Treatment consisting of panitumumab plus FOLFIRI became the dominant treatment option when the monthly transition probabilities were decreased by 10% and monthly cost of panitumumab was decreased by 50%. The ICER value fell below $100,000/QALY when the monthly transition probabilities were decreased by 10% and costs were decreased by 45% (Figure 4.22).

Figure 4.21: Results of Two-Way Sensitivity Analyses on the Effectiveness of First-Line Cetuximab plus FOLFIRI and the Monthly Cost of Cetuximab

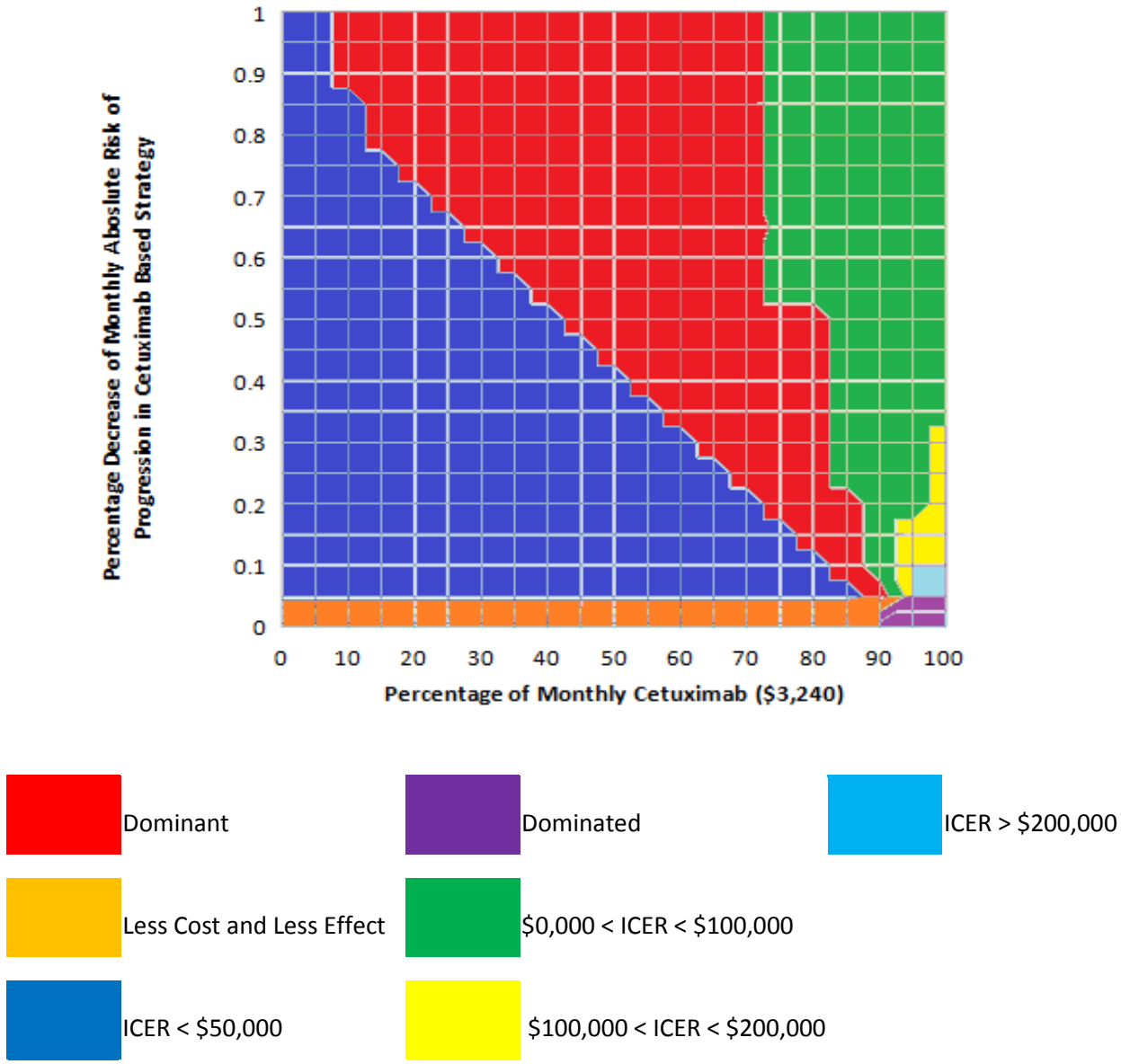


Figure 4.22: Results of Two-Way Sensitivity Analyses on the Effectiveness of First-Line Panitumumab plus FOLFIRI and the Monthly Cost of Panitumumab

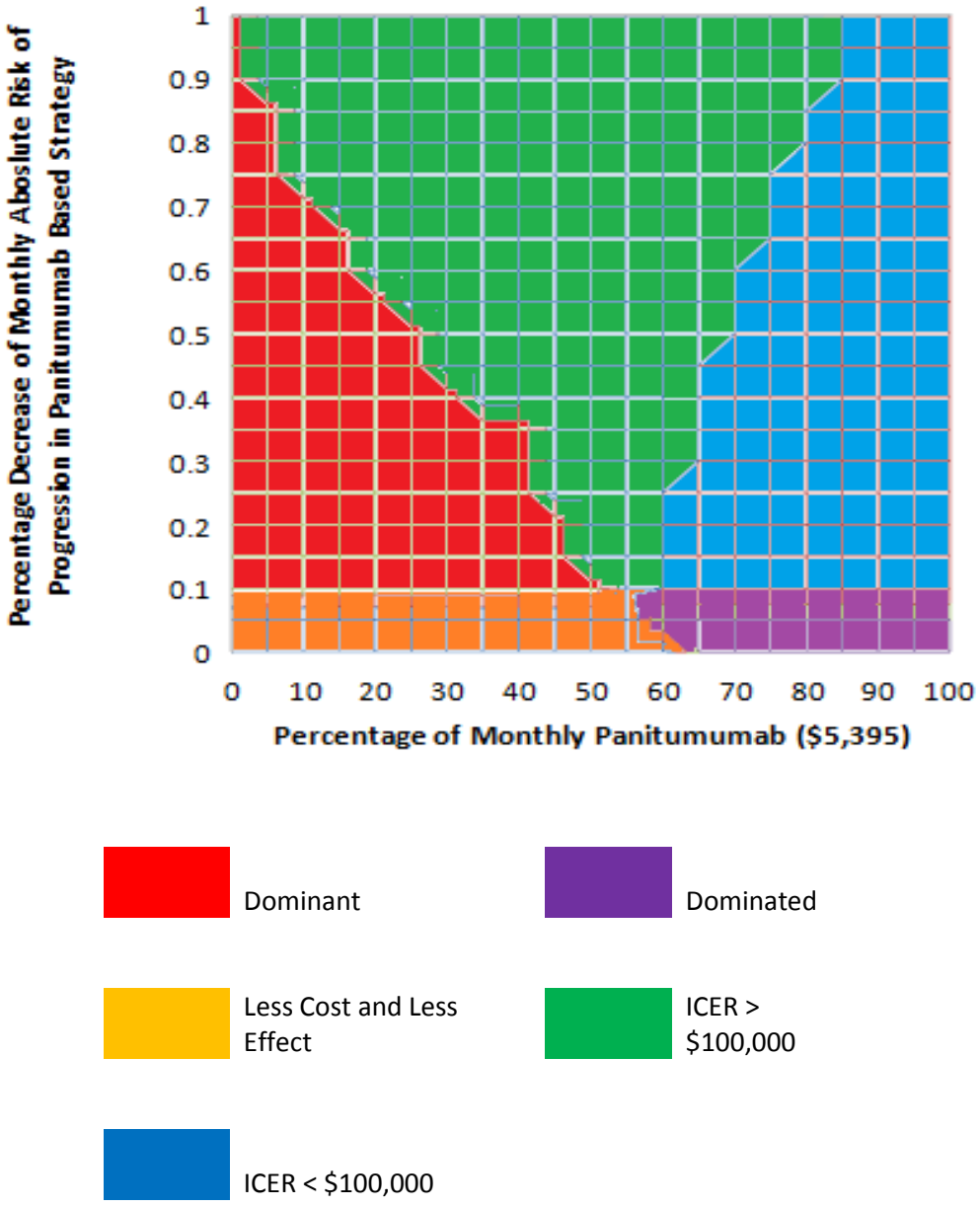


Table 4.4: Results of One-Way Deterministic Sensitivity Analyses.

Variable	Value Multiplier	Strategy	Cost	Incr. Cost	Effectiveness (QALY)	Incr. Effectiveness (QALY)	ICER ($/QALY)
Effectiveness of 1st Line Bevacizumab+ FOLFIRI	0.8	Cetuximab + FOLFIRI	$153,731		1.741		
		Bevacizumab + FOLFIRI	$164,288	$10,557	1.905	0.164	$64,342
	0.9	Cetuximab + FOLFIRI	$153,731		1.741		
		Bevacizumab + FOLFIRI	$156,864	$3,133	1.820	0.079	$39,539
	1.1	Bevacizumab + FOLFIRI	$145,151		1.689		
		Cetuximab + FOLFIRI	$153,731	$8,579	1.741	0.051	$167,676
	1.2	Bevacizumab + FOLFIRI	$140,418		1.638		
		Cetuximab + FOLFIRI	$153,731	$13,313	1.741	0.103	$129,778
Effectiveness of 1st Line Cetuximab+ FOLFIRI	0.8	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$163,772	$13,200	1.864	0.114	$115,448
	0.9	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$158,368	$7,796	1.797	0.048	$164,127
	1.1	Cetuximab + FOLFIRI	$149,688		1.692		
		Bevacizumab + FOLFIRI	$150,572	$884	1.749	0.057	$15,553

Variable	Value Multiplier	Strategy	Cost	Incr. Cost	Effectiveness (QALY)	Incr. Effectiveness (QALY)	ICER ($/QALY)
	1.2	Cetuximab + FOLFIRI	$146,120		1.651		
		Bevacizumab + FOLFIRI	$150,572	$4,452	1.749	0.099	$45,160
Effectiveness of 1st Line Panitumumab+ FOLFIRI	0.8	Bevacizumab + FOLFIRI	$150,572		1.749		
		Panitumumab + FOLFIRI	$187,931	$37,359	1.836	0.087	$428,587
	0.9	Bevacizumab + FOLFIRI	$150,572		1.749		
		Panitumumab + FOLFIRI	$180,385	$29,813	1.771	0.022	$1,375,996
Effectiveness of 2nd Line FOLFOX	0.8	Cetuximab + FOLFIRI	$153,731		1.741		
		Bevacizumab + FOLFIRI	$154,036	$305	1.791	0.051	$6,037
	1.1	Bevacizumab + FOLFIRI	$149,258		1.734		
		Cetuximab + FOLFIRI	$153,731	$4,473	1.741	0.007	$654,587
	1.2	Bevacizumab + FOLFIRI	$148,132		1.721		
		Cetuximab + FOLFIRI	$153,731	$5,598	1.741	0.020	$283,460
Effectiveness of 2nd Line FOLFOX + Bevacizumab	0.8	Bevacizumab + FOLFIRI	$150,572		1.749		

		Cetuximab + FOLFIRI	$160,697	$10,125	1.791	0.042	$242,027

Variable	Value Multiplier	Strategy	Cost	Incr. Cost	Effectiveness (QALY)	Incr. Effectiveness (QALY)	ICER ($/QALY)
Percentage who move to 2nd Line after 1st Line	0.9	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$156,857	$6,285	1.763	0.014	$454,319
	1.2	Cetuximab + FOLFIRI	$148,905		1.706		
		Bevacizumab + FOLFIRI	$150,572	$1,667	1.749	0.043	$38,850
	0.8	Cetuximab + FOLFIRI	$155,130		1.781		
		Bevacizumab + FOLFIRI	$157,595	$2,465	1.833	0.051	$48,012
	1.1	Bevacizumab + FOLFIRI	$147,540		1.714		
		Cetuximab + FOLFIRI	$153,018	$5,478	1.722	0.008	$650,859
	1.2	Bevacizumab + FOLFIRI	$144,765		1.682		
		Cetuximab + FOLFIRI	$152,306	$7,541	1.706	0.023	$324,338
Percentage who move to BSC after 1st Line	0.8	Bevacizumab + FOLFIRI	$155,356		1.794		
		Cetuximab + FOLFIRI	$161,458	$6,103	1.811	0.017	$353,768
Percentage who move to BSC after 2nd Line	0.8	Cetuximab + FOLFIRI	$153,731		1.741		
		Bevacizumab + FOLFIRI	$154,442	$711	1.777	0.036	$19,710

Variable	Value Multiplier	Strategy	Cost	Incr. Cost	Effectiveness (QALY)	Incr. Effectiveness (QALY)	ICER ($/QALY)
	1.1	Bevacizumab + FOLFIRI	$148,964		1.738		
		Cetuximab + FOLFIRI	$153,731	$4,767	1.741	0.003	$1,787,453
	1.2	Bevacizumab + FOLFIRI	$147,525		1.728		
		Cetuximab + FOLFIRI	$153,731	$6,205	1.741	0.013	$486,681
Cost of Bevacizumab	1.1	Cetuximab + FOLFIRI	$155,608		1.741		
		Bevacizumab + FOLFIRI	$155,859	$251	1.749	0.009	$28,980
	1.2	Cetuximab + FOLFIRI	$157,485		1.741		
		Bevacizumab + FOLFIRI	$161,146	$3,661	1.749	0.009	$422,408
Cost of Cetuximab	0.8	Cetuximab + FOLFIRI	$144,914		1.741		
		Bevacizumab + FOLFIRI	$150,572	$5,658	1.749	0.009	$652,855
	0.9	Cetuximab + FOLFIRI	$149,322		1.741		
		Bevacizumab + FOLFIRI	$150,572	$1,250	1.749	0.009	$144,204
Utility 1st Line Bevacizumab + FOLFIRI	0.8	Bevacizumab + FOLFIRI	$150,572		1.569		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.741	0.172	$18,373
	0.9	Bevacizumab + FOLFIRI	$150,572		1.659		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.741	0.082	$38,676

Variable	Value Multiplier	Strategy	Cost	Incr. Cost	Effectiveness (QALY)	Incr. Effectiveness (QALY)	ICER ($/QALY)
Utility 1st Line Cetuximab + FOLFIRI	1.1	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.828	0.079	$40,194
	1.2	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.915	0.166	$19,037
Utility 1st Line Panitumumab + FOLFIRI	1.1	Bevacizumab + FOLFIRI	$150,572		1.749		
		Panitumumab + FOLFIRI	$173,931	$23,359	1.802	0.052	$445,632
	1.2	Bevacizumab + FOLFIRI	$150,572		1.749		
		Panitumumab + FOLFIRI	$173,931	$23,359	1.888	0.138	$168,755
Utility of 2nd Line FOLFOX	0.8	Bevacizumab + FOLFIRI	$150,572		1.692		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.741	0.049	$65,013
	0.9	Bevacizumab + FOLFIRI	$150,572		1.721		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.741	0.020	$157,928
Utility of 2nd Line FOLFOX + Bevacizumab	1.1	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.772	0.023	$140,380

Variable	Value Multiplier	Strategy	Cost	Incr. Cost	Effectiveness (QALY)	Incr. Effectiveness (QALY)	ICER ($/QALY)
	1.2	Bevacizumab + FOLFIRI	$150,572		1.749		
		Cetuximab + FOLFIRI	$153,731	$3,159	1.803	0.054	$58,764

4.5 Probabilistic Sensitivity Analysis

In the probabilistic sensitivity analyses we sampled simultaneously from the distributions inputted for the monthly transition probabilities, state-dependent probabilities, utility values, and costs. From these simulations we were able to construct the cost-effectiveness (CE) scatter plot which plots the incremental cost and incremental effectiveness each simulation being compared. The CE graph for comparing patients receiving first-line cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI can be found in Figure 4.23. Treatment consisting of cetuximab plus FOLFIRI was dominant to treatment with bevacizumab and FOLFIRI in 0.4% of the cases, all of which landed in quadrant I indicating increased cost and increased effect. At a willingness-to-pay (WTP) value of $100,000/QALY 100% of these simulations lie above the threshold. This number did not change when the WTP was increased to $200,000/QALY. Treatment with cetuximab and FOLFIRI was found to be inferior in 30.1% of the simulations, while 69.1% of simulations landed in quadrant III, all of which landed above the WTP threshold (Figure 4.23). From the cost-effectiveness acceptability curve constructed from the data, it was found that at a WTP threshold of 100,000/QALY the probability that treatment with cetuximab plus FOLFIRI would be cost effective when compared to first-line treatment with bevacizumab plus FOLFIRI was 0.008%. This value remained unchanged when the WTP threshold was increased to $200,000/QALY (Figure 4.24).

Figure 4.23: Incremental Cost-Effectiveness Scatter Plot Comparing Cetuximab + FOLFIRI to Bevacizumab + FOLFIRI

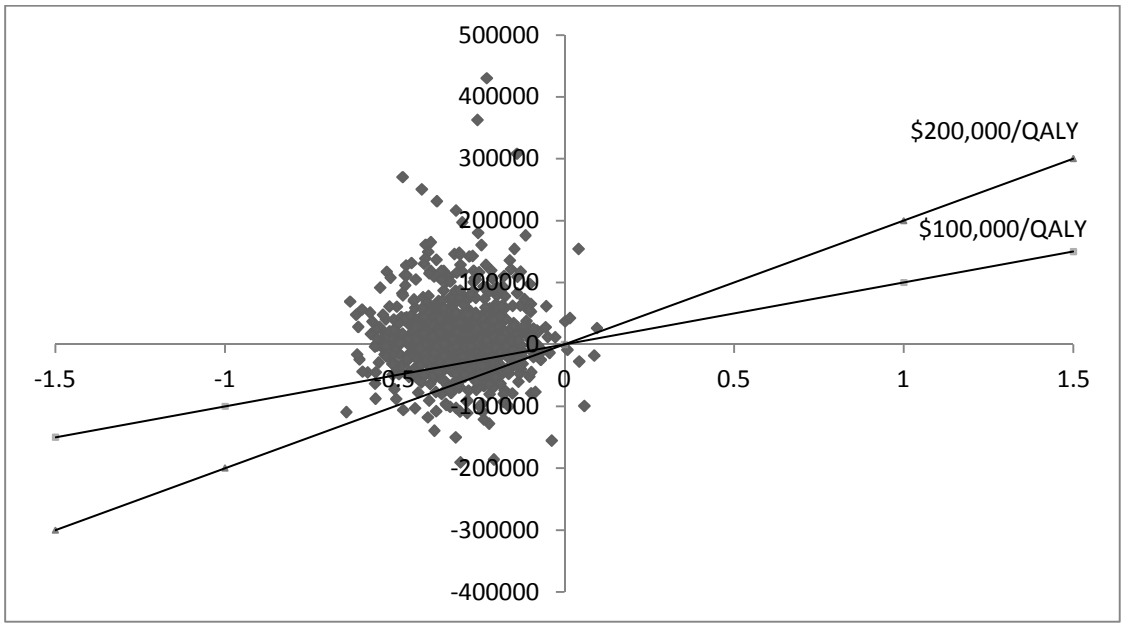
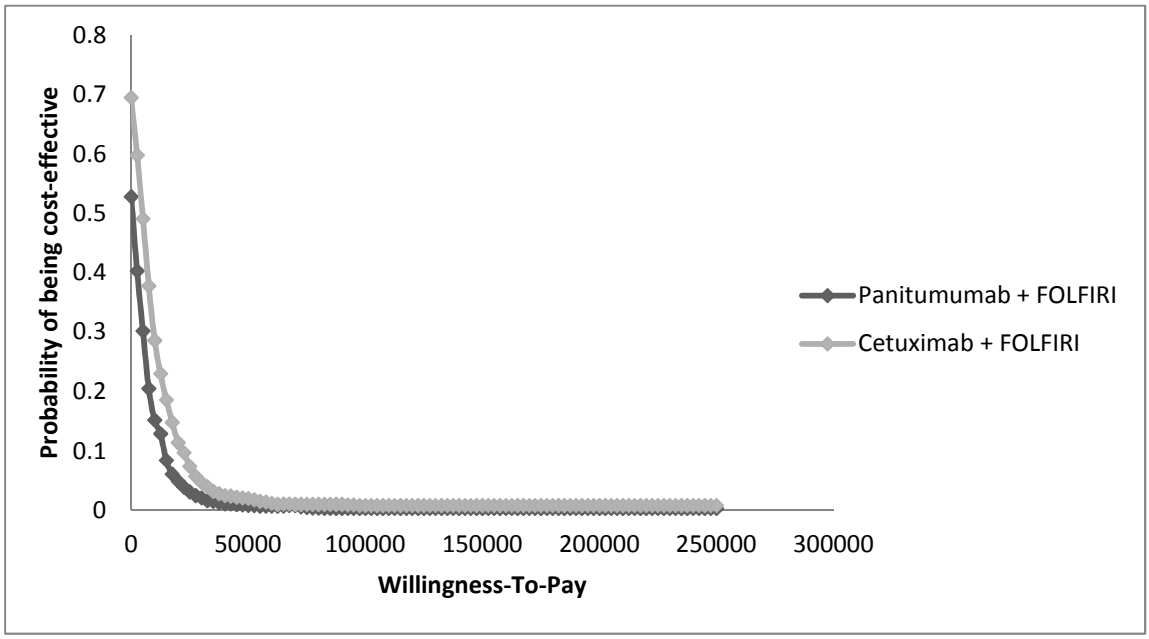
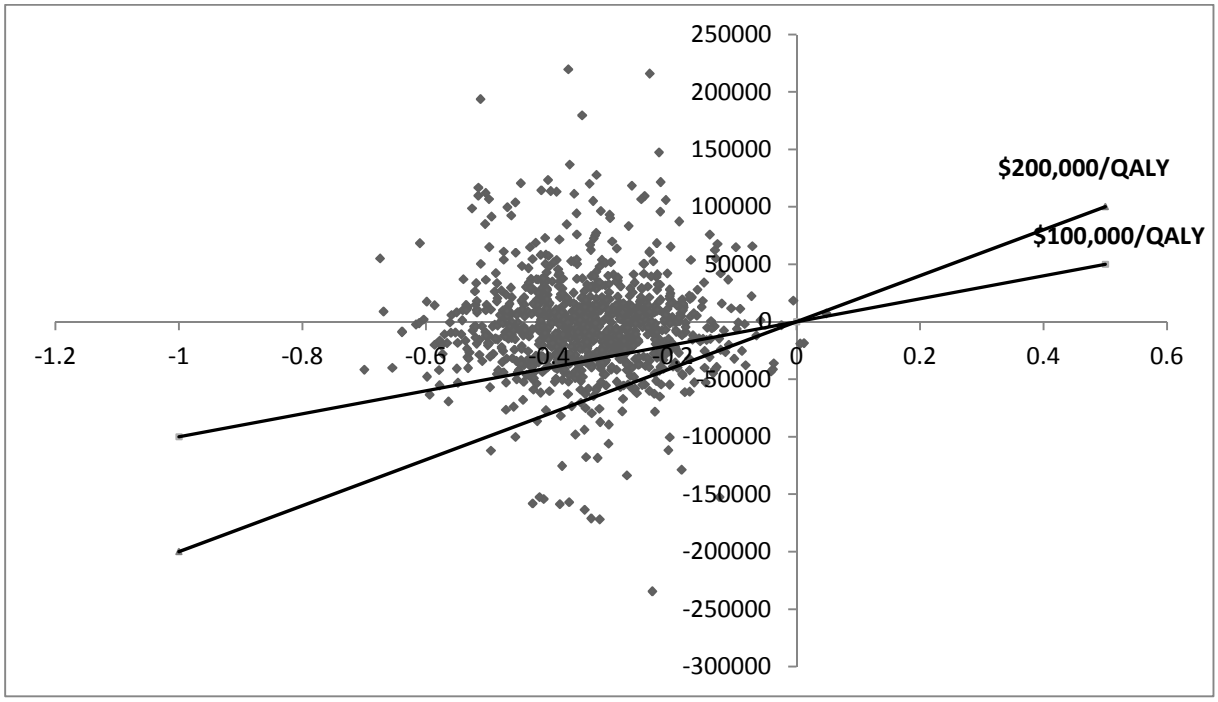


Figure 4.24: Cost-Effectiveness Acceptability Curves for First-Line Cetuximab + FOLFIRI and Panitumumab + FOLFIRI



In the ICE scatter plot comparing treatment consisting of panitumumab plus FOLFIRI was dominant to treatment with bevacizumab and FOLFIRI in 0.2% of the cases, with half of these simulations landed in quadrant I indicating increased cost and increased effect. Treatment with panitumumab and FOLFIRI was found to be inferior in 47.1% of the simulations, while 52.6% of simulations landed in quadrant III, none of which landed below the WTP threshold (Figure 4.25). These values remained unchanged when the WTP was increased to $200,000/QALY. From the cost-effectiveness acceptability curve constructed from the data, it was found that at a WTP threshold of 100,000/QALY the probability that treatment with panitumumab plus FOLFIRI would be cost effective when compared to first-line treatment with bevacizumab plus FOLFIRI was 0.03%, a value remained unchanged when the WTP threshold was increased to $200,000/QALY (Figure 4.24).

Figure 4.25: Incremental Cost-Effectiveness Scatter Plot Comparing Panitumumab + FOLFIRI to Bevacizumab + FOLFIRI



Chapter 5

5 Discussion, Limitations, and Strengths

5.1 Summary

I developed a decision analytic model composed of three Markov models, each one capturing the clinical course of patients diagnosed with metastatic colorectal cancer beginning when they first start treatment until their death. This model was conceptualized based upon the common clinical practice in the province of Ontario for patients receiving first line treatment consisting of either the current standard of care of bevacizumab with FOLFIRI, or alternate treatment consisting of either cetuximab or panitumumab in combination with the FOLFIRI chemotherapy regimen. Using this model I was able to investigate the cost-effectiveness of combination treatment consisting of panitumumab or cetuximab plus FOLFIRI versus bevacizumab plus FOLFIRI for KRAS wild-type metastatic colorectal cancer patients from the perspective of the Ontario healthcare payer.

In the base scenario combination treatment consisting of bevacizumab plus FOLFIRI was found to dominate both other treatment options. Treatment with cetuximab plus FOLFIRI was found to be very similar to treatment with bevacizumab plus FOLFIRI in terms of both cost and effect, differing in cost by less than $3,200 and a difference of only 0.008 QALY. Treatment with panitumumab plus FOLFIRI was found to be both more costly and less effective when compared to treatment with both bevacizumab plus FOLFIRI, and treatment with cetuximab plus FOLFIRI. From this result we can conclude that the current standard of care in Ontario of the use of bevacizumab plus FOLFIRI for first-line treatment of patients with metastatic colorectal cancer is the most cost-effective treatment option for these patients.

After completing one-way deterministic sensitivity analyses these ICER values were determined to be sensitive towards the each first-line treatment's monthly transition probabilities (i.e treatment effectiveness), the acquisition cost of bevacizumab and cetuximab, and the health utility values associated with the first-line treatments. The results of probabilistic sensitivity analysis which tested for uncertainty in all model

parameters found that the use of cetuximab plus FOLFIRI was a superior treatment option to bevacizumab plus FOLFIRI less than 0.4% of the time, and of these cases all of them fell above the willingness-to-pay threshold of $100,000/QALY. Probabilistic sensitivity analysis also showed that treatment with panitumumab plus FOLFIRI was almost always inferior treatment with bevacizumab and FOLFIRI with treatment consisting of panitumumab found to be superior in only 0.2% of simulations.

5.2 Discussion

From this analysis we can conclude that for KRAS wild-type patients with metastatic colorectal cancer the current standard of care consisting of combination treatment with bevacizumab plus FOLFIRI in the first-line represents the most-cost effective treatment option when compared to the other monoclonal antibody plus chemotherapy regimens which are currently available. In Ontario both cetuximab and panitumumab are only prescribed for patients who are found to be KRAS-WT only. The use of cetuximab as a monotherapy is currently used in second-line treatment and in third-line settings in combination with irinotecan while panitumumab monotherapy is currently used in third line treatment [58]. From our analysis we can conclude that in terms of value-for-money these treatment guidelines represent the most cost-effective use of these treatments.

Treatment consisting of bevacizumab and FOLFIRI was found to dominate treatment consisting of panitumumab and FOLFIR in the base case scenario. Over the course of undertaking deterministic sensitivity analysis, certain situations arose where treatment with panitumumab plus FOLFIRI no longer became dominated, however in each of these scenarios the resultant ICERs fell well above the $100,000/QALY threshold which is indicative of “weak evidence for adoption” in Canada [106]. Based on the analysis I can conclude that given that this treatment should not be considered for use in the first line.

In the base case analysis treatment with cetuximab and FOLFIRI was found to be more costly and less effective than treatment with bevacizumab, however both the cost and effect of treatment with cetuximab plus FOLFIRI only differed slightly from that of treatment with bevacizumab plus FOLFIRI. The difference in cost of the two treatments was only $3,159 with the difference in effect being only 0.008 QALY. From these results

it looks as though treatment with cetuximab and FOLFIRI is almost equivalent to treatment with bevacizumab and FOLFIRI. In deterministic sensitivity analysis there were scenarios where treatment consisting of cetuximab plus FOLFIRI was the most cost-effective treatment option, or when this combination treatment was found to have ICER values under the $100,000/QALY willingness-to-pay threshold. This was the case when either the utility of patients receiving bevacizumab plus FOLFIRI decreased or when the utility of patients receiving cetuximab plus FOLFIRI increased. Under these scenarios treatment with cetuximab and FOLFIRI was found to have ICER values ranging between $18,373/QALY to $40,194/QALY.

The results of this analysis differ from the results found in two previous cost-effectiveness analyses that looked at the use of cetuximab and FOLFIRI compared to bevacizumab and FOLFOX [76, 77]. In the study by Asseburg et al, cetuximab and FOLFIRI was found to have an ICER €15,020/LY, while Samyshkin et al found a value of £28,626/QALY. One possible reason for the difference in these estimates is due to the fact that these analyses looked at bevacizumab with FOLFOX, a regimen which is much more expensive than FOLFIRI due to the increased cost of oxaliplatin, as well as differences in the utility values used. The use of FOLFOX in these analyses would have resulted in an increased cost of the total combination treatment, thus resulting in a smaller incremental cost of the use of cetuximab and FOLFIRI and thus lower ICER values. The differences in this analysis may be due to the cause of different modeling assumptions, model structure and extrapolation methods, and data sources.

5.3 Limitations

We recognize that there are several limitations in this study. Firstly, the same quality-of-life value was used for both patients receiving first-line cetuximab plus FOLFIRI and bevacizumab and FOLFIRI. A literature review resulted in these values, however given the inherent differences of bevacizumab and cetuximab it is fair to assume that the utility values for patients receiving these treatments may not be the same in reality. Given the role that quality-of-life was found to play on the resultant ICER through probabilistic

sensitivity analysis, the use of the same health utility values for both treatments may have led to an over/underestimation of the final effectiveness value and therefore affected the final ICERs. Further research should be done to find definitive health utility values for patients receiving bevacizumab or cetuximab along with FOLFIRI in the first-line treatment to facilitate a more accurate approximation of the ICER.

Secondly, given a restriction of the information provided in the ECOG3200 RCT[90] we were unable to use parametric methods to fit a weibull distribution to the PFS curves for patients receiving second line treatment consisting of either FOLFOX or combination FOLFOX and bevacizumab. Due to this patient PFS outside of the course of the clinical trial was extrapolated using the average of the last four months of the trial data. We do not expect this to have a significant impact on the results of the model as in the clinical trials the majority of patients had progressed by the end of the trial window.

From the patient-level data I was able to determine an estimate of PFS for patients receiving second-line FOLFOX, however we did not have patient-level data for patients receiving second-line FOLFOX plus bevacizumab. When the PFS data found from the patient-level data and from the clinical trials were compared it was found that the PFS from the patient-level data was greater than that found in the clinical trials. Given that the ECOG3200 clinical had found that treatment with FOLFOX and bevacizumab was more effective than treatment with FOLFOX alone and given the treatment course of patients receiving each possible first-line combination treatment it was not plausible to use the patient-level second line data in the bevacizumab plus FOLFIRI model and the clinical trial data for the cetuximab plus FOLFIRI and panitumumab plus FOLFIRI arms as this would bias the final cost and effectiveness.

Thirdly, only an approximate cost was used in this analysis for fluorouracil and leucovorin which are used in the FOLFIRI and FOLFOX regimens due to confidentiality in pricing issues. Due to the fact that these two drugs were used in each treatment option we do not expect this to have any effect on the final results.

Finally, the cost estimates for patients in the best-supportive care state may not fully capture the costs of providing treatment as there may be some aspects of providing best-

supportive care that may not have been fully captured in the patient-level data. Given that the cost values used for the BSC state were constant in all three treatment strategies we do not expect this to have an effect on the final ICER values.

5.4 Strengths

To our knowledge this is the first project to examine the cost-effectiveness of the use of panitumumab and FOLFIRI in first-line treatment for patients with metastatic colorectal cancer, as well as the first study to investigate the use of cetuximab plus FOLRIRI and panitumumab plus FOLFIRI treatment options in first-line use for patients with MCRC in the province of Ontario.

Our study was able to conduct OS and PFS survival analyses using patient-level data of individuals who received first-line bevacizumab plus FOLFIRI in the province of Ontario. Using information on treatment line and the date each treatment was received, a PFS curve was able to be constructed from which monthly transition probabilities were eventually derived. The use of the NDFP database, along with the OHIP, HCD, CIHI-DAD, NACRS, and ODB databases also allowed for the determination of monthly state-dependent healthcare utilization costs. This allowed for a more representative portrayal of the costs incurred by the health care payer in Ontario for patients diagnosed with MCRC from first-line treatment until death. This analysis may play an important role in helping inform health care decision makers on future discussions as to whether to expand the number of options for first-line treatment of MCRC by adding cetuximab plus FOLFIRI or panitumumab plus FOLFIRI to their provincial formularies. This analysis may also give an ideal on potential budget impact.

6 Conclusion

We conducted a cost-effectiveness analysis examining both cetuximab plus FOLFIRI, and panitumumab plus FOLFIRI compared to bevacizumab plus FOLFIRI using patient-level data from administrative databases in the province of Ontario as well as relevant published data from randomized clinical trials. In the base case scenario treatment with bevacizumab and FOLFIRI was found to dominate both other treatment options. The

ICER value for cetuximab and FOLFIRI was very sensitive and fell well below the $100,000/QALY threshold when the utility value of first line cetuximab plus FOLFIRI increased by 10% or the utility of bevacizumab plus FOLFIRI decreased by 10%. The utility of patients receiving these treatments in first-line therapy should be further investigated to improve the estimate of cost-effectiveness. This economic evaluation will help guide decision makers with reimbursement and policy decisions in light of the available information.

7 References or Bibliography

References

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8 Appendices

Appendix A: Economic Evaluation in Healthcare

A.1 What is an Economic Evaluation?

The use of economic evaluation in health care sector was initially introduced in the 1960's and has increasingly become an important tool for health care decision makers over time, being applied to both medical technologies as well as pharmaceutical agents. The aim of economic evaluations in health care settings is to identify and reallocate resources to those health care interventions and programs that offer the greatest health returns from money allocated within a limited healthcare budget [115]. This is achieved as economic evaluations provide information of the relative value for money offered by competing treatments either among or between different treatment classes, comparing both the costs incurred and final consequences of alternative interventions [115, 116]. Since the 1990's cost-effectiveness analyses have been required for an intervention to be eligible for reimbursement under public sector drug plans in the province of Ontario [115, 117].

Unlike other markets, the health care market has an irregular market structure as supply and demand are not brought together in a market through price mechanisms, but instead health care resources are delivered and/or financed, to varying degrees, by governments [115]. Economic evaluation becomes critical in this situation as these governments have a limited pool of scarce resources which they must allocate to health care without having marketplace signals of what consumers value. This being the case, governments must aim to efficiently allocate their health care resources among various competing demands [115].

Central to economic evaluations is an understanding of the concept of opportunity cost. Opportunity cost measures the value of competing options when budgets are finite and when investment in one program/intervention will be at the expense of a loss of opportunity in another program/intervention [115]. Economic evaluation is used as it offers a framework for identifying, measuring, and valuing the resource inputs of a health care program and the health benefit outputs associated with the intervention [118].

A.1.1 Components of an Economic Evaluation

There are four key components of an economic evaluation. Firstly, a research question relevant to the end decision maker(s) must be formulated [117]. This research question must clearly define the population of interest (eg. specific genotype, tumor etc), provide a complete description of all the alternatives which are being compared,and state the perspective in which the evaluation will be carried out in [117].

The second step to performing an economic evaluation is to assess the cost and consequences of each alternative [117, 118]. Key to determining these costs and consequences is the perspective in which the analysis is undertaken. The perspective in which an economic evaluation is carried out can range from narrow, for example that of an individual hospital, to wide such as the full societal view. In practice four different perspectives are commonly used when undertaking an economic analysis; the society, the patient, the provider, and the payer [118]. The differences in each of the perspectives in which an analysis is undertaken can greatly influence the final analysis as different costs and consequences can be included or excluded depending on the viewpoint of the analysis [106, 107, 108,109, 110,111, 112, 113, 114,115, 116, 118]. More narrow perspectives may only focus on direct costs and benefits i.e. those costs and benefits directly attributed to providing the intervention/program, while more broad perspectives will take into account the indirect costs (ex. Productivity losses, lost wages) and intangible costs (ex. Pain and suffering) and benefits associated with a program/ intervention [118].

The third step in an economic evaluation is to carry out the actual analysis. The main types of economic evaluation used in health care settings; cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA), cost comparison analysis, cost-consequence analysis, and cost-minimization analysis (CMA). The method for the identification of costs and their measurement into monetary units for each of the four methods is similar, however where each approach is differentiated in terms of how they quantify and value the consequences of the interventions [115, 117, 118]. The selection of what type of analysis to undertake is determined by the research question, the condition/disease of interest, and the availability of outcome data [117, 118].

The final stage of the analysis is to address any variability and uncertainty of the results. This is achieved through the use of either deterministic or probabilistic sensitivity analyses which aim to verify the robustness of the initial results and to adjust for any variability or uncertainty surrounding the parameters used in the analysis such as health outcomes, cost, resource utilization, or probabilities [117, 118].

Once the analysis is complete it is then open to the interpretation of policy-makers who use these analyses as a tool to determine whether certain health interventions or programs should be funded or not. Economic evaluations are a valuable tool for use by decision and policy makers in a number of scenarios. Economic evaluations are used by payers such as insurance companies or governments to make coverage decisions, using these analyses in the context with their inherent budget constraints to ensure that they can provide access to pharmaceuticals and other healthcare services [119]. Economic evaluations can also be used by health care providers, especially in regards to making formulary decisions [119]. In this context the decision maker would use the results of the economic evaluation and along with efficacy and safety information to determine whether a particular drug or intervention should represents appropriate cost for value and therefore whether it should be funded or not. Economic analyses can also be used by also by those involved in selecting healthcare performance measures and developing treatment guidelines [119].

A.2 Types of Economic Evaluations

In this section I will examine the different type of economic evaluations which can be undertaken.

A.2.1 Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) is a method of economic evaluation which compares both the cost and effect of different interventions, and is the most common type of economic evaluation undertaken when comparing pharmaceuticals or programs in the health care sector [116, 120]. The use of CEA is most useful to decision makers who are operating with a limited budget and who can only consider a limited number of options within a given field. The use of cost-effectiveness analysis is dependent upon the

measure of effectiveness selected for the chosen outcome for which the alternative programs/interventions will be compared. Ideally a CEA should use an effectiveness measure which is related to final outcomes such as life-year gained, however this may not be feasible given the information on which the analysis is formulated [118]. In some cases intermediate effectiveness measures such as number of cases detected, episode-free days, or some clinical measure may be used.

Two different cost-effectiveness ratios are important outcomes in economic evaluations. Both consist of a ratio of the costs to the effectiveness of a medical intervention where the numerator is the cost of the intervention in monetary units and the denominator is expressed in some measure of effectiveness in its appropriate health units [120].

The average cost-effectiveness ratio is determined for an intervention by dividing the cost of the intervention by a measure of its effectiveness. Average cost-effectiveness ratios can be determined for various interventions and along with the use of an acceptability threshold value can be used by decision makers to assign priorities for resource allocation [120]. In Canada $75 000- $100,000 per life year saved is used as a widely used as the acceptable threshold value for cancer treatments [117]. Interventions which are above this threshold are considered to not be of value for money or "bad buys" and should not be implemented, while those which fall below this threshold are considered good value for money and should be implemented [120].

Ideally an economic evaluation should compare the costs and consequences of competing alternatives. Average cost-effectiveness ratios fail to consider the competing interventions which could possibly be used for the treatment of the same medical problem and this lack of comparison represents a weakness in the use of the average cost-effectiveness ratio in economic evaluations. To address this issue the Incremental Cost-Effectiveness Ratio (ICER) was designed.

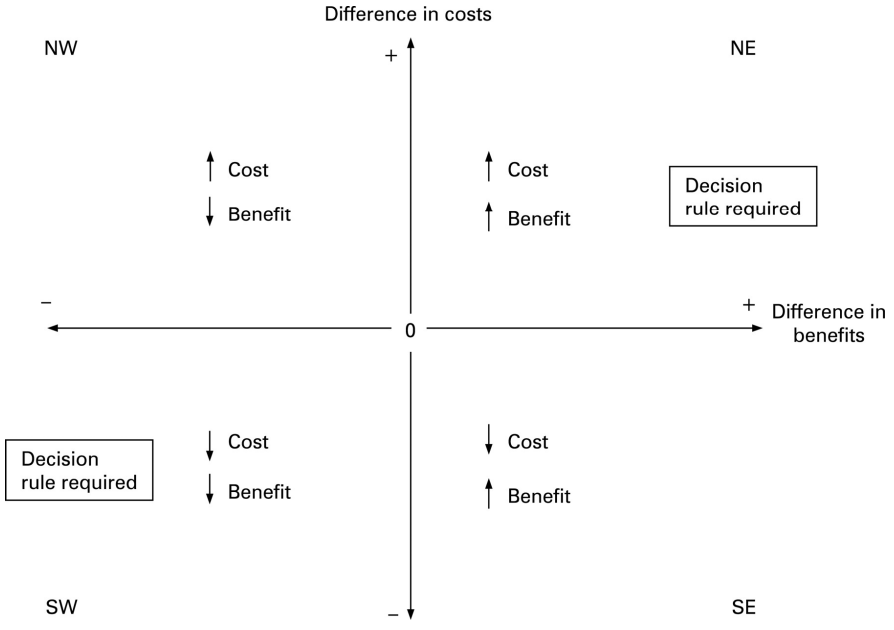
Figure 8.1: The Incremental Cost-Effectiveness Ratio

$$ICER = \frac{Cost_{New} - Cost_{Old}}{Effect_{New} - Effect_{Old}}$$

The ICER examines the differences in cost divided by the differences in the effectiveness of two competing alternatives, given that the measure of effect of the two alternatives being compared is the same. The resultant ICER represents the cost per unit of health benefit gained from switching from one alternative to another, and represents a more informative tool in the decision making process for heath care decision makers than the average C/E ratio [120].

Cost Effectiveness ratio's can be expressed graphically with the use of a four quadrant diagram called the cost-effectiveness plane (Figure 8.2). The horizontal axis of the cost-effectiveness plane represents the difference in effectiveness, while the vertical axis represents the difference in cost of the treatment options being compared [118, 120].

Figure 8.2: The Cost-Effectiveness Plane



A health care intervention of interest can be expressed as a point in one of the four quadrants when it is being compared to an alternate health care intervention. The more

costly an intervention is, the higher its point will be on the vertical axis, while the more effective the intervention the more rightward its point will fall. If a point falls in the south-east quadrant the intervention is said to be "dominant" in that it is more effective and less costly than its alternative, while if it lands in the north-west quadrant the intervention is more costly and less effective than its alternative and is said to be "dominated". The use of a willingness-to-pay cost-effectiveness ratio comes into play when points land in the north-east and south-west quadrants. Points landing in the north-east quadrant the intervention are more effective and more costly than its alternative, while points landing in the south-west represent interventions which are less effective and less costly. On the cost-effectiveness plane the willingness-to-pay threshold may be represented with the use of a line whose slope reflects the amount that the payer is willing to pay for a one unit health gain. Points which lay above this line exceed the willingness-to-pay threshold and therefore may not represent good value for money, while points which lie underneath it are below the threshold value and may be worthwhile implementing.

A.2.2 Cost-Utility Analysis

Cost-Utility analysis (CUA) is based upon the same principle as CEA, however it focuses on the quality of the health outcome produced or forgone by the programs/interventions of interest [118]. In CUA the incremental cost of a program is found in the same manner as in CEA, however it differs from CEA in that in CUA the health improvement of a program is quantified in terms of some measure of health-related preferences, often using quality-adjusted life-years (QALYS). QALY's are determined through the use of multi-attribute utility instruments such as the Euroqol (EQ-5D), Health Utility Index (HUI), Quality of Well-Being (QWB), or Short Form 6D (SF-6D) [117, 118]. An advantage of the use of cost-utility analyses is that the use of the QALY provides a standard measure of effectiveness, allowing for the comparison of a broad scale of interventions which may have different primary effectiveness measures, allowing for the allocation of resources based upon the maximization of health gains [117, 118]. The use of the QALY as standard effectiveness measure also allows for the comparison of different programs/interventions where multiple effectiveness measures may be of interest, as well as allows for the

incorporation of changes to both the quantity and the quality of life gained or lost through the implementation of an intervention/program to be quantified in a single measure [116-118]. Cost- utility analyses are primarily used when the health-related quality of life is the most important outcome of a program, when a number of different outcomes are of interest, or when the implementation of a program can affect both morbidity and mortality.

A.2.3 Cost-Benefit Analysis

Cost-benefit analysis (CBA) is a form of economic evaluation where the consequences of a program are valued in monetary terms, allowing for the direct comparison of the "program's incremental cost with incremental consequences in commensurate units of measurements, be they dollars, pounds, or yen" [118]. The goal of CBA is to determine whether a program's benefits exceed its costs [116-118]. Programs which show a positive net social benefit by having benefits exceeding its costs will represent a program whose implementation will be worthwhile. One advantage of the use of CBA is that is has a broader scope than CEA and CUA and can be used when comparing health care program to programs outside of the health care sector [117, 118]. However the use of cost-benefit analysis in health care settings is complicated by the need to value intangible health outcomes into monetary values. These monetary values are determined primarily through the use of three different approaches; (1) the human capital approach which places monetary weights on healthy time using market wage rates and the value of the program is assessed in terms of its present value and future earnings, (2) Revealed preferences which examines the health risks associated with a hazardous job and the wage rates that individuals would require to accept that job, and (3) with the use of stated preferences of willingness to pay [118]. A number of methodological issues have been raised with the use of these three approaches to value non-monetary health outcomes and thus has limited the use of CBA in health care economic evaluations [116].

A.C Decision Analytic Modeling

Decision analytic models are used to find detailed estimates of both the cost and consequences of interventions using data from a number of sources including clinical

trials, observational trials, public health statistics, insurance databases etc [119]. The use of decision analytic modeling in economic evaluations for health care programs/interventions involves the use of mathematical techniques to integrate clinical and economic outcomes, providing a framework for health care decision-making under conditions of uncertainty [118, 119].

The development of a decision analytic model involves four stages. First the decision problem must be defined. This involves defining the recipient group, and the options which are to be compared in the model. Secondly, the boundaries of the model must be defined. This involves the deciding upon an appropriate time horizon, the choice of perspective, and the selection of appropriate measures of cost and effectiveness [118]. Once the problem and boundaries are defined, the structure of the model must be determined. The structure of the decision analytic model is based on decisions regarding how model parameters are related and deciding how to characterize the clinical event(s) of interest. When structuring the model an analyst must take into account the occurrence of events (occurs once or multiple times), whether the probabilities of an event occurring is constant or changes over time, how to extrapolate data which may only represent a short period of time in to the future, and how to incorporate all the appropriate costs and effects [117, 118].

A.3.1 Types of Decision Analytic Models

There are three main types of decision analytic models; (1) Decision Tree (2) Markov Model, and (3) Microsimulation Models.

A.3.2 Decision Trees

Decision trees are the most commonly used structure for decision models in economic evaluation. A decision tree is a graphical analytic model, ordered left to right composed of different branches, each of which represent different events and their possible outcomes [117, 118]. Within the decision tree different events are represented by different shapes called “nodes”. There are three types of nodes:

Decision Nodes  : decision nodes represent a decision which is being addressed in the model. Decision nodes are represented in a decision tree with the use of a square box [118].

Chance Nodes  : Chance nodes are used to represent the range of possible, mutually exclusive outcomes which can occur after a decision has been made. Each branch coming out from a chance node represents a possible outcome, the sum of each of the branches starting at chance outcomes must equal 1.0 [118]. Chance nodes are represented in the decision tree with the use of a circle.

Terminal Nodes  : Terminal nodes represent the endpoint of each possible pathway, and are also referred to as the path payoff and can be measured in terms of cost or effectiveness ($, life-year, QALY, etc) [118]. Terminal nodes are represented in the decision tree with the use of a triangle.

A.3.3 Markov Models

Markov models are a type of decision analytical modeling which is used to represent random processes which evolve over time and where individuals have an ongoing risk over that period of time such as in chronic or progressive diseases [121, 122]. An attractive feature of Markov models for their use in economic evaluation of health care programs/interventions is that estimates of both cost and health care outcome can be attached to various Markov states, and with the use of various transition probabilities, long term cost and outcomes associated with a particular disease or intervention can be determined [121].

In Markov models, the disease is defined in a number of discrete states which are chosen based on clinically or economically important events which occur in the disease process [121] . A specific set of rewards can be attributed to each state such as a specific utility, cost, or outcome associated with being in that state for every cycle [118]. Markov states must be mutually exclusive in that a patient can not be in more than one Markov state at any one time [121, 122].

In each Markov model the desired time horizon is divided into equal increments of time (month, years, day etc) called Markov cycles. Within each Markov cycle patients can transition between the unique Markov states except for one state which is known as the absorbing state, the state from which it is impossible to leave. In most Markov models the absorbing state is death. In situations where an event that only has short-term effects occurs, it is possible to make use of temporary states [121, 122]. Temporary states are defined by only having transitions to other states and not to themselves which ensures that a patient can only stay in that state for one cycle [122]. In certain situations where the temporary adjustment from the addition of a temporary state is desired for more than one cycle tunnels can be used. A tunnel consists of a number of temporary states arranged so that each temporary state transitions to the next in a fixed sequence. A specific health utility and cost can be attributed to each specific Markov state [121, 122]. The movement of a patient through the Markov states within each Markov cycle is determined with the use of transition probabilities. Transition probabilities define the speed at which patients move through the different Markov states, and for a Markov model with k states, the number of all possible transitions between the states are given by a k x k transition matrix [115] . A number of assumptions are made with the use of transition probabilities, firstly it is assumed that patients with progressive disease do not recover from their disease after they move to a progressive stage thus eliminating any transitions from more advanced to less advanced disease stages[115, 118].

The second assumption made is often called the Markovian Assumption, and is also called the memory-less feature of Markov models. The Markovian assumption states that the probability of a patient moving out of a state is independent of the states which they may have previously experienced before entering their current state i.e. it has no memory of earlier cycles [115, 117, 118].

A weight of 1 is assigned to every Markov state in which the patient is alive, and a weight of 0 is given to the dead state, and after running the model for a large number of cycles an estimate of the patients expected life expectancy can be found [118]. When the outcome of interest is quality adjusted life years, the weight of each state is multiplied by the state specific utility to give a final outcome of quality adjusted life years.

A.3.4 Microsimulation Models

Microsimulation models make use of the Monte-Carlo simulation technique which generates individual patient histories by applying a set of transition probabilities to individual patients. This results in the ability to track changes in that patient's state, resulting in changes in their overall costs and benefits over time [115]. In microsimulation models individuals randomly walk through the model generating individual outcomes. This process is carried out numerous times resulting in an aggregate result for the expected value for each patient. Due to the fact that a microsimulation generates outcomes for individual patients microsimulation models can be used to track outcomes to individual patient characteristics. This tracking of individual characteristics cannot be done through the use of Markov modeling, as Markov models use transition probabilities on a homogenous cohort [115].

Appendix B: Model Parameters

B.1 Monthly Costs

Table 9.1:Monthly State- Specific Costs Determined from Patient-Level Data and Linear Regression.

First-Line		
Month	**Total Cost - Patient Level**	**Total Cost - Linear Regression**
1	3,520.17	3,053.77
2	2,676.71	2,942.34
3	2,742.86	2,830.91
4	2,738.33	2,719.48
5	3,112.64	2,608.05
6	2,301.70	2,496.62
7	2,009.13	2,385.19
8	1,777.57	2,273.76
9	1,844.78	2,162.33
10	1,635.25	2,050.90
11	1,907.94	1,939.47
12	1,389.65	1,828.04
13	1,465.26	1,716.61
14	1,837.70	1,605.18
15	1,031.59	1,493.75

16	1,010.89	1,382.32
17	1,325.96	1,270.89
18	853.21	1,159.46
19	1,381.26	1,048.03
20	579.04	936.60
21	642.95	825.17
22	539.19	713.74
23	618.15	602.31
24	918.65	490.88
Second-Line		
Month	**Total Cost - Patient Level**	**Total Cost - Linear Regression**
1	3,191.43	2,944.30
2	2,527.02	2,817.30
3	2,653.80	2,690.30
4	2,402.88	2,563.30
5	2,703.16	2,436.30
Month	**Total Cost - Patient Level**	**Total Cost - Linear Regression**
6	2,214.06	2,309.30
7	1,758.58	2,182.30
8	2,253.72	2,055.30
9	1,971.27	1,928.30
10	1,761.97	1,801.30
11	1,543.22	1,674.30
12	2,096.02	1,547.30
13	1,009.04	1,420.30
14	1,408.79	1,293.30
15	1,398.88	1,166.30
16	1,155.43	1,039.30
17	1,220.80	912.30
18	868.60	785.30
19	508.82	658.30
20	328.41	531.30
21	363.01	404.30
22	186.08	277.30
23	63.85	150.30
24	20.66	23.30
Third-Line		
Month	**Total Cost - Patient Level**	**Total Cost - Linear Regression**

1	3,780.82	3,297.03
2	3,209.99	3,069.26
3	3,122.11	2,841.49
4	2,812.68	2,613.72
5	1,622.53	2,385.95
6	2,280.53	2,158.18
7	1,989.14	1,930.41
8	1,271.74	1,702.64
9	1,245.74	1,474.87
10	1,141.05	1,247.10
11	537.87	1,019.33
12	297.59	791.56
13	1,078.87	563.79
14	411.76	336.02
15	236.33	108.25
16	0.00	0.00
17	32.57	0.00

Best Supportive Care		
Month	**Total Cost - Patient Level**	**Total Cost - Linear Regression**
1	3,016.60	2,581.71
2	1,898.75	2,235.82
3	1,817.73	1,889.93
4	1,288.39	1,544.04
5	1,079.83	1,198.15
6	1,220.67	852.26
7	486.35	506.37
8	1,542.44	1,149.18
9	344.44	1,021.59
10	532.18	894.00
11	1,489.36	766.41
12	846.32	638.82
13	401.77	511.23
14	208.69	383.64
15	276.11	203.32
16	125.48	176.72
17	154.13	150.12
18	69.33	123.52
19	113.55	96.92
20	15.67	70.32
21	96.89	43.72
22	30.33	17.12

Table 9.2: Monthly Costs Determined from Patient-Level Data

First-Line					
Month	**Clinic**	**Home Care**	**Hospital**	**ODB**	**OHIP**
1	$1,761.73	$309.65	$819.83	$347.78	$281.18
2	$1,150.20	$252.36	$657.65	$332.07	$284.43
3	$1,048.44	$252.49	$708.70	$394.71	$338.52
4	$1,041.93	$252.04	$693.30	$413.10	$337.96
5	$882.20	$250.02	$1,199.33	$359.95	$421.14
6	$772.02	$217.98	$586.05	$341.55	$384.10
7	$705.48	$205.58	$487.79	$319.09	$291.19
8	$551.50	$173.10	$468.60	$246.30	$338.07
9	$473.03	$164.49	$696.33	$222.65	$288.28
10	$377.34	$148.57	$534.29	$291.07	$283.98
11	$449.80	$136.61	$812.25	$249.06	$260.22
Month	**Clinic**	**Home Care**	**Hospital**	**ODB**	**OHIP**
12	$316.20	$120.95	$449.88	$239.19	$263.43
13	$307.09	$122.80	$615.59	$163.94	$255.84
14	$310.46	$96.97	$976.63	$195.95	$257.69
15	$379.22	$100.75	$42.07	$313.35	$196.20
16	$269.55	$78.42	$294.64	$161.73	$206.55
17	$233.75	$68.12	$569.23	$203.13	$251.73
18	$276.97	$56.71	$178.46	$141.10	$199.97
19	$195.85	$49.70	$666.25	$127.11	$342.35
20	$132.35	$52.10	$91.69	$125.41	$177.49
21	$96.61	$35.63	$154.68	$118.02	$238.01
22	$87.42	$34.65	$104.68	$88.43	$224.01
23	$76.73	$24.30	$239.62	$80.47	$197.03
24	$83.87	$23.20	$516.52	$121.37	$173.69
Second-Line					
Month	**Clinic**	**Home Care**	**Hospital**	**ODB**	**OHIP**
1	$1,764.80	$309.28	$407.65	$470.78	$238.92
2	$1,043.90	$271.26	$502.82	$416.66	$292.38
3	$1,017.70	$251.33	$640.48	$416.50	$327.79
4	$906.23	$246.25	$554.29	$378.84	$317.27
5	$830.32	$229.88	$935.36	$361.84	$345.76
6	$722.96	$222.58	$610.91	$328.48	$329.13
7	$759.41	$206.74	$202.51	$310.03	$279.89
8	$564.06	$244.91	$901.69	$308.91	$234.15

9	$453.94	$217.75	$655.85	$248.23	$395.5
10	$531.91	$191.06	$490.97	$269.06	$278.97
11	$450.74	$174.29	$436.79	$259.01	$222.39
12	$435.40	$115.80	$1,128.98	$176.02	$239.82
13	$383.33	$87.96	$153.01	$193.99	$190.75
14	$396.74	$107.45	$426.88	$223.41	$254.31
15	$325.79	$113.17	$570.80	$194.14	$194.98
16	$277.54	$87.68	$316.23	$219.67	$254.31
17	$323.46	$75.55	$470.96	$152.85	$197.98
18	$304.14	$124.84	$0.00	$235.79	$203.83
19	$115.32	$22.70	$0.00	$121.18	$249.62
20	$0.00	$14.43	$0.00	$93.02	$220.96
21	$0.00	$46.18	$0.00	$40.48	$276.35
22	$0.00	$59.83	$0.00	$29.02	$97.23
23	$0.00	$0.00	$0.00	$0.00	$63.85
24	$0.00	$0.00	$0.00	$0.00	$20.66

Third Line

Month	Clinic	Home Care	Hospital	ODB	OHIP
1	$1,504.60	$278.44	$1,285.40	$279.42	$424.56
2	$1,001.50	$331.06	$988.85	$324.69	$584.61
3	$771.07	$358.23	$4,905.00	$309.04	$504.37
4	$881.47	$270.64	$1,005.50	$351.89	$328.82
5	$938.37	$210.73	$0.00	$172.38	$301.05
6	$467.58	$0.00	$0.00	$144.58	$306.27
7	$520.24	$334.46	$814.02	$135.42	$202.06
8	$450.76	$172.13	$280.57	$151.02	$223.14
9	$643.34	$120.00	$0.00	$54.07	$428.33
10	$322.99	$349.51	$0.00	$289.03	$179.52
11	$0.00	$184.51	$0.00	$267.49	$85.87
12	$0.00	$127.63	$0.00	$51.81	$118.15
13	$0.00	$0.00	$0.00	$602.38	$476.49
14	$0.00	$0.00	$0.00	$0.00	$411.76
15	$0.00	$0.00	$0.00	$0.00	$236.33
16	$0.00	$0.00	$0.00	$0.00	$0.00
17	$0.00	$0.00	$0.00	$0.00	$32.57

Best Supportive Care

Month	Clinic	Home Care	Hospital	ODB	OHIP
1	$100.44	$316.49	$1,363.11	$296.78	$939.78
2	$54.60	$256.08	$681.57	$352.03	$554.47
3	$62.54	$166.78	$839.50	$276.85	$472.06

4	$81.84	$155.25	$522.53	$235.11	$293.66
5	$42.14	$138.01	$548.35	$159.62	$191.71
6	$5.93	$123.03	$733.82	$159.37	$198.52
7	$4.12	$54.80	$192.60	$84.81	$150.02
8	$0.00	$102.41	$1,108.60	$116.89	$214.54
9	$2.99	$95.58	$0.00	$100.85	$145.02
10	$0.00	$70.40	$0.00	$38.69	$423.09
11	$0.00	$114.27	$1,214.93	$55.83	$104.33
12	$0.00	$134.84	$493.44	$57.33	$160.71
13	$0.00	$80.84	$218.67	$40.60	$61.66
14	$0.00	$52.30	$77.58	$27.78	$51.03
15	$8.26	$27.99	$124.09	$34.81	$80.96
16	$0.00	$23.22	$0.00	$35.77	$66.49
17	$0.00	$9.54	$0.00	$76.64	$67.95
18	$0.00	$0.00	$0.00	$42.42	$26.91
19	$0.00	$0.00	$0.00	$41.58	$71.97
20	$0.00	$0.00	$0.00	$1.79	$13.88
21	$0.00	$0.00	$0.00	$73.96	$22.93
22	$0.00	$0.00	$0.00	$0.00	$30.33

B.2 Transition Probabilities

Table 9.3: Monthly Transition Probabilities

Month	Beva + FOLFIRI	Cetux + FOLFIRI	Panit + FOLFIRI	FOLFOX	FOLFOX + Beva	TL Panit	BSC
1	0.0317	0.0113	0.0141	0.0513	0.0461	0.0116	0.0418
2	0.0436	0.0228	0.026	0.0513	0.0461	0.0195	0.0636
3	0.0496	0.0309	0.0338	0.0513	0.0461	0.0242	0.0755
4	0.0539	0.0377	0.0401	0.1181	0.0801	0.0279	0.0844
5	0.0573	0.0436	0.0455	0.1181	0.0801	0.0311	0.0917
6	0.0603	0.049	0.0504	0.2441	0.0955	0.0338	0.098
7	0.0628	0.0541	0.0548	0.2441	0.0955	0.0362	0.1035
8	0.065	0.0587	0.0588	0.2094	0.1455	0.0385	0.1084
9	0.067	0.0631	0.0626	0.2094	0.1455	0.0405	0.1129
10	0.0689	0.0673	0.0662	0.2929	0.2339	0.0424	0.117
11	0.0706	0.0713	0.0696	0.2929	0.2339	0.0442	0.1208
12	0.0722	0.0751	0.0728	0.2254	0.1611	0.0459	0.1244
13	0.0737	0.0788	0.0759	0.2254	0.1611	0.0475	0.1278
14	0.0751	0.0824	0.0788	0.1835	0.2053	0.0491	0.131
15	0.0764	0.0858	0.0817	0.1835	0.2053	0.0506	0.134

16	0.0776	0.0891	0.0844	0.1835	0.2404	0.052	0.1369
17	0.0788	0.0923	0.087	0.1835	0.2404	0.0534	0.1397
18	0.0799	0.0955	0.0896	0.2929	0.1181	0.0547	0.1423
19	0.081	0.0985	0.0921	0.2929	0.1181	0.0559	0.1448
20	0.0821	0.1015	0.0945	0.2929	0.0742	0.0572	0.1473
21	0.0831	0.1044	0.0968	0.2929	0.0742	0.0583	0.1496
22	0.084	0.1072	0.0991	0.1544	0.2929	0.0595	0.1519
23	0.0849	0.11	0.1013		0.2929	0.0606	0.1541
24	0.0859	0.1127	0.1035		0.1453	0.0617	0.1563
25	0.0867	0.1154	0.1056			0.0628	0.1583
26	0.0876	0.118	0.1077			0.0638	0.1603
27	0.0883	0.1205	0.1097			0.0648	0.1621
28	0.0892	0.1231	0.1117			0.0659	0.1643
29	0.09	0.1256	0.1138			0.0668	0.1657
30	0.0907	0.128	0.1156			0.0678	
31	0.0915	0.1304	0.1175			0.0687	
32	0.0921	0.1329	0.1194			0.0696	
Month	**Beva + FOLFIRI**	**Cetux + FOLFIRI**	**Panit + FOLFIRI**	**FOLFOX**	**FOLFOX + Beva**	**TL Panit**	**BSC**
33	0.0928	0.135	0.1211			0.0705	
34	0.0936	0.1373	0.1229			0.0714	
35	0.0941	0.1398	0.1248			0.0723	
36	0.0948	0.1419	0.1264			0.0731	
37	0.0955	0.144	0.1282			0.0739	
38	0.096	0.1462	0.1296			0.0747	
39	0.0967	0.1482	0.1315			0.0756	
40	0.0975	0.1505	0.1333			0.0763	
41	0.0979	0.1527	0.1347			0.0772	
42	0.0983	0.1541	0.1361			0.0779	
43	0.0992	0.1565	0.1379			0.0786	
44	0.0996	0.1592	0.1393			0.0795	
45	0.1002		0.141				
46	0.1006		0.1418				
47	0.1014						
48	0.1018						
49	0.1022						
50	0.1029						
51	0.1032						
52	0.1032						
53	0.1046						

Table 9.4: Fixed monthly transitions from first-line treatment to cancer free after surgery for metastases.

Model	Transition Probability
Bevacizumab to Cancer Free	0.001536953
Cetuximab to Cancer Free	0.003423096
Panitumumab to Cancer Free	0.008284798

Curriculum Vitae

Name:	Emmanuel Ewara
Post-secondary Education and Degrees:	University of Western Ontario London, Ontario, Canada 2005-2010 BMSc.
Honours and Awards:	Schulich Graduate Scholarship, The University of Western Ontario 2011, 2012
Related Work Experience	Research Assistant University of Western Ontario July 2011- September 2012
Publications:	