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Cost-Effectiveness Of Bevacizumab Concomitant With The Standard Of Therapy For Newly Diagnosed Glioblastoma

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

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Abstract

Glioblastoma Multiforme (GBM), a glioma – cancer of the brain’s glial cells – is the most common and deadly malignant primary central nervous system tumor in developed countries. Two recently completed clinical trials investigating the use of bevacizumab (BEV), a monoclonal antibody, to treat newly diagnosed GBM concomitant with the standard-of-care (SOC) showed mixed survival and quality of life outcomes. In this study, a cost utility study was conducted to investigate if BEV should be used to treat newly diagnosed GBM. A three stage time-dependent Markov model was built using survival estimates from the two clinical trials, costs from Ontario residents diagnosed with GBM between 2003 and 2011, and literature utility values. The expected incremental cost utility ratio for BEV plus the SOC compared to the SOC alone is 8,393,212 \$/quality adjusted life year over a six year period. Therefore, BEV plus the SOC is not cost-effective as a first-line therapy.

Keywords

Cost Utility, Bevacizumab, Glioblastoma Multiforme, Cancer, Ontario.

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Chapter 1

1. Introduction

Glioblastoma Multiforme (GBM), a glioma – cancer of the brain’s glial cells – is the most common and deadly malignant primary central nervous system (CNS) tumor in developed countries [1]. Approximately three in 100,000 will be diagnosed with GBM each year, making it the most common glioma, accounting for approximately 82% of all gliomas, and contributing approximately 5% of all adult tumors [2]. There are two variants of GBM, giant cell glioblastoma and gliosarcoma (Figure 1). The World Health Organization (WHO) uses a four-tier system to classify gliomas. The classification increases from one to four based on tumor aggressiveness, anaplasia, and degrees of differentiation [1]. The WHO grades GBM as a level 4, the most severe and poorest prognostic correlate [3]. The aggressive and incurable nature of GBM has made it a burden not only for patients and their families, but for healthcare systems too. As the cancer progresses, patients will become dependent on care, increasingly confined to their bed, and eventually die from progressive brainstem failure in a comatose state [4, 5].

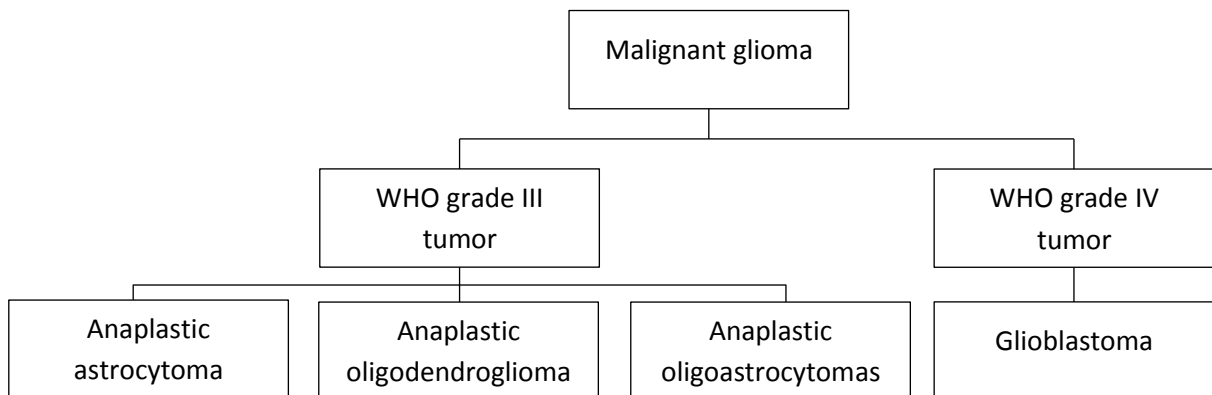


Figure 1. Classification flow chart of malignant gliomas

Primary GBM, when the original tumor is GBM, is very difficult to treat and has the tendency to progress, transform, or recur; these evolved tumors are termed secondary GBMs [3]. Overall, one-year survival probability is 17-30% for newly diagnosed GBM

patients with either a primary or secondary subtypes. Two-year survival dramatically drops to 3-5% and five-year survival rates remain at a similar 1-3% for patients between 15 and 45 years of age [6]. Survival, however, drops to 1% for patients aged 75 years and above [3].

In contrast, anaplastic astrocytoma, a grade three malignant glioma, has a one-year survival probability of 60.1% and a five-year survival of 49.4% [5]. Recurrent GBM, when the cancer returns after a period of no tumor detection, has a progression free survival (PFS) rate of nine to 10 weeks [7]; one-year survival for recurrent GBM is 20 to 25% [7, 8]. Response to treatment is seen in fewer than 10% of recurrent GBM patients [3]. Additionally, survival does not differ between men and women patients [3]. GBM randomized control trials (RCTs) show the best prognosis for patients, with a marked increase to 13-26% for overall two-year survival [9]. Early diagnosis has not been seen to improve survival outcomes [3].

No molecular factor has been generally acknowledged as a prognostic indicator; however, patients with methylation of the promoter O6- methylguanine-DNA methyltransferase (MGMT) and IDH1 mutations are associated with longer survival rates [10, 11]. Still, age and Karnofsky performance status (KPS) – a performance scale used by clinicians to determine a patient’s ability to survive chemotherapy – are the primary prognostic factors [12]. Moreover, while not fully meeting the quality of life (QoL) definition, the KPS is the earliest measure of QoL in GBM and still is widely used as a QoL outcome measure [13].

Primary onset GBM has a relatively older mean age of approximately 62 years, while secondary GBM has a younger mean onset age of 45 years [6, 14]. There is a larger standard deviation in age for secondary GBM than for primary GBM [6, 15]. Moreover,

primary GBM occurs three times more often in males than females while secondary GBM occur more often in females than males [6, 15].

Two clinical trials investigating the use of bevacizumab (BEV), a humanized monoclonal antibody targeting vascularization factors, to treat GBM have recently completed and showed mixed results in survival and quality of life outcomes [16, 17]. While BEV may have a positive clinical effect on treated patients, the cost of treatment is expensive [18]. Therefore, the goal of this thesis is to investigate if the cumulative benefits derived from BEV treatment can justify the incurred costs in newly diagnosed GBM.

Chapter 2

2. Literature Review

2.1. Genetic Pathology

The GBM tumor usually has a homogenous histology; however, it is genetically heterogeneous. Histologically, GBM has significant cellularity, vascularization, mitotic activity, and necrosis [7]. Several genetic events can result in GBM proliferation, requiring cumulative and subsequent genetic mutations, making it unlikely that one mutation can indicate GBM development. Therefore, to increase efficacy and specificity, therapies must be tailored to a patient's specific GBM genotype.

Genetic screens of GBM show scattered mutations throughout the genome, with concentrations in the 1p, 6q, 9p, 10p, 10q, 13q, 14q, 15q, 17p, 18q, 19q, 22q and Y-chromosomes [19-24]. Specifically, the 20q13.33 (RTEL), 7p11.2 (EGFR), 9p21.3 (CDKN2BAS), 5p15.33 (TERT), 11q23.3 (PHLDB1), and 8q24.21 (CCDC26) genes have been weakly associated with the GBM susceptibility. Studies have noted that several of these mutations may have been caused by tumorigenesis instead of causing the tumor. The most common mutation in GBM, 60-80% of cases, is found on chromosome 10 [25].

2.2. Molecular Biology

The phenotypic effects of GBM mediated mutations augment several signaling pathways and their normal function. Broadly, the most commonly altered pathways in GBM neoplastic cells are repair pathways such as nucleotide excision repair, base excision repair, mismatch repair, and direct reversal of lesions in recombination [26, 27]. Ultimately, the neoplastic cells have a reduced ability to repair DNA damage and mutations. This is why patients with an active O6- methylguanine-DNA

methyltransferase (MGMT) expression show better prognosis than those with an inactive MGMT [28]. The MGMT promoter is responsible for a tumor suppressor pathway that works by protecting against alkylating agents [11].

Research on GBM altered pathways appears to show that mutation of the epidermal growth factor receptor (EGFR) and other tyrosine kinase receptor autocrine signaling pathways are often necessary for GBM progression [29]. Tyrosine kinase receptor autocrine signaling pathways are responsible for growth, proliferation, migration, and tumor vascularization. Mutation of this pathway in GBM results in over expression and an amplified effect on neoplastic cells. Moreover, mutation of this pathway results in resistance to certain anticancer therapies by limiting the effects of drugs on cell death pathways. Tyrosine kinase receptor autocrine signaling amplifications are found more often in primary GBM tumors (40-60%) more often than secondary GBM tumors (<10%) [30].

Additionally, GBM patients commonly have inactivating mutations in the TP53 and retinoblastoma pathways [31, 32]. The TP53 pathway, also known as the guardian of the genome, mediates DNA repair by halting the cell cycle in response to radiation or toxin exposure and DNA strand breaks [33]. If the damage to the cell is too great, the TP53 pathway will initiate apoptosis and stop replication. The retinoblastoma pathway interacts with the TP53 pathway to pause the cell cycle for maintenance when damage occurs. Inactivation mutations in either of these pathways will hinder the cell's ability to limit mutation propagation and undergo apoptosis, ultimately allowing tumorigenesis.

2.3. Etiology and Diagnosis

The causes of GBM are unknown and the risk factors for tumorigenesis are poorly understood. Ionizing radiation exposure is the only environmental factor recognized to

cause GBM [34]. However, a study examining children exposed to nuclear bomb radiation found no increased risk of GBM [34]. Other exposures like chemical carcinogens, vinyl chloride, pesticides, and second-hand smoke have been proposed as a cause of GBM; however, etiology has not conclusively been proven [35]. Caucasians are at a higher risk of developing GBM when compared to Asians or Africans [14]. Interestingly, research has shown that increased socio-economic status can increase the risk of GBM development [36]. Additionally, preventative life-style changes are ineffectual in deterring GBM. While rare, a familial medical history of GBM has been shown to double one's risk of developing the neoplasm. Ultimately, it is agreed that GBM generally spawns from a combination of genetic and environmental factors [15].

Population studies have shown that a few heredity syndromes are correlated with increasing GBM risks. These syndromes include Li-Fraumeni neurofibromatosis type 1 and type 2, Turcot, tuberous sclerosis, Cowden, and familial schwannomatosis [35].

GBM is highly invasive, characteristically spreading through the parenchyma with the majority of GBM tumors located in the frontal lobes of the supratentorial compartments. GBM can also occur in the brain stem, spinal cord, cerebellum, and cortical areas. In most cases, the neoplastic cells are clumped together near the tumor bed or within two centimeters of the enhancing borders. Examiners commonly see vascularization and necrosis in GBM, and these characteristics are used to differentiate the tumor from lower-grade gliomas [37]. Despite GBM's tendency to metastasize, it does not propagate outside the CNS [3].

2.4. Clinical Presentation and Initial Evaluation

The most common symptoms of GBM are progressive focal neurologic deficits, seizures, and headaches – found in 50% of presenting patients. It is becoming more common to

find GBM tumors that are asymptomatic [3]. In patients aged 50 and above, symptoms such as new-onset headache, headache localization, and progressive headache severity are used to differentiate a typical headache from a possible GBM diagnosis.

Typically, when a patient presents with GBM symptoms, cerebral MRI images are taken to examine for neoplasms [3]. Since neoplasms look similar to benign radiation necrosis, more complicated techniques such as MR perfusion, F18-fluorodeoxyglucose-position emission tomography, and Magnetic Resonance Spectroscopy are sometimes needed for diagnosis [38]. Modern imaging techniques have become integral in selecting treatment options because they can help identify glioma subgroups [38]. Even though GBM can be identified using imaging techniques, a neuropathologist will only make a final diagnosis of GBM after confirming a positive brain tumor biopsy [39].

2.5. Disease Management

Several hundred studies and trials for the clinical treatment of GBM have been published since the 1960s [3]. In the late 1960s, whole brain radiation therapy (RT) became the standard-of-care (SOC) in GBM management, effectively doubling median survival time from four to six months to 10 to 11 months [3]. However, due to certain CNS region's sensitivity to ionizing radiation, RT treatment needed to be limited in intensity and duration. Moreover, only patients older than three years old could receive any amount of RT treatment due to a newborn's sensitivity to radiation.

While radiosensitizers and alternative RT strategies have been tried to overcome RT limitations, none have shown a clear increase in patient survival [3]. Targeted RT rather than whole brain RT is the only change to the treatment showing equal effectiveness at destroying GBM tumors with the beneficial side effect of reducing harm to healthy peripheral tissue.

Prior to 1999, new treatments shifted to the addition of nitrosourea variants, a DNA alkylating chemotherapy that can cross the blood-brain-barrier (BBB) forming inter-strand crosslinks in DNA, preventing replication [9]. A meta-analysis showed that some nitrosoureas (e.g. BCNU) could add up to two months of survival to a patient, and therefore a recommendation was made to add BNCU to the SOC regiment [9]. In 2003, the use of BNCU has evolved to placing wafers infused with the chemotherapy drug into the resection site of the removed tumor [40, 41]. This way, the oncologist can target the therapy onto the affected tissue, instead of issuing a systemic treatment affecting non-neoplastic cells. In the end though, BNCU was not adopted as a GBM management tool due to local side effects and costs.

Currently, surgical excision of the tumor has become the first line treatment of GBM. Removal of greater than 98% of the tumor has been shown to double survival time up to one additional year. However, this amount of excision is difficult as the tumor migrates to neighboring parenchymal cells and follows an infiltrative growth pattern rather than an expansive one [39, 42, 43]. However, any substantial excision, even less than 98% of the tumor mass, reduces intracranial pressure and therefore intracranial related symptoms resulting in temporarily improved QoL [44]. While removing less than 98% of the tumor reduces immediate mass effect, it does little to improve prognosis [43, 45]. Moreover, the residual tumor has shown to behave erratically and aggressively in a malignant fashion [43].

2.6. Standard-of-Care

2.6.1. First Line Treatment

In 2005, temozolomide (TMZ), another DNA alkylating agent, was added to the SOC for newly diagnosed GBM because it had the same benefit as BNCU, as validated by meta-

analysis, when treated in co-occurrence with RT. TMZ treatment, however, has fewer and less intensive severe side effects [46]. Moreover, patient QoL was not negatively impacted by adding the TMZ treatment as compared to BNCU [39]. Overall, surgery, TMZ, and RT can improve a patient's overall survival time by up to 14 months [46]. TMZ is an imidazotetrazine derivative of dacarbazine and is converted into its active form, monomethyl triazone imidazole carboxamide (MTIC), during circulation at physiologic pH where it nonspecifically inhibits DNA replication [46]. TMZ, like all GBM chemotherapy drugs, has the quality of passing the BBB.

Patients are treated with TMZ in two phases. The first phase, the concurrent phase, starts with maximal resection, followed by concurrent RT and oral 75 mg/m² day TMZ, five days a week, for a maximum of seven weeks. The second phase, the maintenance phase, starts after a four-week break and consists of six cycles. Each cycle is defined as two weeks of 150-200 mg/m² TMZ treatments at five days per week, followed by a two-week break [16, 17, 47, 48].

2.6.2. Second-Line Treatment

Virtually all patients will undergo tumor progression during or after first-line treatment [49]. A second surgical resection is generally considered to reduce mass effect and update tumor molecular and histological characteristics. For a majority of patients through, tumor location and physical performance will limit the extent or ability to perform surgery [50].

Second-line chemotherapy options include TMZ, BEV, and nitrosoureas. Moreover, alternative dosing and scheduling schedules have been explored as options. Nitrosoureas such as carmustine and lomustine are usually used to treat recurrent GBM, resulting with modest survival effectiveness at best [51]. After TMZ and BEV treatment regimens fail,

the patient's prognosis is extremely poor with a median survival of three to four months [50].

2.7. Cognition and Quality of Life

As GBM is a cancer of the CNS and occurs in the frontal lobes, cognition – the ability to learn, reason, and communicate – can be severely affected during disease progression [52]. The effect of cognitive degeneration is difficult to measure because one's ability to learn and reason is tied to their ability to communicate. While a physician is able to measure physical performance using a KPS with relative ease, assessing a patient's ability to reason and learn when they have difficulty to communicate is not trivial. It has been shown that while cognitive limitations will have a less visible effect on QoL than a physical limitation, the impact of cognitive limitations on a patient's QoL can be as great or greater [53]. However, it should be noted that cognition loss is noticed more frequently in severe GBM than less progressed GBM [54]. Larger tumor size is correlated to lower QoL [55].

In addition to the difficulties in noticing and measuring cognition loss and the resulting QoL change, treatment can usher further negative cognitive effect. RT treatment for GBM, by its nature, is directed at the brain and has been found to be a cause of cognitive decline [56]. Corticosteroid use, necessary to reduce peritumoral edema, has also been found to have negative effects such as myopathy and insomnia [57]. As a tumor progresses, a high-dose of corticosteroids is required resulting in clinically significant negative effects on the patients. While no study to date has evaluated corticosteroid impact on QoL, the adverse side effects are widely regarded to result in reduced QoL [52, 57, 58]. While less studied than corticosteroids, antiepileptic drugs, usually given in conjunction with corticosteroids, have been found to impair working memory capacity more than RT [56, 59]. Altogether, the tumor, GBM-related epilepsy, RT, chemotherapy,

corticosteroids, anti-epileptic drugs, and psychological distress of cancer will contribute to cognitive degeneration and loss in QoL.

Early studies used KPS as a proxy for QoL linking physical ability to mental ability [60, 61]. The studies found that physical performance was maintained after diagnosis for a period that is relatively long compared to the survival time a patient has after diagnosis. The problem researchers faced was that cognition and psychological condition worsened during this period as measured with a patient-oriented questionnaire [62]. Therefore, physical performance was not a good measure of cognition and by extension QoL, highlighting a need for more accurate, and hopefully patient-oriented, QoL measurement strategies [63]. Moreover, as GBM is incurable, the treatment goal is to prolong life and increase QoL requiring an accurate measure of both.

Several neurocognitive assessment tools have been developed to meet this need and are being used in several clinical trials [44, 64]. The most notable questionnaires are the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy cancer-specific scales (FACT) [65].

2.8. Bevacizumab

GBM tumors are highly vascularized tumor bodies due their large nutrition requirements. Therefore, targeting angiogenic pathways limits vascularization, restricting nutrient supply to the growing tumor, and ultimately hindering tumor growth [66]. Current strategies to limit vascularization consist of $\alpha v\beta 5$ integrins, hepatocyte growth factors, and antibodies of vascularization factors like Vascular Endothelial Growth Factor (VEGF). The benefit of some of these therapies is that they can target tumor vasculature directly [66].

BEV is a humanized monoclonal antibody that selectively binds to human VEGF thus preventing vascularization. It has shown the most promising clinical results to treat GBM to date [67, 68]. Manufactured by Genentech/ Roche, BEV is sold under the trade name Avastin and is stored in a 25mg/ml vial [69]. BEV is already approved in the United States and Europe as a standard treatment for metastatic colorectal cancer, advanced non-small cell lung cancer, and metastatic breast cancer [70]. The first studies to evaluate BEV in GBM comes from two phase 2 RCTs: the BRAIN and NCI 06-C-0064E studies, which spawned two additional large phase 3 RCTs for further clinical study [17, 64, 68].

The multicenter, non-comparative, phase 2, BRAIN RCT enrolled 82 recurrent GBM patients and treated them with BEV with and without irinotecan, a topoisomerase inhibitor [71]. For the combination therapy, the investigators found a 38% response rate with a six-month progression free survival of 50% and a median overall survival of 8.6 months [72]. This is a 50% increase in overall survival compared to historical rates [66, 72, 73]. As a single therapeutic agent, BEV had a 28% response rate with a six months progression free survival of 42.6% and median overall survival of 9.2 months [72].

The NCI study enrolled 48 patients with recurrent GBM and treated them with BEV as a single therapeutic agent [74]. The study had favorable results: the median progression free survival was 16 weeks, 29% six months progression free survival, and median overall survival of 31% [74].

Due to these two studies, the FDA accelerated approval of the phase 2 BEV drug to treat recurrent GBM following RT and TMZ therapy. However, the EMEA, the European drug regulatory agency, did not approve BEV as a treatment for recurrent GBM [75].

A meta-analysis of BEV trials found that of a total 621 GBM patients, BEV treatment had a median overall survival was 9.3 months (95% CI: 7.9 to 10.6) and SOC had a median overall survival of 8.1 months (84, 85). Moreover, six-month progression free survival was 45.2% and overall six-month survival was 76.4% [76]. Altogether, BEV has shown promise in treating GBM.

In addition to the potential increase in overall survival and progression free survival, BEV has the added benefit in recurrent GBM patients of reducing or eliminating the need of corticosteroids [77, 78]. In clinical trials, reduced corticosteroid use resulted in increased cognitive function and QoL [71, 78]. Moreover, BEV treated patients maintained their KPS levels longer than SOC patients [71].

Most of the side effects of BEV are already known due to its use in other cancer therapies, with BEV having the same toxicity in GBM treatment [71, 77]. The most common adverse effects of BEV in GBM are low-grade bleeding, hypertension, impaired wound healing, and proteinuria. Most of these adverse effects are typical in therapies targeting VEGF and are found on-target. Grade two bleeding has been found to occur in 5.3% of patients, while serious gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome, cardiac failure, and wound-healing events occur in fewer than 2% of patients [66, 71, 77]. Approximately 3% or fewer of patients will experience life-threatening intracranial hemorrhages. BEV trials have found a high risk of thromboembolism in patients (1.6% to 12.5%); however, the nature of GBM increases the risk of thromboembolism on its own [79]. Overall, BEV has been shown to have clinically low risks of life-threatening complications.

As no phase 1 RCT was performed for BEV for newly diagnosed GBM, no BEV SCO dose has been established; however, the manufacturing company (Genentech/ Roche) recommends 10mg/kg every two weeks for GBM treatment [77]. Two large phase 3

RCTs used the recommended BEV dosing during their concurrent treatment phases [17, 80].

2.9. Bevacizumab plus SOC for First Line Glioblastoma Treatment

Reaction to the FDA's approval of BEV in recurrent GBM was mixed, with many healthcare professionals questioning the interpretation of study results [48]. While the FDA approved BEV, the EMEA rejected the use of BEV because they questioned the accuracy of the CT or MRI scans used to evaluate tumor progression [81]. BEV acts to reduce VEGF, and therefore normalize tumor vascularization, which in turn decreases cerebral vessel permeability in the scans. This has the effect of reducing contrast-enhanced components even if the tumor was progressing [82].

Additionally, the FDA evaluated the uncontrolled BEV clinical trial data against historical controls. Effectively, BEV was compared against a control group that may have experienced different environmental exposures and treatment [83].

Two phase 3, double-blinded, randomized control clinical trials were completed to evaluate BEV for first line GBM. The Avastin in Glioblastoma (AVAglio) trial was industry sponsored [16], while the Radiation Therapy Oncology Group (RTOG) 0825 clinical trial was publicly sponsored [17]. The results from both trials were presented at the 2013 American Society of Clinical Oncology (ASCO) meeting [48]. Currently, BEV has not been added to the SOC [48].

2.9.1. AVAaglio Clinical Trial

The F. Hoffmann-La Roche sponsored AVAaglio trial enrolled 921 patients from 120 sites in 23 countries to evaluate concomitant BEV plus the SOC to treat newly diagnosed GBM patients [16, 64]. The trial had two co-primary endpoints: progression free survival and overall survival. The first co-primary endpoint, progression free survival, was 80% powered to detect a 0.77 (two sided alpha of 1%) hazard ratio, with the second co-primary endpoint, overall survival, 80% powered to detect a 0.80 (two sided alpha of 4%) hazard ratio [64]. The overall significance divide was weighted towards overall survival, as it is a typical endpoint in phase 3 clinical trials. QoL measurements were defined as a secondary endpoint and therefore mandatory for all patients. Exploratory analysis was performed to investigate predictive biomarkers intended to aid clinicians in identifying future candidates receptive to BEV for first line treatment [64].

The patient population was defined as those greater or equal to 18 years of age, with newly diagnosed, histologically confirmed, supratentorial GBM [64]. The main exclusion criteria include prior chemotherapy or immunotherapy for GBM or low-grade astrocytoma, prior radiation therapy to the brain, recent intracranial hemorrhage, history of intracranial abscess, non-healing wound, active ulcer, and untreated bone fracture [64].

Eligible patients received tumor excision or biopsy and were randomized to a treatment arm between 28 and 49 days post-surgery. All patients received 2Gy of local irradiation, five days per week, for six weeks concomitant with 75mg/m² oral TMZ every day, for a maximum of 49 days during the concomitant phase. The maintenance phase commenced after a four-week break where patients were given 150-200 mg/m² of oral TMZ daily on days one to 5, each week, for four weeks. The maintenance phase cycle was repeated six times for a maximum total of 24 weeks. BEV plus the SOC patients received 10 mg/kg intravenous every two weeks during the concomitant phase and maintenance phase, and 15 mg/kg every three weeks during the monotherapy phase, post maintenance phase, until

disease progression. SOC patients were given placebo instead of BEV [64]. Imaging used to evaluate tumor progression was evaluated by central review [64].

Once the patient experienced tumor progression, the study protocol allowed patient arm crossover for progression treatment at the discretion of the treating physician. 31% of the overall study patient population received further BEV treatment and 35.6% were treated with TMZ [84]. Moreover, up to 30% of control patients are estimated to have received BEV during tumor progression [85].

The AVAglio trial showed a significant improvement in progression free survival, but failed in overall survival. The median BEV plus the SOC arm progression free survival was 10.6 month compared to the control's 6.2 months ($p < 0.0001$; hazard ratio=0.64); median overall survival was similar, albeit slightly longer, between the BEV plus the SOC and SOC arm (16.8 months vs. 16.7 months; $p = 0.10$; hazard ratio=0.88). No new toxicities were seen in the BEV plus the SOC treated population; however, serious adverse events were more common in the experimental arm compared to the SOC arm [16].

The AVAglio trial investigated QoL measures using a pre-specified five dimensions from the EORTC QLQ-C30 survey with brain module (global health status, communication deficits, physical function, social function, motor dysfunction). The trial found a significantly longer period of deterioration free survival in the BEV plus the SOC arm compared to SOC. Moreover, BEV patients had a statistically longer period without corticosteroids and a Karnofsky performance score above 70 [16].

No biomarker evaluated in the exploratory analysis was determined to be a good predictor of BEV response [16].

2.9.2. RTOG 0825 Clinical Trial

The Radiation Therapy Oncology Group (RTOG) who collaborated with the North Central Cancer Therapy Group (NCCTG), and Eastern Co-operative Oncology Group (ECOG) sponsored the RTOG 0825 trial. 637 patients from were included in the study [17]. Similar to the AVAglío study, the RTOG 0825 trial had two co-primary endpoints: progression free survival and overall survival. The co-primary endpoints were jointly 80% powered to detect a 30% reduction (two sided alpha of 0.4%) in progression free survival hazard and 25% reduction (two sided alpha of 4.6%) in overall survival hazard. QoL measures were classified as a tertiary endpoint, and therefore not mandatory for patients to complete. Similarly to the AVAglío trial, exploratory analysis was conducted to identify bevacizumab efficacy biomarkers [17].

The study population was similar to the AVAglío trial, with patients only receiving tumor biopsy excluded. All RTOG 0825 patients were randomized to a trial arm within three to five weeks post-surgery, and received a similar treatment regimen to patients in the AVAglío trial. Main differences in treatment were that BEV plus the SOC arm patients received three weeks of BEV during the concomitant phase, rather than six weeks in the AVAglío trial, and 12 weeks of TMZ and BEV during the maintenance phase, rather than a maximum of 24 weeks in the AVAglío trial. Imaging used to evaluate tumor progression was evaluated to clinical investigators.

Similar to the AVAglío trial, once tumor progression occurred, the protocol allowed for patient arm crossover. Crossover was pre-specified to either BEV, concomitant BEV plus TMZ, or concomitant BEV and irinotecan therapies. 20.9% of patients in the BEV arm received a BEV regimen, while 40.9% of patients in the SOC arm received a BEV regimen during progression treatment.

Neither of the RTOG 0825's primary endpoints, progression free survival or nor overall survival, reached significance. BEV was associated with a longer median progression free survival (10.3 vs. 7.3 months; $p=0.007$; hazard ratio=0.79) compared to the SOC arm. Median overall survival, however, was slightly shorter in the BEV arm compared to placebo (15.7 vs. 16.1 months; $p=0.021$; hazard ratio=1.13) [17].

The RTOG 0825 trial evaluated QoL by longitudinal analysis of two QoL surveys (MD Anderson Symptom Inventory Brain Tumor survey and EORTC QLQ-C30 with brain module). The trial reported that BEV patients experienced a significant worsening of QoL as compared to control patients [17].

The RTOG 0825 trial did find a molecular signature showing a relationship of increased overall survival in BEV patients [17]; however, the observation requires prospective validation [84].

2.9.3. Controversy Between AVAglio and RTOG 0825

Both the AVAglio and RTOG 0825 trials employed similar study designs and reported similar trends in survival outcomes (Table 1). However, contradictory progression free survival and QoL results were reported, in addition to a puzzling overall survival outcome. These differences are described in more detail below.

2.9.3.1. Differences – Progression Free Survival Outcomes

The AVAglio and RTOG 0825 trials reported an increased progression free survival in the BEV plus the SOC arm in comparison to the SOC arm (10.6 and 10.3 in the BEV plus

the SOC arm compared to 6.2 and 7.3 months in the SOC arm respectfully). However, the difference was reported as significant in the AVAglio trial and non-significant in the RTOG 0825 trial. The difference in significance result is due to a larger alpha value attributed to progression free survival in the AVAglio trial as compared to the RTOG 0825 trial (1% and 0.4% respectively). Therefore, the AVAglio trial reached its significance level while the RTOG 0825 trial did not.

2.9.3.2. Differences – Quality of Life Measures

QoL measures reported between the two trials were also contradictory. The AVAglio trial reported that QoL of patients receiving BEV was maintained for a three to four month longer period of time as compared to control patients. The RTOG 0825 trial, however, reported that BEV patients experienced a decrease in QoL as compared to control patients. This contrast in study results is likely multifactorial, and may be associated to study design differences specified in each trial. The AVAglio trial had looser eligibility criteria as compared to the RTOG 0825 in that AVAglio accepted patients whom only received biopsy while the RTOG 0825 did not. Therefore, the AVAglio trial would allow patients with a larger tumor burden into the study [86]. Moreover, the AVAglio trial specified QoL measures as a secondary outcome requiring all patients to complete the surveys, while the RTOG 0825 specified QoL as a tertiary outcome. As seen in reported outcomes, the RTOG 0825 QoL assessment saw significant patient attrition over the trial period [17].

Additionally, the AVAglio trial measured QoL as the median time to a ≥ 10 point QoL survey deterioration from baseline with no improvement, disease progression or death whereas the RTOG 0825 trial also looked at progression free patients but measured QoL using discrete time point analysis and longitudinal general linear modeling. The two methods analyzing QoL outcomes are very different and make a direct comparison difficult.

Finally, the RTOG 0825 measured radiological response using the traditional Macdonald criteria which does not account for non-enhanced tumor progression, while the AVAglio study used similar response criteria as defined by the Response Assessment in Neuro-Oncology Working Group which does account for non-enhanced disease progression [87]. The consequence of the study design difference could be that the RTOG 0825 trial would disproportionately and incorrectly classify early progression BEV patients as progression free, compared to control patients, and include them in the progression free QoL analyses [85].

Numerically, the RTOG 0825 saw 79.4% of its population complete a baseline QoL questionnaire, while the AVAglio study had all patients complete a baseline questionnaire. No statistical differences, using a 5% alpha, were found between the baseline characteristics of patient who completed the baseline questionnaire versus those who did not in the RTOG 0825 RCT.

Table 1. Summary of the AVAglio and RTOG 0825 clinical trials

Point of Comparison	AVAglio	RTOG 0825
Study Design	Double blind placebo-controlled	Double blind placebo-controlled
Primary Endpoint	PFS and OS co-primary	PFS and OS co-primary
Secondary Endpoint	QoL	-
Tertiary Endpoint	-	QoL and neurocognitive function
Eligibility	Biopsy only patients allowed; multifocal tumors allowed	Biopsy only patients excluded; multifocal tumors excluded
Statistical Significance	Overall $\alpha=0.05$, PFS $\alpha=0.01$; OS $\alpha=0.04$	Overall $\alpha=0.05$, PFS $\alpha=0.004$; OS $\alpha=0.046$

Table 2 Continued. Summary of the AVAglio and RTOG 0825 clinical trials

Point of Comparison	AVAglio	RTOG 0825
Start of Chemotherapy	>28 and ≤ 49 days after surgery	>21 and ≤ 35 days after surgery
Number of TMZ Cycles	6	12
Start of BEV	Day 1	Day 28
Continuation of BEV	Until progression	Until progression
Assessment of Progression	Enhanced and non-enhanced imaging; clinical assessment	Enhanced imaging; clinical assessment
Unbinding and Arm Crossover at Progression	Not planned, but anticipated	Planned
Number of Patients	921	637
Percentage of Patients with Total Tumor Resection	41% Bev, 42.3% TMZ	63% Bev, 59% TMZ
PFS Months (Median)	Bev – 10.6 TMZ – 6.2	Bev – 10.7 TMZ – 7.3
PFS Hazard Ratio	0.64 (95% CI 0.55-0.74)	0.79 (95% CI 0.66-0.94)
OS Months (Median)	Bev – 16.8 TMZ – 16.7	Bev – 15.7 TMZ – 16.1
OS Hazard Ratio	0.88 (95% CI 0.76-1.02)	1.13 (95% CI 0.93-1.37)
QoL	Longer time to definitive deterioration with BEV	Worsening with BEV for some QoL components

2.9.3.3. Overall Survival Outcomes

It is interesting that both trials showed a marked increase in progression free survival, while no increase in overall survival. Several theories as to why this result was reported have been published without any conclusive response.

The first theory focuses on the study arm crossover design used in both trials, which allowed patients in both arms to receive BEV during tumor progression. Therefore, it is possible that BEV slows tumor development, an effect nulled by patients in the SOC arm receiving BEV [48]. The second theory explores tumor resistance to BEV therapy by upregulating pro-angiogenic signaling pathways already upregulated by BEV treatment. Therefore, new blood vessels develop from pre-existing vessels through angiogenesis, rather than de novo formation of endothelial cells via vasculogenesis [88, 89]. The third theory is based on increased tumor aggressiveness post BEV treatment. Moreover, the BEV experienced tumors did not seem to respond to additional or subsequent BEV treatments [90, 91]. As study arm crossover at tumor progression was allowed in both the AVAglio and RTOG 0825 trials, and no SOC arm was designed in the BRAIN study, it is currently unclear whether BEV can extend overall survival.

Overall, the current BEV studies did not find a significant increase in overall survival for newly diagnosed GBM. It does, however, show that progression free survival is increased, a state that is considered to have higher QoL compared to progression, at the expense of increased toxicity [44]. The current lineup of therapies for newly diagnosed GBM is limited and similarly does not provide solutions to increased overall survival. Clinicians are starting to question, in the interim of finding a solution for overall survival, whether attention should be focused on progression free survival and QoL [48, 84, 85, 92, 93].

Chapter 3

3. Chapter: Research Question

The purpose of this study is to conduct a cost-utility assessment of BEV treatment for newly diagnosed GBM concomitant with TMZ, the SOC, compared to the SOC alone across all health states. It evaluates the incremental cost utility ratio of BEV plus the SOC compared to the SOC using real-world costs and event rates to understand if the new BEV plus the SOC is cost-effective, and therefore a candidate, to treat GBM as a first-line therapy.

Chapter 4

4. Materials and Methods

An economic model was constructed to compare the cost utility of BEV plus the SOC compared to the SOC. A microsimulation model was used to calculate an incremental cost utility ratio (ICUR) to allow to for time dependent transition probabilities, time dependent event and costs, and time dependent quality of life measures. Survival data from the AVAglio and RTOG 0825 trials was used to calculate transition probabilities. Health records from Ontario patients were used to calculate costs and event distributions for the SOC arm. Relative risks from the AVAglio and RTOG 0825 applied to the SOC arm was used to calculate cost and event distributions for the BEV plus SOC arm. Published utility measures were used for both arms.

4.1. Cost Effectiveness Model

4.1.1. Model Structure

GBM patient health states segment into three categories: progression free tumor, tumor progression, and death (Figure 2) [94-96].

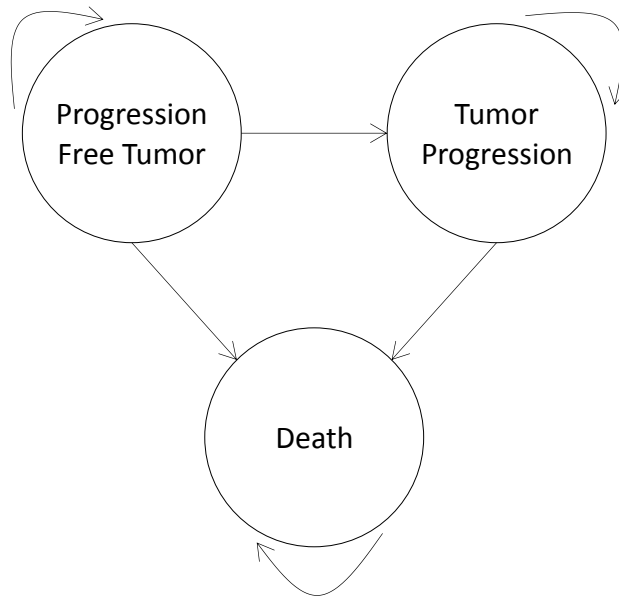


Figure 2. Progression states and transition directions in Markov model of GBM treatment during each one-month cycle

The progression free tumor state is where a patient is diagnosed and treated for GBM, but the disease does not progress in severity or size. The patient can remain in this state as long as treatment remains effective. If however, the GBM tumor stops responding to treatment and starts to progress, the patient transitions from the progression free state to the tumor progression state. Once in the progression state, the patient cannot return to the progression free state, but remains in the progression state until they transition into the death state. Additionally, due to background death rates, a patient in the progression free state can enter the death state.

Pooled AVAglio and RTOG 0825 survival data was used to calculate and populate the transition probabilities from progression free to progression states, called progression free survival, and the transition probabilities from progression to death for both the TMZ and

BEV. The existing RCTs do not directly evaluate the transition probabilities from progression to death; they instead calculate the probability of transferring through the entire model, from progression free to death termed overall survival. Therefore, both the model's progression free survival and overall survival matched progression free survival and overall survival seen in the literature.

A Markov model was built in TreeAge to analyze the cost-effectiveness of BEV concomitant with the SOC compared to the SOC along in newly diagnosed GBM [97]. As represented in Figure 2's model structure, the TreeAge Markov model had three states (Figure 3): progression free, progression, and death.

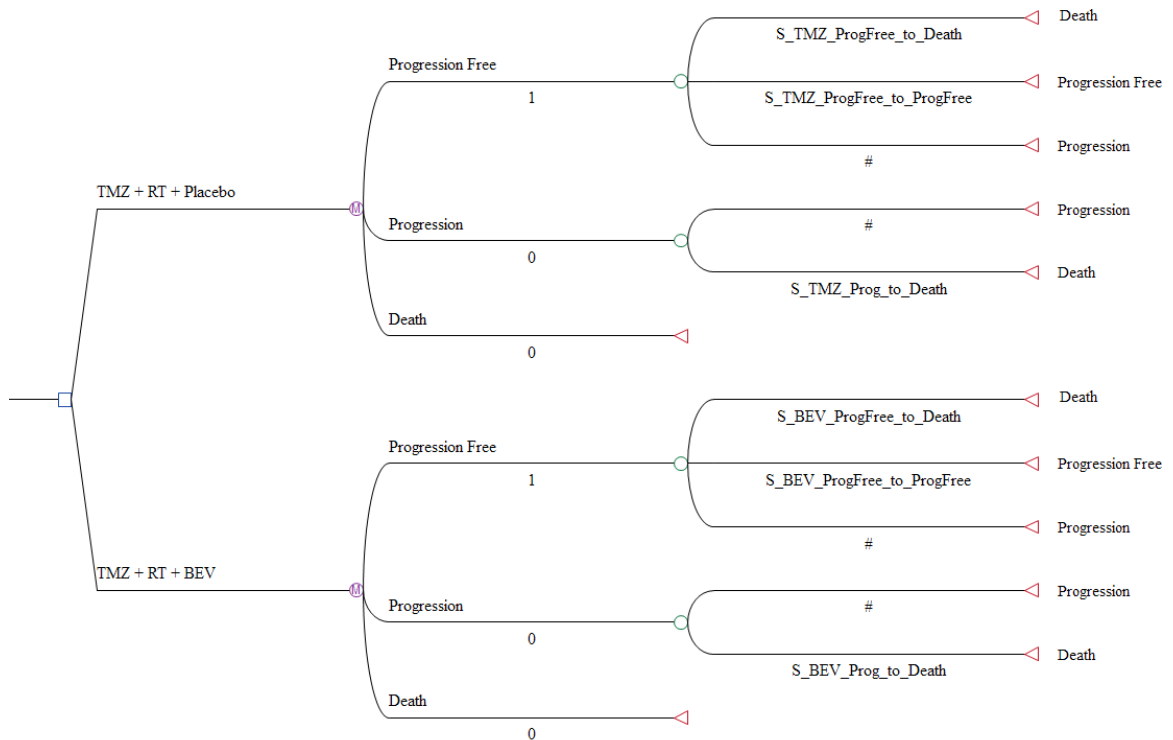


Figure 3. A TreeAge diagram of a Markov model used to calculate the cost-effectiveness of BEV added to the standard of care compared to the SOC for newly diagnosed GBM

This cost-effectiveness study is conducted from the public payer's perspective. This study will use a WTP threshold of three times the 2014 GDPC as reported by the World Bank: \$132,264 [98].

4.2. Data Sources

4.2.1. Survival Probabilities

The model's survival probabilities were collected from the AVAglio and RTOG 0825 published progression free survival and overall survival Kaplan-Meier curves [16, 17]. These phase 3 double blind randomized controlled trials directly compared the two interventions examined in this cost-effectiveness study.

4.2.2. Costs

Costs parameters for this study were collected from patient-level Ontario administrative health records through the CD-Link program (Table 3). The CD-Link program access the primary, secondary, tertiary, and drug claim costs when submitted to the Ontario Ministry of Health and Long-Term Care for reimbursement. Patient level records are linked using each Ontario resident's Ontario Health Insurance Plan (OHIP) number and tracked longitudinally. Patients were identified as diagnosed with GBM using the Ontario Cancer Registry (OCR) and tracked using several databases: OHIP, Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), New Drug Funding Program (NDFP), and Ontario Drug Benefit (ODB). The OHIP database captures primary and secondary care, the DAD captures inpatient hospitalizations and same-day-surgeries, while the NACRS captures emergency department visits. The ODB database captures listed out of hospital pharmacy claims while the NDFP was used to capture in hospital chemotherapy administration.

Table 3. List and description of healthcare databases accessed under the CD-Link program to evaluate the costs incurred by glioblastoma patients in Ontario

Database Name	Database Description
Ontario Cancer Registry (OCR)	Contains the diagnostic test results, diagnosis, treatment information of cancer patients in Ontario
Ontario Health Insurance Plan (OHIP)	Contains the billing claims of ~94% of Ontario physicians with a fee-for-service practice
Discharge Abstract Database (DAD)	Contains administrative, clinical, and demographic discharge notes from acute care and same-day surgery hospitalizations
National Ambulatory Care Reporting System (NACRS)	Contains administrative, clinical, and demographic discharge notes from emergency department visits
New Drug Funding program (NDFP)	Contains financially covered intravenous cancer drugs approved for treatment in Ontario hospitals
Ontario Drug Benefit (ODB)	Contains the prescriptions billing claims made to the Ontario Ministry of Health and Long-Term Care

As no patients in Ontario received BEV, the NDFP was used to identify patient height, weight, progression state costs, and BEV cost per kg in non-GBM cases.

Prior studies have shown the OHIP, DAD, and OCR databases to accurately represent the Ontario general population with excellent coverage [99-101].

4.2.3. Utilities

Health utility values were gathered from a study by Garside et al. [44], which evaluated the cost-effectiveness of carmustine implants, and TMZ in newly diagnosed GBM. The Garside et al. study used the standard gamble method to calculate the utility of a GBM patient receiving the SOC during the concomitant and maintenance phase of their treatment. Therefore, the relationship between the health state and the QoL was determined by actual GBM patients within a health state describing their QoL. As was stated in the Garside et al. study, health utility values in the progression free state were assumed to remain constant at the progression free value. Once a patient progresses into the progression state, the utility value would decrease by 0.02 quality adjusted life years (QALY) for each incremental month until the patient entered the death state. [44]. Health utility values for patient in the progression state were restricted to a minimum of 0 QALY.

4.3. Survival Analysis

4.3.1. Reconstructing Individual Patient Values

Results from both the AVAglio and RTOG 0825 clinical trials were included in this study; however, individual patient data was not published for either study. For a cost utility analysis, a placebo or base case arm and treatment effect is required for transition probabilities into various health states. The placebo arm can be estimated using least squares or graphical methods from the published graphs while treatment effect is typically reported as a hazard ratio [102-104].

The drawbacks of least square or graphical methods include accuracy of the digitizing software, the applicability of the parametric model used to recreate the survival curve, and the assumptions required to extrapolate treatment horizons. Additionally, the use of a hazard ratio to estimate the treatment arm implies the proportional hazard's assumption – an assumption that is rarely tested [104]. Moreover, this study requires evidence synthesis of the two trials. Therefore, an algorithm developed by Guyot et al. was used to estimate individual patient data using digitized Kaplan-Meier curves and pooled together to generate transition probabilities [105].

Published in 2012, the Guyot et al. method uses an iterative algorithm that first estimates the number of censored cases within an interval. Using this initial estimate, the number of censored cases between Kaplan-Meier coordinates is calculated. The algorithm then calculates the number of events within the interval and number at risk at the start of the next interval. If the number reported at risk and the number estimated at risk do not equal, the process is repeated until the two numbers are aligned [102, 105].

Wan et al. used Monte Carlo simulations to test the Guyot et al. algorithm and estimate its accuracy. They found that the method's estimates were better than least squared and graphical methods when tested on Weibull distributed survival outcomes. Moreover, the Guyot et al. method performed better than an alternative method developed by Hoyle and Henley when tested on lognormal distributed survival outcomes [102].

4.3.2. AVAglio Survival Analysis

Published progression free and overall survival Kaplan-Meier curves from the AVAglio study were digitized, converted into individual patient data using the Guyot et al. method, and recreated for validation. The AVAglio trial reported a progression free survival hazard ratio of 0.64 (95% CI, 0.55-0.74) and a statistically significant difference in

survival distributions using a log-rank test ($p < 0.001$) (Figure 4). The recreated progression free survival Kaplan-Meier curves reported a hazard ratio of 0.65 (95% CI, 0.56-0.75) with a significant log-rank test ($p < 0.001$) closely approximating the original curve (Figure 4).

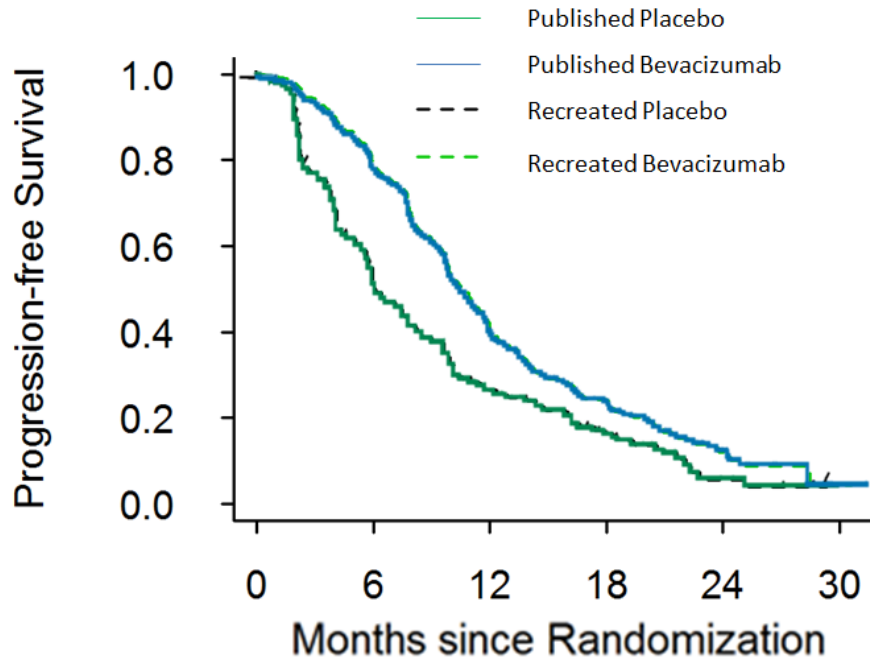


Figure 4. Published and recreated AVAglio clinical trial progression free survival Kaplan-Meier curves of the two treatment arms

The AVAglio trial reported an overall survival hazard ratio of 0.88 (95% CI, 0.79-1.02) with no statistical difference in survival distribution ($p = 0.10$) (Figure 5). The recreated AVAglio overall survival reported a hazard ratio of 0.90 (95% CI, 0.78-1.05) with no statistical difference in survival distribution ($p = 0.194$). Similar to the recreated progression free survival Kaplan-Meier curves, the overall survival recreated Kaplan-Meier curves closely approximate the published AVAglio overall survival Kaplan-Meier curves (Figure 5).

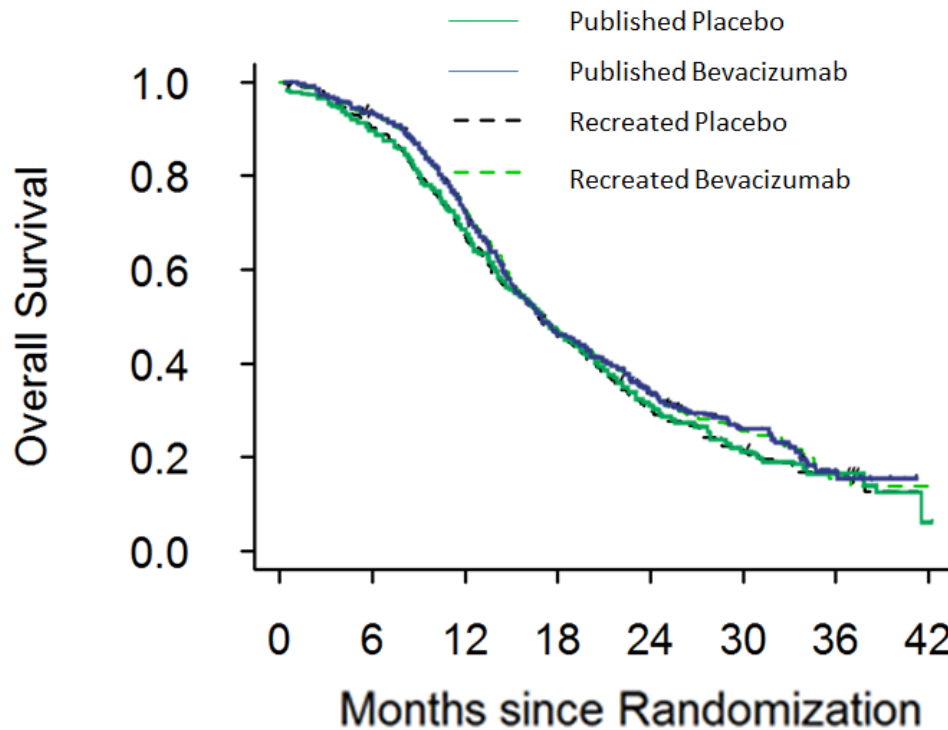


Figure 5. Published and recreated AVAglio clinical trial overall survival Kaplan-Meier curves of the two treatment arms

4.3.3. RTOG 0825 Survival Analysis

Similar to the AVAglio trial, the RTOG 0825 clinical trial published progression free survival and overall survival Kaplan-Meier curves. Both the published charts were digitized, converted into individual patient data using the Guyot et al. method and recreated for validation [105]. The RTOG 0825 reported a progression free survival hazard ratio of 0.79 (95% CI, 0.66-0.94) with a statistical difference in survival distributions as per a log-rank test ($p=0.007$) (Figure 6). The recreated progression free survival outcomes had a 0.78 hazard ratio (95% CI, 0.65-0.92) with a statistical difference in survival distribution ($p=0.004$). The recreated Kaplan-Meier curves closely

approximate the published RTOG 0825 progression free survival Kaplan-Meier curves (Figure 6).

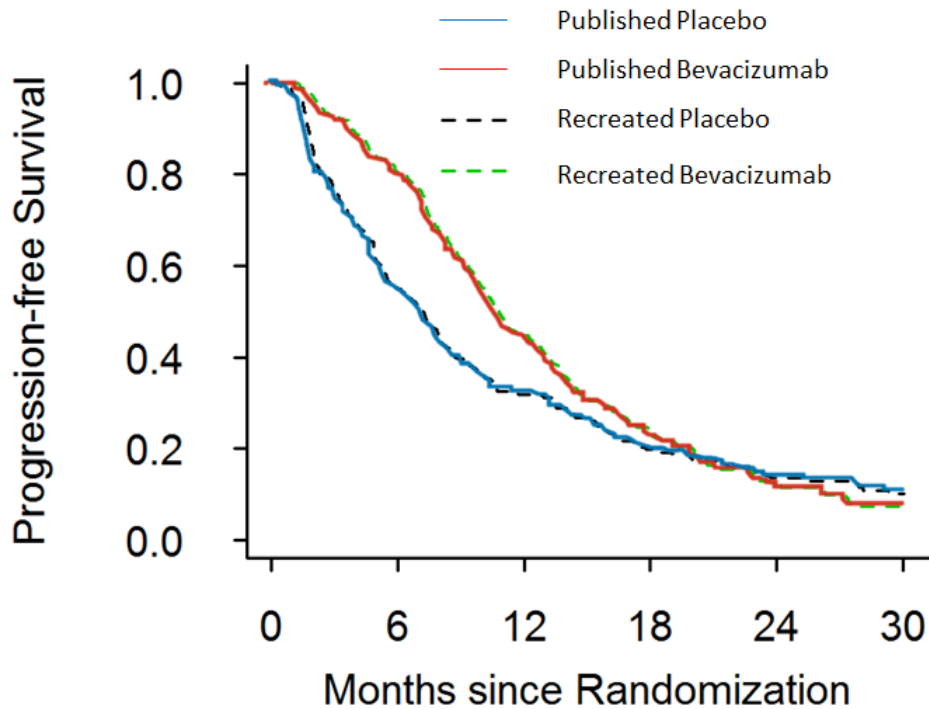


Figure 6. Published and recreated RTOG0825 clinical trial progression free survival Kaplan-Meier curves of the two treatment arms

The RTOG 0825 trial reported an overall survival hazard ratio of 1.13 (95% CI, 0.93-1.37) with no statistical difference in survival distribution ($p=0.21$) (Figure 7). The recreated individual patient data reported an overall survival hazard ratio of 1.11 (95% CI, 0.92-1.35) with no statistical difference in survival distributions ($p=0.29$). The recreated Kaplan-Meier curves closely approximate the published RTOG 0825 overall survival Kaplan-Meier curves (Figure 7).

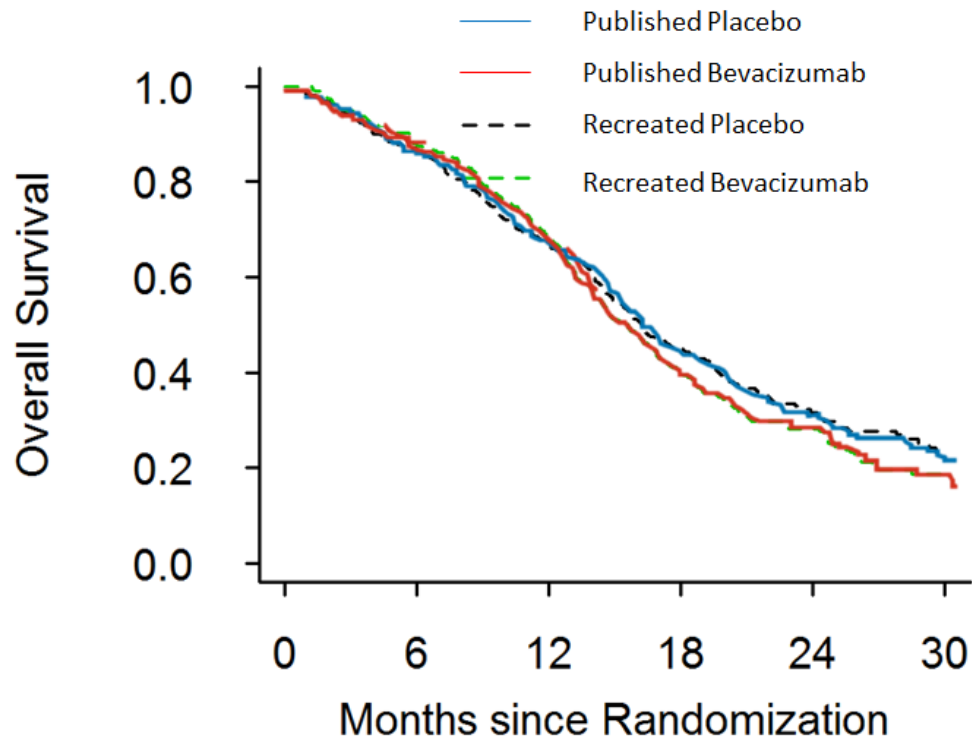


Figure 7. Published and recreated RTOG 0825 clinical trial overall survival Kaplan-Meier curves of the two treatment arms

4.3.4. Pooled Survival Analysis

To incorporate both clinical trials into the cost-effectiveness analysis, each respective trials' progression free survival and overall survival outcomes needed to be synthesized into a single progression free and overall survival metric. A meta-analysis of the hazard ratios could be used, however, the proportional hazard's assumption needs to hold true for an accurate pooled metric [104, 105]. To test the proportional hazard assumption two methods were used: graphical evaluation of the estimated log transformed survival curves (e.g. $\ln(-\ln(\text{survival probability}))$), and goodness-of-fit test [106].

The graphical estimated log transformed survival curves transform the estimated survival curves for each outcome by calculating the negative natural log of each curve twice. Therefore, if the proportional hazards assumption holds, the transformed survival curves should be approximately parallel [106].

The goodness-of-fit test is appealing to researchers because it requires less discretion on whether the transformed survival curves are parallel. To test the proportional hazards assumption using a goodness-of-fit test, the Schoenfeld residuals were evaluated on functions of time. For the proportional hazard's assumption to hold, the Schoenfeld residuals over time should have a non-significant zero slope. If the slope p-value is less than 0.05, we can determine that the proportional hazards assumption does not hold [106].

Using the graphical test evaluating the proportional hazards assumption, we can see that the progression free survival curves for both the AVAaglio (Figure 8) and RTOG 0825 (Figure 9) clinical trials are not parallel. Moreover, the Schoenfeld residuals slope has a statistically significant slope (AVAaglio p-value <0.0001, ROTG 0825 p-value<0.0001). The transformed overall survival curves, however, are parallel for both the AVAaglio (Figure 10) and RTOG 0825 trials (Figure 11), with the Schoenfeld residuals slope not having a statistically significant slope (AVAaglio p-value =0.387, ROTG 0825 p-value=0.0642).

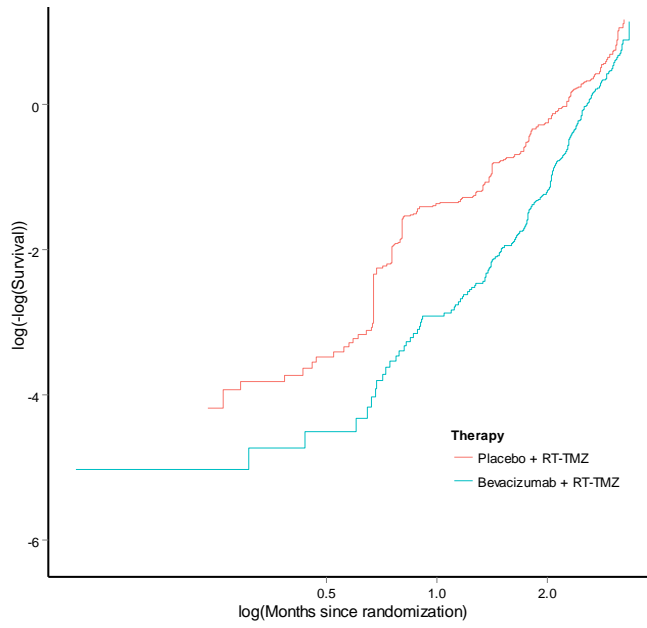


Figure 8. Transformed published AVAglio progression free survival curves of the two treatment arms

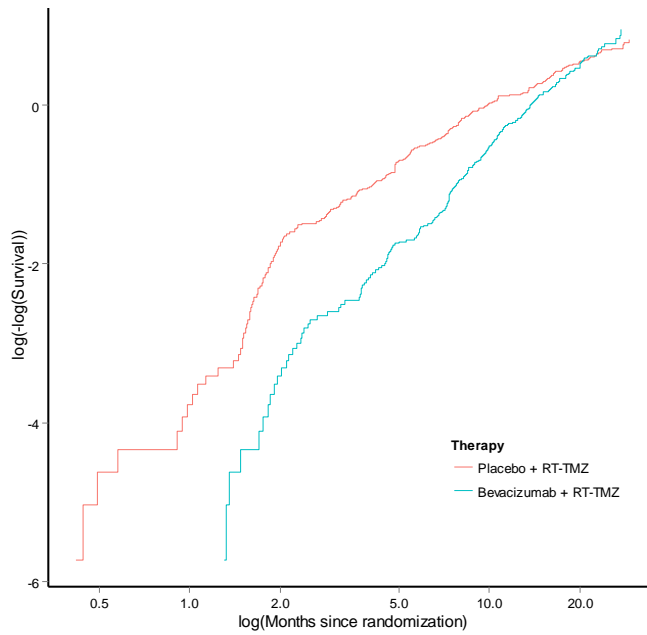


Figure 9. Transformed published RTOG 0825 progression free survival curves of the two treatment arms

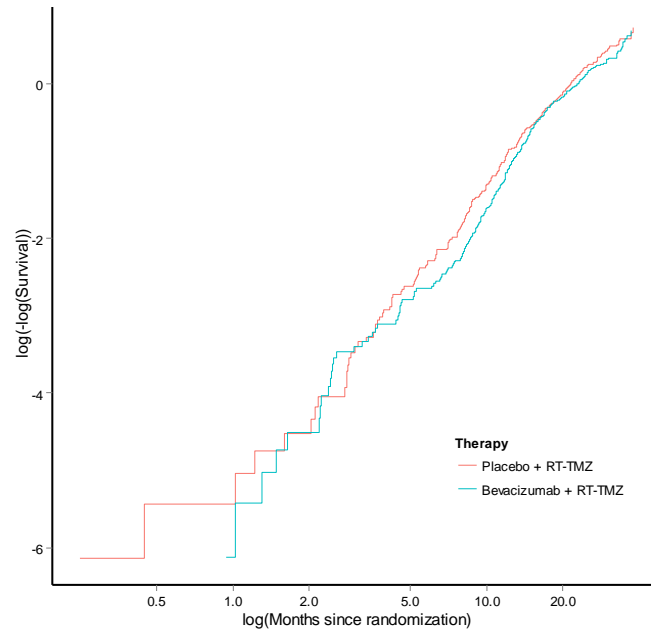


Figure 10. Transformed published AVAglio overall survival curves of the two treatment arms

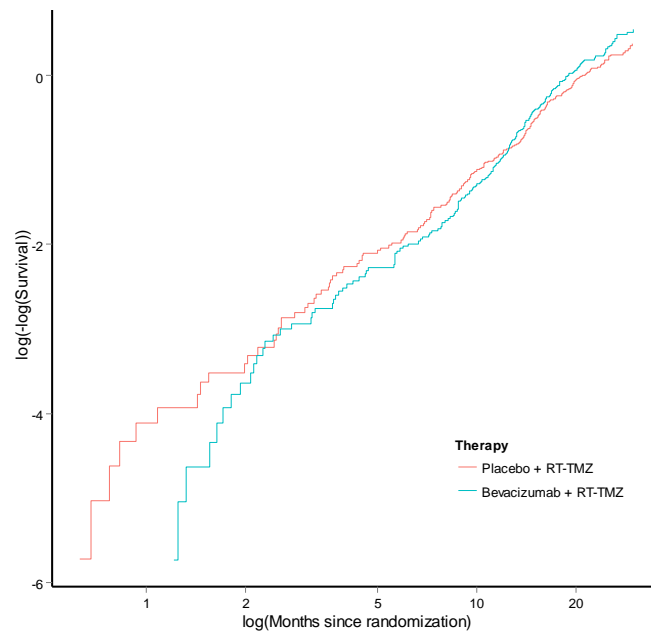


Figure 11. Transformed published RTOG 0825 overall survival curves of the two treatment arms

As the proportional hazards assumption does not hold for the progression free survival outcomes for both the AVAglio and RTOG 0825 clinical trials, a meta-analysis of the hazard ratios is not appropriate. Therefore, both trials' progression free survival and overall survival individual patient data is aggregated respectively to estimate the pooled progression free survival curve (Figure 12) and overall survival curve (Figure 13). As the proportional hazards assumption does not hold for the progression free survival curves, a hazard ratio is not appropriate. However, a log-rank test shows that the survival distributions of the two curves are statistically different (p-value < 0.001). Contrastingly, the proportional hazards assumption does hold for the overall survival curves, and therefore a hazard ratio can be reported. The overall survival hazard ratio is 0.98 (95% CI, 0.87-1.10) indicating a non-significant benefit to using BEV plus SOC compared to SOC alone for first-line GBM. Similarly, a log-rank test shows no statistical difference in overall survival distributions (p-value = 0.709).

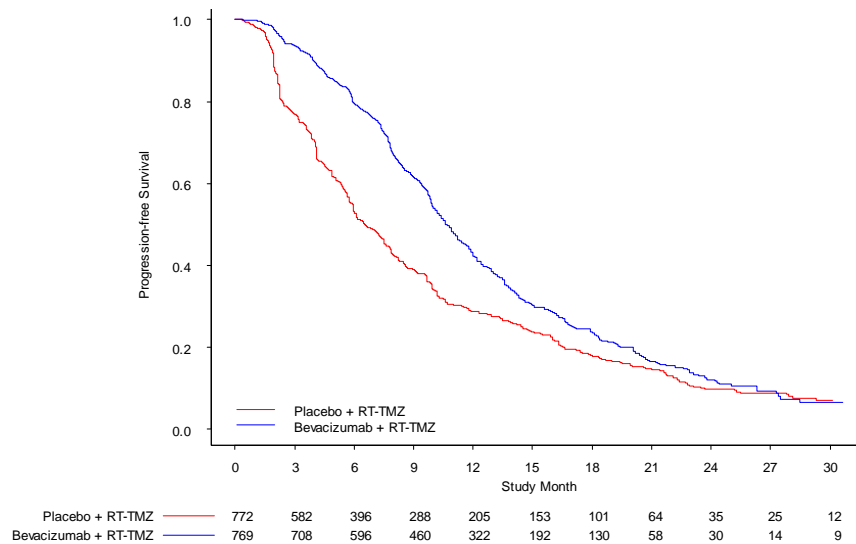


Figure 12. Pooled recreated progression free survival curves from the AVAglio and RTOG 0825 clinical trials of the two treatment arms

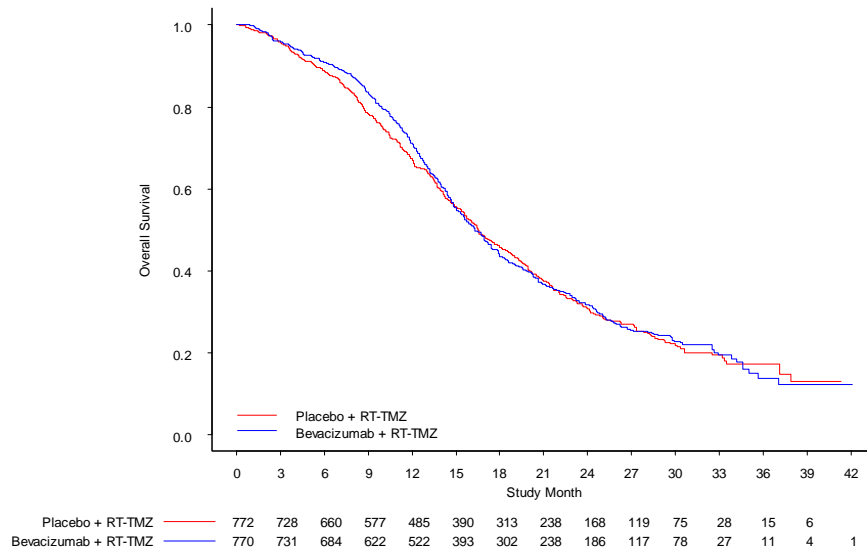


Figure 13. Pooled recreated overall survival curves from the AVAglio and RTOG 0825 clinical trials of the two treatment arms

4.3.5. Survival Analysis Time Horizon

Given the pooled survival outcomes, the maximum time horizon that can be modeled is 30 months. However, five-year overall survival outcomes are published and are valid time horizons for GBM [5]. Therefore, the pooled progression free survival and overall survival curves should be projected forward to estimate survival percentages up to five years.

To project the pooled progression free and overall survival curves forward to a five year (60 months) time horizon, a parametric model was fitted to the existing curves and estimated forward. The following distributions were tested for fit: Generalized gamma, Generalized F, Log-normal, Gamma, Weibull, Exponential, and Gompertz.

For each of the fitted models, the Akaike Information Criterion (AIC) value was calculated. The model with the smallest AIC was chosen as the model with the best fit [107]. Afterwards, a graphical validation of fit was performed between the pooled survival curve and the parametric curve. The final five-year survival curve used pooled survival estimates where possible, after which the best-fit parametric function was used.

The pooled progression free survival SOC arm was best fit by a generalized gamma distribution (Table 4), while the BEV plus SOC arm was best fit by a Generalized F distribution (Table 5). Verifying fit using a graphical method, the two parametric models align well with the pooled progression free survival arms (Figure 13).

Table 4. Calculated AIC of fitted parametric models to pooled progression free survival SOC arm

Distribution	AIC
Gompertz	4337.317
Exponential	4335.481
Weibull	4321.851
Gamma	4306.599
Log-normal	4231.256
Generalized F	4229.912
Generalized gamma	4227.909

Table 5. Calculated AIC of fitted parametric models to pooled progression free survival BEV plus SOC arm

Distribution	AIC
Exponential	4465.777
Gompertz	4363.153
Weibull	4282.523
Log-normal	4276.911
Gamma	4264.200
Generalized gamma	4262.964
Generalized F	4260.803

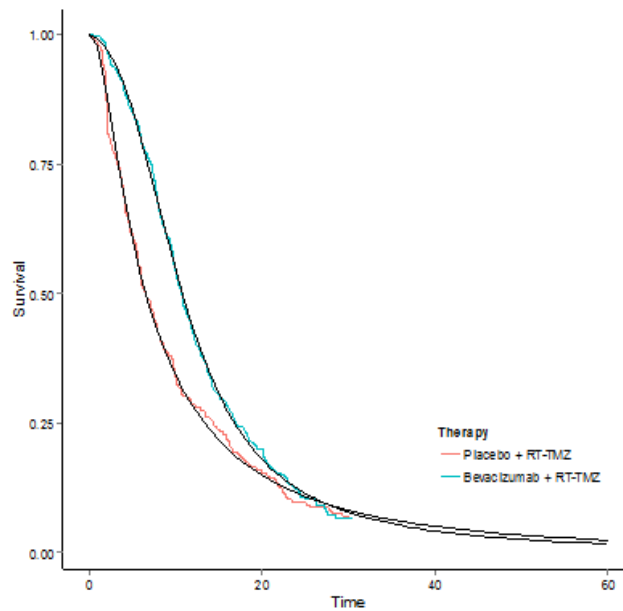


Figure 14. Best fit parametric models overlaid on pooled progression free survival curves

Using the same approach, all parametric models were fitted to the pooled overall survival curve and the AIC was calculated. The SOC (Table 6) and BEV plus SOC (Table 7)

survival curves were better fit by a Generalized F model. When we graphically check the fit of the parametric models, we can see an overall alignment (Figure 15).

Table 6. Calculated AIC of fitted parametric models to pooled overall survival SOC arm

Distribution	AIC
Exponential	4464.264
Gompertz	4396.818
Log-normal	4390.113
Weibull	4353.332
Generalized gamma	4351.129
Gamma	4349.144
Generalized F	4344.056

Table 7. Calculated AIC of fitted parametric models to pooled overall survival BEV plus SOC arm

Distribution	AIC
Exponential	4542.277
Gompertz	4451.422
Log-normal	4409.961
Weibull	4390.536
Generalized gamma	4383.37
Gamma	4381.543
Generalized F	4353.962

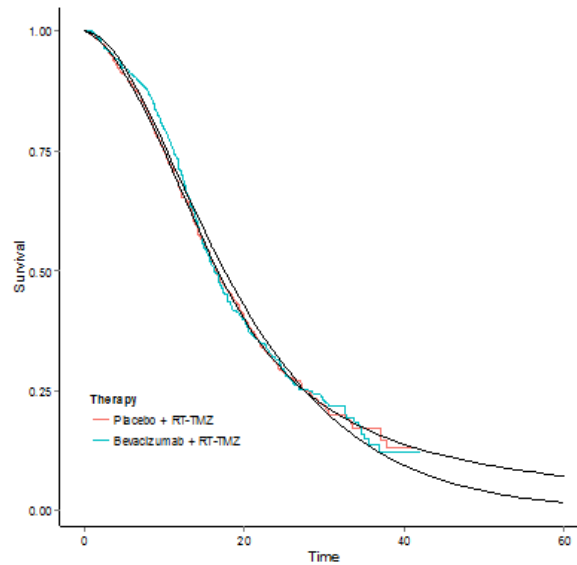


Figure 15. Best fit parametric models overlaid on pooled overall survival curves

4.3.6. Markov Model Transition Probabilities

The transition probabilities guiding the chances of changing health states were derived using the pooled progression free and overall survival curves. Strictly, a Markov model is governed by the Markov property – the memoryless property of a stochastic process [108]. That is to say, the probability of changing health states is dependent only on the current health state, and therefore requires no memory of the time spent in that health state or any state prior. This would imply that the chances of tumor progression would not change if someone were in the progression free state for a short period or a long period. In order to accommodate time dependent transition probabilities, an adapted Markov process – time-varying transition probability Markov model – was used in this study’s model. Therefore, the time spent within a health state can impact the chance of changing health states.

The progression free survival to progression health state transition probabilities were calculated using Equation 2 [108]. The probability of transitioning from a progression to

death health state was solved using a trial and error method until the modeled and true overall survival curves aligned.

Equation 1. Formula used to calculate the survival estimates for the progression free survival arms

$$\hat{S}(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i} = \prod_{t_i < t} Pr(PFS\ survival)_i \quad (1)$$

Equation 2. Formula used to calculate the transition probabilities for progression free survival arms

$$Pr(PFS\ Survival)_i = \frac{\hat{S}(t+1)}{\hat{S}(t)} \quad (2)$$

4.3.7. Validation of Markov Model

The true progression free and overall survival SOC and SOC and BEV survival arms were compared to the modeled progression free and overall survival SOC and SOC and BEV survival arms to ensure similarity. Using the graphical method, we can see that the modeled arms closely align with the true survival arm for all four survival curves – SOC progression free survival (Figure 16), SOC overall survival (Figure 17), SOC and BEV progression free survival (Figure 18) and SOC and BEV overall survival (Figure 19).

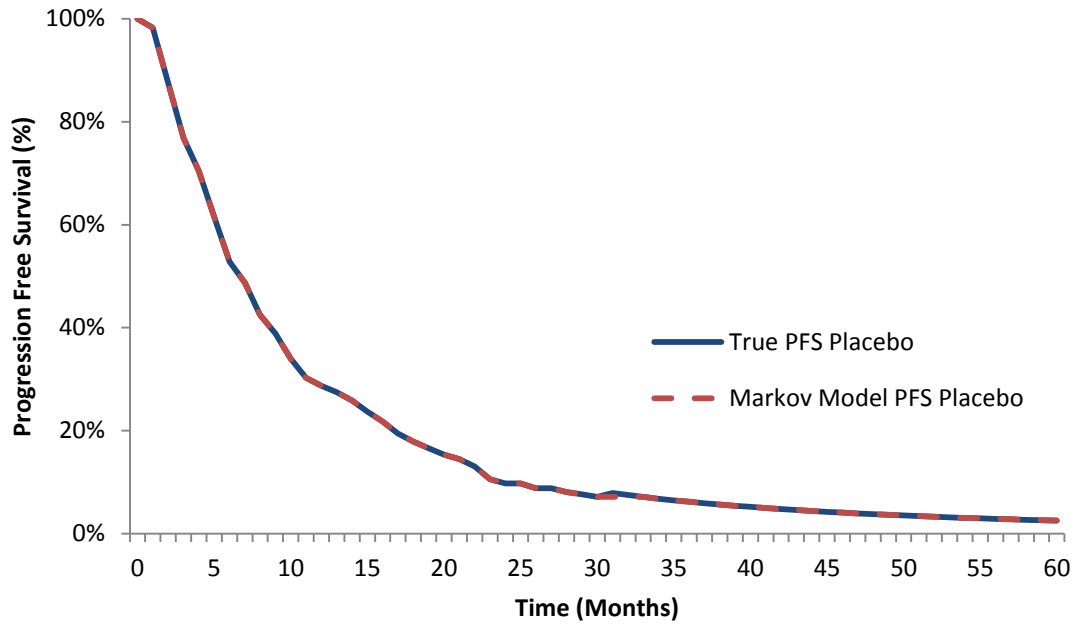


Figure 16. Modeled and true SOC progression free survival curves

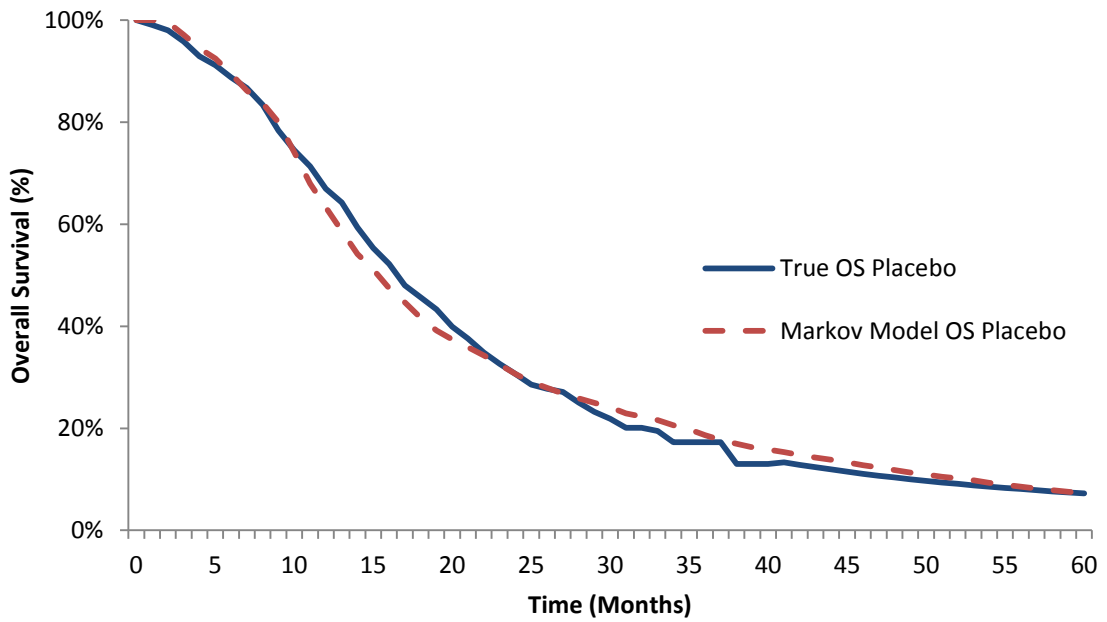


Figure 17. Modeled and true SOC overall survival curves

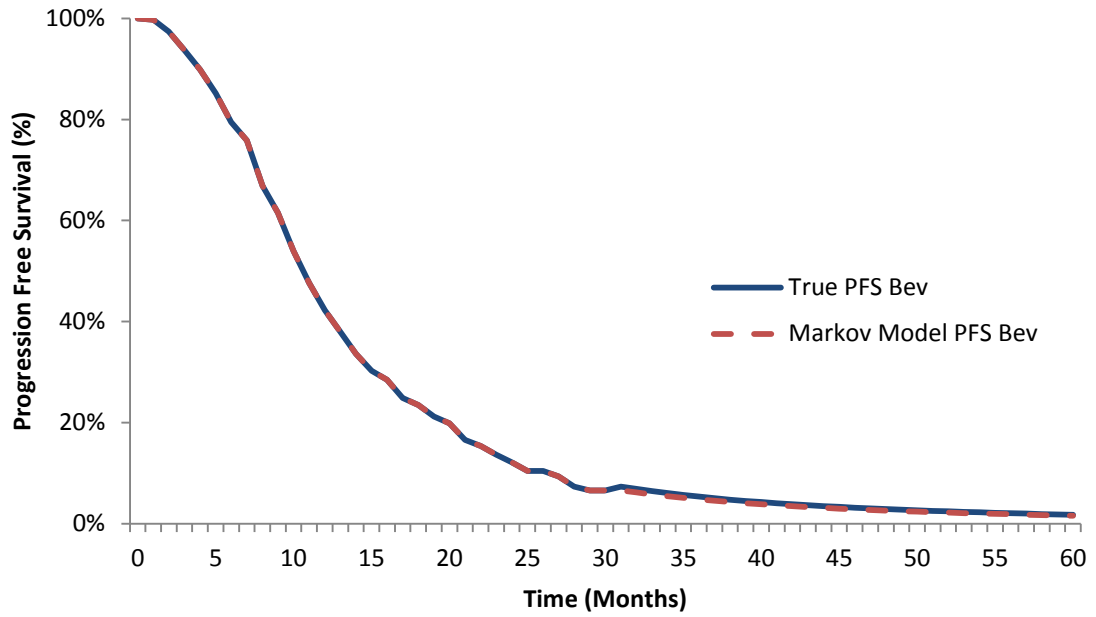


Figure 18. Modeled and true SOC and BEV progression free survival curves

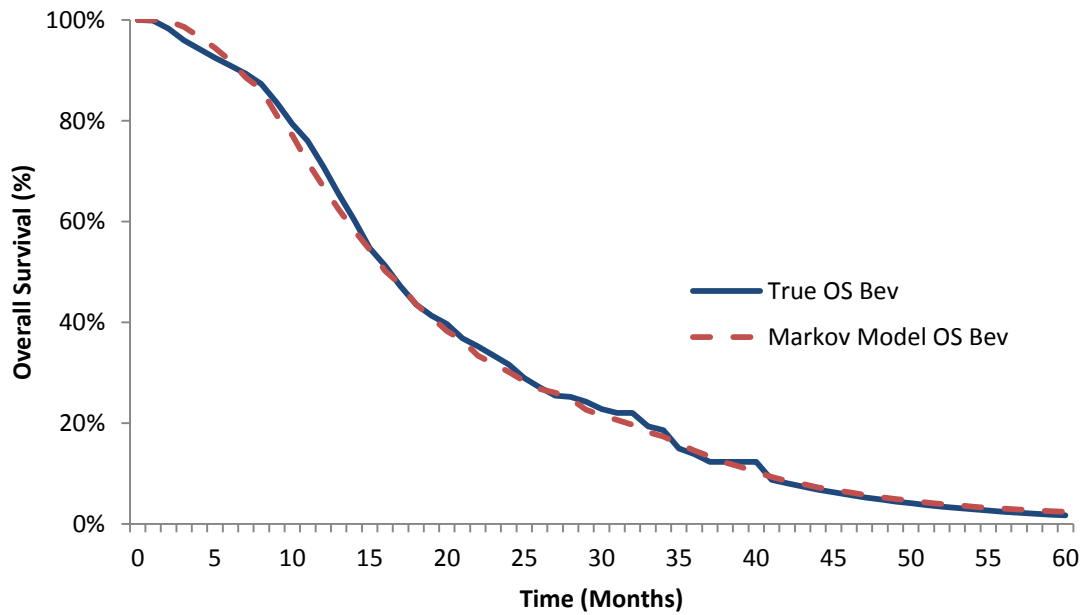


Figure 19. Modeled and true SOC and BEV overall survival curves

4.4. Costs and Event Distributions

In this study, costs were estimated in \$CAD (2011) per unit of resource consumed. Total costs are composed of two components: the dollar per procedure/diagnosis, and the number of procedures/diagnosis. Therefore, we can evaluate the total costs as the product of dollar per unit and the number of units. As this study evaluated the SOC and SOC and BEV option over the course of time, the distribution of events is of importance.

In Ontario, which is the source of the cost and event distribution data for this study, SOC and BEV are not approved as a first-line therapy for GBM. Therefore, the costs and event distributions for the SOC and BEV plus the SOC arm are estimated using a combination of adverse events (AE) reported in the AVAaglio and RTOG 0825 clinical trials, and the SOC AE event and costs in the Ontario health record data.

4.4.1. Patient Selection

In order to align the population in the AVAaglio and RTOG 0825 clinical trials, and the population contributing event distribution and costs, the same inclusion exclusion criteria were used [17, 64]. To be selected for the cost component for the study, a patient must have:

1. Newly diagnosed with histologically confirmed supratentorial GBM between 2003- 2012,
2. Received TMZ therapy,
3. Aged 18 or older,
4. Not have had a prior malignancy, except for non-melanotomatous skin cancer within the three years prior to index,
5. Not have metastasis below the tentorium,
6. Not have prior head or neck radiosensitizers,
7. Not have other co-morbidities or complications within various pre-index periods – Appendix

A full list of exclusion criteria with diagnosis codes can be found in the appendix (Appendix). Overall, costs were extracted from 967 Ontario patients (Table 8).

Table 8. Cohort patient characteristics N= 967

Index Year	Distribution
2003	7.65%
2004	9.93%
2005	9.82%
2006	10.55%
2007	12.10%
2008	11.17%
2009	13.24%
2010	14.27%
2011	11.27%
Cause of Death	
GBM	48.60%
Other	4.24%
Unknown	47.16%
Age Category	
18-29	2.38%
30-34	1.96%
35-39	2.28%
40-44	4.24%
45-49	7.86%
50-54	12.10%
55-59	12.72%
60-64	15.93%
65-69	19.03%
70-74	12.62%

Table 9 Continued. Cohort patient characteristics N= 967

Age Category Continued	Distribution
75-79	6.93%
80-84	1.55%
85-high	0.41%
Number of Primary Cases of Cancer	
1	92.66%
2	6.93%
3	0.41%
Gender	
Female	36.92%
Male	63.08%

4.4.2. Medical and Drug Events and Costs

In order to calculate the overall cost for each treatment arm, the event rates needed to be quantified and multiplied by their respective costs. Four general costs were reported and used in the cost-effectiveness model: protocol costs, adverse event costs, background treatment costs, and progression costs. The protocol, adverse, and background treatment costs pertain to the progression-free health state, while the progression events pertain to the progression health state. Expected protocol costs and adverse event costs were evaluated by multiplying the expected rate of events per one month period by the average cost per event. Background treatment and progression costs were evaluated directly from Ontario hospital records from the identified cohort of interest.

4.4.2.1. Protocol Events

Protocol events are all events that were specified within the AVAglio and RTOG 0825 protocols; this includes radiation and chemotherapy [17, 64]. As the survival curves used to estimate the transition probabilities used in the model were weighted to their respective

population sizes, so too were protocol events; a total of 1,542 patients participated: 921 from the AVAglio study and 621 from the RTOG 0825 study [16, 17].

The AVAglio study followed the following treatment regimen (Figure 20), split into three phases [64]:

1. The first phase termed the concurrent phase starts between 28 and 49 days since debulking surgery or biopsy. In the SOC arm, patients are treated with radiation therapy five days per week for six weeks concomitant with 75 mg/m² of body surface area TMZ once a day. The BEV plus the SOC arm adds 10 mg/kg of BEV every two weeks concomitant with the SOC arm.
2. The second phase termed the maintenance phase follows a four week treatment break. In the SOC arm, patients receive six cycles of 150 mg/m² TMZ once a day, five days per week followed by a 23 day break. The BEV plus the SOC arm adds 10 mg/kg or BEV every two weeks concomitant with the SOC arm.
3. The third phase termed the monotherapy phase only applies to the BEV plus the SOC arm where patients receive 15mg/kg BEV every three weeks until tumor progression.

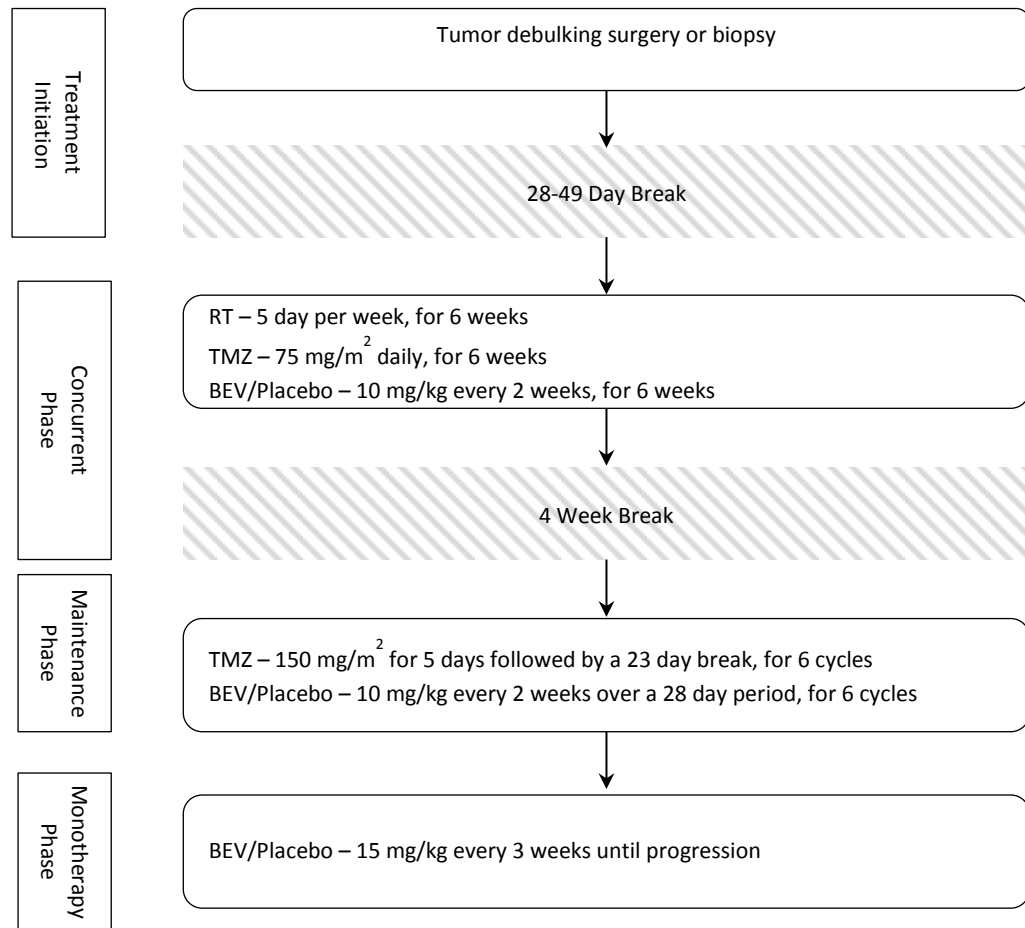


Figure 20. AVAglio treatment regiment

The RTOG 0825 protocol is split into two treatment phases (Figure 21):

1. The first phase, termed the concurrent phase, started between 21 and 35 days after surgery. In the SOC arm, radiation therapy is administered five days per week for six weeks. TMZ is administered at 75mg/m² of body surface area per day for six weeks. In the BEV plus the SOC arm, BEV is administered at 10 mg/kg every two weeks starting at week four of radiotherapy, concomitant with the SOC arm.

2. The second phase termed the maintenance phase follows a 28 days treatment break. In the SOC arm, 12 cycles of TMZ is administered at 150 mg/m^2 five days per week followed by 23 days of no TMZ treatment. In the BEV plus the SOC arm, 10 mg/kg of BEV is administered every two weeks concomitant with the

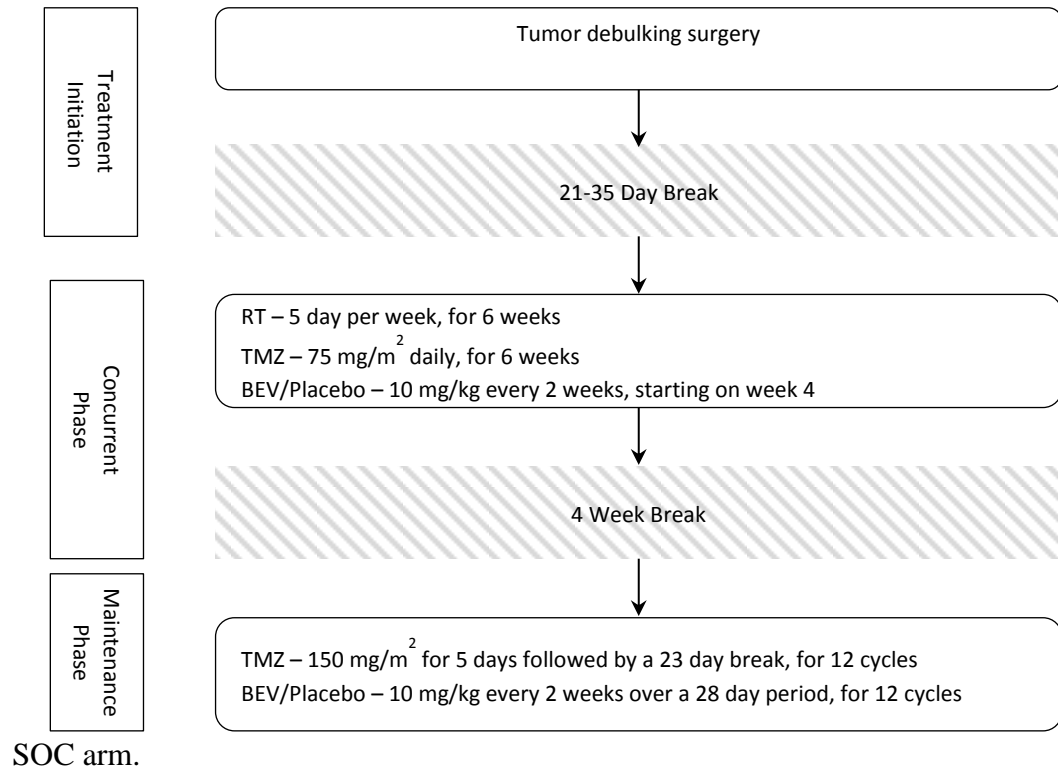


Figure 21. RTOG 0825 treatment regimen

As reported in the patient-level Ontario medical records, an average weight of 77.25 kg and an average height of 168.92 cm was used to calculate BEV plus TMZ dosing (Table 10). This weight is similar to weights used in other GBM cost-effectiveness studies [96]. The Mosteller equation was used to calculate the body surface area for TMZ dosing [109].

Table 10. Biological parameters used to calculate TMZ and BEV dosing

Biological parameter	Mean	Std. Deviation
Height (cm)	168.9233	8.2931
Weight (kg)	77.2527	16.5020

4.4.2.2. Protocol Costs

Protocol costs were composed of either baseline debulking surgery or biopsy, radiation therapy or chemotherapy. Costs were identified from the Ontario health records using Canadian Classification of Health Intervention (CCI) codes. These codes were used by hospitals to record the procedures that were administered to the patients. A list of CCI codes used to identify procedures can be found in the appendix (Appendix). BEV plus TMZ costs were calculated using health records: the cost of BEV was calculated by multiplying the mean weight by the cost per kg; the cost of TMZ was calculated by multiplying the milliliter per body surface area by the body surface area, $(\text{height (cm)} \times \text{weight (kg)} / 3600)^{1/2}$, multiplied by the cost per milliliter. All protocol costs are reported in Table 11.

4.4.2.3. Adverse Events

Both the AVAglio and RTOG 0825 clinical trials reported progression free adverse event frequencies for both arms. As no BEV was administered to Ontario patients, real-world event rates could not be used to populate the BEV plus the SOC arms of this study. Therefore, the real-world SOC arm adverse event rate distribution was calculated using data from Ontario health records, and adjusted for the BEV plus the SOC arm using the AVAglio and RTOG 0825 reported event probabilities. The reported AE probabilities in the AVAglio and RTOG 0825 trials were assumed to remain constant over the trial period, and converted into rates to estimate the BEV AE rates using Equation 3 [108].

Equation 3. Formula used to calculate the probability of a adverse event occurring per period time

$$p = 1 - e^{-rt} \quad (3)$$

A full list of reported adverse events, relative risks, and their respective OHIP and International Classification of Disease version 10 (ICD-10) diagnosis codes are reported in the appendix (Appendix).

4.4.2.4. Adverse Event Costs

Similar to protocol costs, an AE cost was calculated from the Ontario health records using OHIP and ICD-10 diagnosis codes. A full list of reported AEs and their respective OHIP, and ICD-10 diagnosis codes are reported in the appendix (Appendix).

4.4.2.5. Background Treatment Costs

Background treatment events are defined as all recorded medical events that are not classified as protocol events or AEs. As the AVAglio and RTOG 0825 clinical trials did not report differences in events not classified as AEs, this study assumed the background event costs is the same for the two treatment arms. Average background treatment costs were extracted from Ontario health records and used in the study.

4.4.2.6. Progression Costs

Once a patient progresses from the progression free to the progression health state, patients in both treatment and SOC arms in the AVAglio and RTOG 0825 clinical trials had the opportunity to cross arms. However, the number of patents crossing over, their treatment regimens, and event distributions were not reported. Therefore, it is difficult to accurately model the incurred costs to reflect the AVAglio and RTOG 0825 RCTs within the progression state. So, progression event distributions were extracted from all patients

who were deemed to have progressed from the progression free state in the Ontario health records.

As the Ontario health records are administrative, and therefore do not record tumor progression, a patient was assumed to be in the progression state if they did not receive TMZ for greater than five weeks after they started TMZ. A greater than five week gap was chosen because the longest period where a patient could have a TMZ treatment gap would be the four week treatment break between the concurrent and maintenance phase. Moreover, due to the severity of GBM and the amount of medical treatment a patient would receive, it was assumed that a GBM patient would be compliant to treatment guidelines.

A Canadian survey on newly diagnosed GBM treatment practice has shown that 56% of respondents use in-house or center specific treatment guidelines with 64% of respondents using a one phase approach [110]. This means that concurrent RT and TMZ use will be highly correlated in the administrative records. The maintenance phase, which consists only of TMZ therapy, would not be practiced by those physicians using a one phase approach. Two scenarios are therefore possible in practice: a monotherapy phase is not used and therefore not reflected in the administrative records, or a monotherapy phase is used and therefore reflected in the administrative records. As TMZ is correlated with RT use, in the one phased approach, lack of TMZ would indicate the patient entered the progression state as they have failed on TMZ. In the second scenario, a monotherapy phase is used, a gap in TMZ use would indicate a patient is either taking a four week break before starting monotherapy or they have entered the progression state and are not receiving TMZ. As we used a five week gap threshold of no TMZ use, we can establish that the patient is not taking a break before starting monotherapy, rather has entered the progression state as they have failed on TMZ. All costs incurred after the five week TMZ gap should therefore be incurred in the progression state. We chose not to use RT cessation as an indicator of entering the progression state, as this indicator would not

correctly classify patients who stopped receiving RT due to a monotherapy phase of treatment. A five week gap in TMZ could be too short and a patient could be on a five or six week treatment break before starting their monotherapy phase. This should not be a challenge as a single phased approach is used by the majority of Canadian oncologists and the majority of administrative records should not exhibit a significant treatment break. For those Canadian oncologists who do use a monotherapy phase, we assumed that their guidelines would be similar to both the RTOG 0825 and AVAglio treatment guidelines. Therefore, a five week TMZ treatment gap should not overstate the number of patients progressing into the progression state early in their treatment and not run the risk of incurring progression free state costs in the progression state.

4.4.3. Model Medical and Drug Costs

Table 11. Costs used in base scenario for cost-effectiveness model

Cost Group	Cost	Mean	Source
Protocol Cost	Excision/Biopsy	\$16,098.1500	DAD/NACRS
	Pharmacotherapy Administration	\$1,406.5500	DAD/NACRS
	Radiation	\$642.9356	DAD/NACRS
	TMZ (\$/mg)*	\$1.5869	ODB
	BEV (\$/kg)*	\$25.0231	NDFP
	Adverse Event Cost	Abscesses Fistulae	\$444.8700
Anemia		\$609.3700	OHIP/DAD/NACRS
Arterial Thromboembolic Events		\$7,461.8800	OHIP/DAD/NACRS
Cerebral Hemorrhage		\$6,003.9200	OHIP/DAD/NACRS
Congestive Heart Failure		\$99.4900	OHIP/DAD/NACRS
Fatigue		\$1,272.7300	OHIP/DAD/NACRS
Gastrointestinal Perforation		\$444.8700	OHIP/DAD/NACRS

Table 12 Continued. Costs used in base scenario for cost-effectiveness model

Cost Group Continued	Cost	Mean	Source	
Adverse Event Cost Continued	Hemorrhage	\$610.7000	OHIP/DAD/NACRS	
	Hypertension	\$42.8500	OHIP/DAD/NACRS	
	Leukopenia	\$4,265.1600	OHIP/DAD/NACRS	
	Lymphopenia	\$36.8100	OHIP/DAD/NACRS	
	Mucocutaneous Bleeding	\$97.7500	OHIP/DAD/NACRS	
	Nausea and Vomiting	\$864.4000	OHIP/DAD/NACRS	
	Neutropenia	\$4,265.1600	OHIP/DAD/NACRS	
	Proteinuria	\$38.0500	OHIP/DAD/NACRS	
	Thrombocytopenia	\$98.4500	OHIP/DAD/NACRS	
	Thromboembolic Disease	\$921.4400	OHIP/DAD/NACRS	
	Venous Thromboembolic Events	\$77.5200	OHIP/DAD/NACRS	
	Visceral Perforation	\$58.5000	OHIP/DAD/NACRS	
	Wound Healing Complications/ Wound Dehiscence	\$68.0700	OHIP/DAD/NACRS	
	Background Medical Cost		Varying by month	OHIP/DAD/NACRS
	Progression Costs		Varying by month	OHIP/DAD/NACRS

*Note: As reported in the NDFP and ODB units. BEV cost \$5.0000/ mg.

4.5. Discounting

An annual 5% discount rate was applied to the model in accordance with the Canadian Agency for Drugs and Technologies in Health recommendations [111, 112] . However, 0% and 3% discounting rates were considered.

4.6. Health Utilities

Health utility values were gathered from a study by Garside et al. [44], which evaluated the cost-effectiveness of carmustine implants and TMZ in newly diagnosed GBM. As the AVAglio and RTOG 0825 clinical trials report conflicting QoL measures between BEV plus TMZ patients, this study assumed that the two treatment arms experience the same QALY and QALY progression over their treatment. The mean QALY was used for this study; all QALYs used for this study are reported in Table 13.

Table 13. QALY estimates used in base scenario for cost-effectiveness model

Scenario	Mean QALY	Median QALY	QALY Std. Dev
PFS + concurrent treatment phase	0.7426	0.7875	0.2021
PFS + maintenance/ monotherapy phase	0.7331	0.7750	0.1991
Progression state	0.7314	0.7750	0.2067

4.7. Sensitivity Analysis

4.7.1. Deterministic Sensitivity Analysis

Deterministic sensitivity analysis (DSA) was performed on all transition probabilities, health utility values, and costs. Transition probabilities and health utility values were varied by $\pm 5\%$ to a maximum of 100% and a minimum of 0% (Table 14); costs were varied by $\pm 20\%$ (Figure 15). The DSA was performed by varying each utility and cost point estimate by their respective percentage amount, and recalculating the ICUR to evaluate the differential effect.

As the survival curves for each treatment arm was projected to a five year horizon, sensitivity was performed on the projection by altering the survival slope past the 30 month of RCT determined survival. Rather than projecting forward using the best fit model, a constant slope was implemented.

Table 14. Deterministic Sensitivity Model QoL Utilities

Scenario	High QALY(+5%)	Low QALY (-5%)
PFS + concurrent treatment phase	0.7797	0.7055
PFS + maintenance/ monotherapy phase	0.7698	0.6964
Progression state	0.7680	0.6948

Table 15. Deterministic Sensitivity Model Costs

Cost Group	Cost	High (+20%)	Low (-20%)
Protocol Cost	Excision/Biopsy	\$19,317.7800	\$12,878.5200
	Pharmacotherapy Administration	\$1,687.8600	\$1,125.2400
	Radiation	\$771.5227	\$514.3485
	TMZ (\$/mg)	\$1.9043	\$1.2695
	BEV (\$/kg)	\$30.0277	\$20.0185
Adverse Event Cost	Abscesses Fistulae	\$533.8440	\$355.8960
	Anemia	\$731.2440	\$487.4960
	Arterial Thromboembolic Events	\$8,954.2560	\$5,969.5040
	Cerebral Hemorrhage	\$7,204.7040	\$4,803.1360
	Congestive Heart Failure	\$119.3880	\$79.5920
	Fatigue	\$1,527.2760	\$1,018.1840
	Gastrointestinal Perforation	\$533.8440	\$355.8960
	Hemorrhage	\$732.8400	\$488.5600
	Hypertension	\$51.4200	\$34.2800
	Leukopenia	\$5,118.1920	\$3,412.1280

Table 16 Continued. Deterministic Sensitivity Model Costs

Cost Group	Cost	High (+20%)	Low (-20%)
Adverse Event Cost	Lymphopenia	\$44.1720	\$29.4480
Continued	Mucocutaneous Bleeding	\$117.3000	\$78.2000
	Nausea and Vomiting	\$1,037.2800	\$691.5200
	Neutropenia	\$5,118.1920	\$3,412.1280
	Proteinuria	\$45.6600	\$30.4400
	Thrombocytopenia	\$118.1400	\$78.7600
	Thromboembolic Disease	\$1,105.7280	\$737.1520
	Venous Thromboembolic Events	\$93.0240	\$62.0160
	Visceral Perforation	\$70.2000	\$46.8000
	Wound Complications/ Dehiscence	\$81.6840	\$54.4560
	Background Medical Cost	Varying by month	
Progression Costs	Varying by month		

4.7.2. Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was also performed on all transition probabilities, health utility values, and costs. A beta distribution was fit to transition probabilities and health utility values (Table 17), while a lognormal distribution was used for costs (Table 18) [113]. PSA utility and cost estimates were entered into the cost-effectiveness model by substituting the point estimates used in the base case model with the appropriate utility and cost distributions. A 1000 iteration Monte Carlo simulation was performed, sampling from independent distributions within each iteration.

Table 17. PSA Model QoL Utilities

Scenario	Alpha	Beta
PFS + concurrent treatment phase	120.8911	41.9033
PFS + maintenance/ monotherapy phase	125.9155	45.8421
Progression state	116.9758	42.9583

Table 18. PSA Model Costs

Cost Group	Cost	Mean (Ln)	Std Dev (Ln)
Protocol Cost	Excision/Biopsy	\$9.4483	\$0.5719
	Pharmacotherapy	\$6.6029	\$0.7602
	Administration		
	Radiation	\$6.0033	\$0.7590
	TMZ (\$/mg)	\$0.4160	\$0.7596
	BEV (\$/kg)	\$3.2160	\$0.0856
Adverse Event Cost	Abscesses Fistulae	\$6.0180	\$0.5725
	Anemia	\$3.8753	\$1.7540
	Arterial Thromboembolic	\$8.0144	\$1.6024
	Events		
	Cerebral Hemorrhage	\$7.6654	\$1.5981
	Congestive Heart Failure	\$3.9642	\$1.1148
	Fatigue	\$6.0917	\$1.2942
	Gastrointestinal Perforation	\$6.0180	\$0.5725
	Hemorrhage	\$4.0717	\$1.7339
	Hypertension	\$3.4712	\$0.6751
	Leukopenia	\$4.6773	\$2.7228
	Lymphopenia	\$3.3297	\$0.7990
	Mucocutaneous Bleeding	\$3.8237	\$1.1487
	Nausea and Vomiting	\$6.0680	\$1.5269

Table 19 Continued. PSA Model Costs

Cost Group	Cost	Mean (Ln)	Std Dev (Ln)
Adverse Event Cost	Neutropenia	\$4.6773	\$2.7228
Continued	Proteinuria	\$3.6389	\$0.0001
	Thrombocytopenia	\$4.0696	\$0.9901
	Thromboembolic Disease	\$4.2847	\$1.9706
	Venous Thromboembolic	\$3.8035	\$1.4263
	Events		
	Visceral Perforation	\$3.8559	\$0.7119
	Wound Healing Complications/ Wound Dehiscence	\$3.8815	\$0.7643
Background Medical Cost	Varying by month		
Progression Costs	Varying by month		

4.8. Software

Digitizeit was used to digitize the plotted points on the AVAglio and RTOG 0825 Kaplan-Meier curves [114]. R v3.1 was used to analyze the individual AVaglio and RTOG 0825 Kaplan-Meier curves and estimate the pooled Kaplan-Meier curves [115-120]. Excel 2010 was used to calculate transition probabilities from the pooled Kaplan-Meier curves [121]. SAS v9.3 was used to analyze the Ontario healthcare datasets and estimate costs [122]. TreeAge Pro 2011 was used to construct the economic impact model [97].

Chapter 5

5. Results

5.1. Base Case Cost Effectiveness of Bevacizumab

The cumulative expected cost from the public payer's perspective over a five year period for BEV plus the SOC is \$632,602, while the cumulative expected cost of the SOC alone is \$199,284. The cumulative expected QALY over a five year period for BEV plus the SOC is 1.16 QALY, while the cumulative expected QALY for the SOC is 1.11 QALY. As costs and utility values are the same for the progression state in both the SOC and SOC and BEV arms, the incremental costs and QALY is due to the increased time spent in the progression free state the additional costs for BEV for the SOC and BEV arm compared to the SOC arm. The expected ICUR for BEV plus the SOC compared to the SOC alone is \$8,393,212 per QALY. As can be seen in Table 20, the majority of the costs in both arms are incurred within the first 12 months of treatment.

As both the AVAglio and RTOG 0825 RCTs contributed a minimum of 30 month of survival data, the ICER at 30 months and five years were compared to establish the effect of projecting the survival estimates. Figure 22 graphically displays the ICER between BEV and SOC compared to SOC for each month since treatment initiation. At 30 months, the ICER was \$6,189,191 compared to the base case five year ICUR of \$8,393,212. While the ICUR was higher for the five year mark, the 30-month ICUR was similarly high. Therefore, projecting the survival curves did not influence the ICUR towards a cost-effective BEV plus SOC result. Moreover, the ICUR remained at similar levels from 18 months onwards indicating that projecting survival resulted in similar ICURs as would be calculated at several points within the RCT survival data.

Table 20. Cumulative mean cost and QALY for the BEV plus the SOC treatment arm and SOC treatment arm by treatment month

Months Since Diagnosis	SOC		BEV plus SOC		ICUR
	Cum. Exp. Cost	Cum. Exp. QALY	Cum. Exp. Cost	Cum. Exp. QALY	ICUR If Time Horizon Ended Here
1	\$39,541	0.03	\$49,917	0.03	-
6	\$136,843	0.32	\$338,698	0.33	\$26,594,590
12	\$181,537	0.60	\$566,435	0.63	\$13,810,726
18	\$192,096	0.78	\$623,161	0.83	\$8,509,066
24	\$194,403	0.90	\$628,627	0.96	\$6,670,973
30	\$196,002	0.97	\$630,274	1.04	\$6,189,191
36	\$197,174	1.02	\$631,345	1.09	\$6,194,425
42	\$197,917	1.06	\$631,891	1.12	\$6,562,069
48	\$198,493	1.08	\$632,235	1.14	\$7,115,435
54	\$198,956	1.10	\$632,467	1.15	\$7,762,653
60	\$199,284	1.11	\$632,602	1.16	\$8,393,212

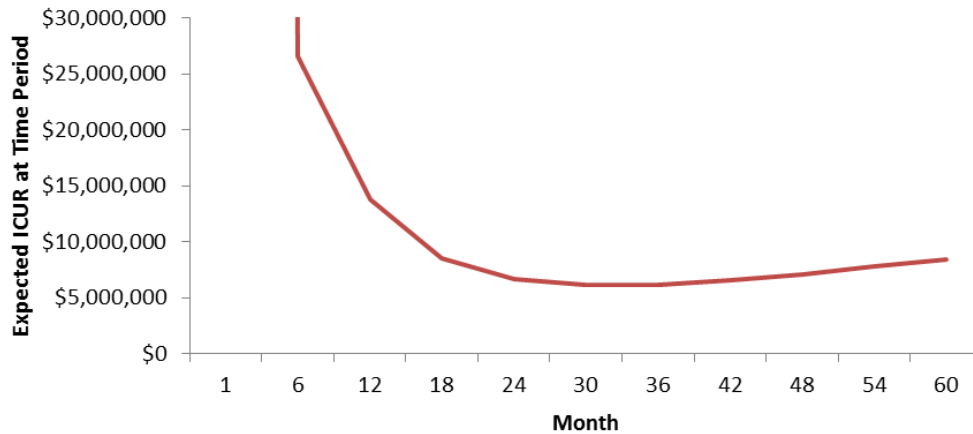


Figure 22. Expected ICUR between BEV plus the SOC compared to the SOC for the first five years from diagnosis of newly diagnosed GBM

5.1.1. Incurred Costs per Month

Monthly state-specific costs were estimated for each treatment arm, BEV plus the SOC and the SOC. The total majority of costs are incurred within the progression free state for both the BEV plus the SOC treatment arm (Figure 23) and the SOC treatment arm (Figure 24). Compared to the progression free arm, low amounts of expected costs are incurred in the progression arm for both treatment arms. A graphical summary of costs may appear jagged within the first six weeks of treatment as large cost items – such as BEV – are modeled to be administered using both the AVAglio and RTOG 0825 regimens. The two regimens outlining BEV dosing, the first from the AVAglio and the second from the RTOG 0825 trial, call for differing timing in BEV administration, and the model is a summation of the two regimes; when BEV is administered at staggered time points, the total costs appear to be smooth. However, when the regimens’ time points align in BEV dosing, the total costs appears to be jagged, such as at the cost point for two months since GBM diagnosis.

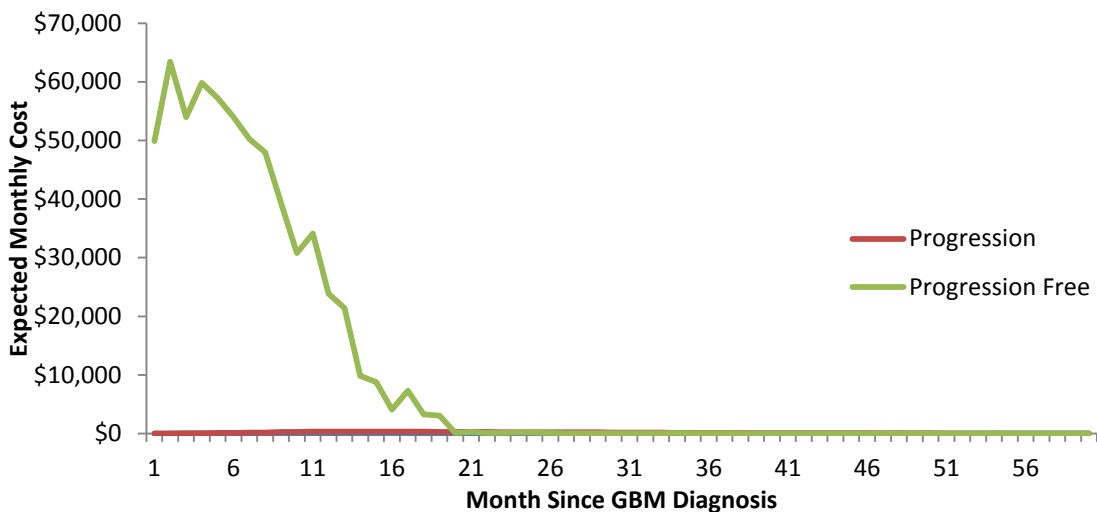


Figure 23. Expected monthly costs by health state to treat GBM with BEV plus the SOC

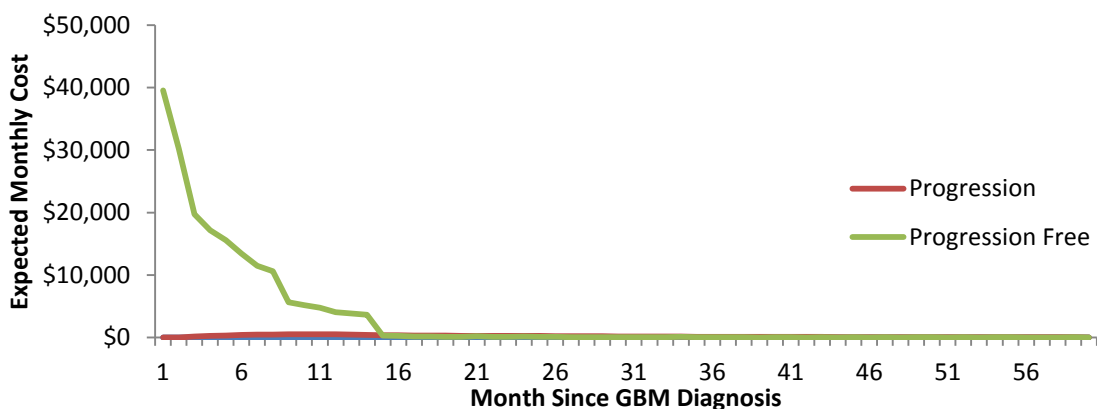


Figure 24. Expected monthly costs by health state to treat GBM with the SOC

Between Figure 23 and Figure 24, the difference in expected costs within the progression free state is mostly due to the cost of BEV therapy. As one can see, the costs incurred in the BEV and SOC progression free arm are incurred at a later month since GBM diagnosis as compared to the SOC arm, which reflects the increased duration patients remain the progression free state when treated with BEV and the SOC. The progression costs are quite low comparatively to progression free state as treatment is not continued.

The two arms are quite similar in progression costs as this study assumed the same monthly cost.

5.1.2. Expected Value of Perfect Information

Using an expected Canadian annual GBM population of 354 patients [123], discounted at 5% over a 10 year period, the population expected value of perfect information at the calculated ICUR of \$8,393,212 per QALY is \$5,485,641,778. However, at the WTP used for this study, \$132,264, the value of perfect information is \$4,271, which indicates that it is not worth conducting further research in BEV plus the SOC for GBM as the returns will not justify the research costs.

5.2. Deterministic Sensitivity Analysis

5.2.1. One-Way Deterministic Sensitivity Analysis

One-way sensitivity analysis was performed on model inputs that were specific to BEV plus the SOC (Table 21). Altering the probability of remaining in progression free state had the largest effect on ICUR as compared to all costs and QoL metrics. Decreasing the probability of remaining in the PFS state by 5% resulted in a -\$1,223,601 per QALY while increasing the progression free state transition probability by 5% resulted in an \$853,904 per QALY ICUR. The negative ICUR resulting from a 5% decrease in the progression free state transition probabilities is due to a resulting negative incremental utility.

Following the transition probabilities, QoL metrics had the second largest impact on ICUR. Decreasing the BEV plus the SOC arm progression free state utility by 5% resulted in a \$44,537,392 per QALY ICUR, while increasing the progression free state utility by 5% resulted in a 4,633,174 per QALY ICUR. A small change in ICUR was

observed when adjusting costs by $\pm 20\%$. Altering the drug costs of BEV resulted in the largest changes in ICUR. A decrease in BEV cost by 20% resulted in a \$6,964,463 per QALY, while increasing BEV costs by 20% resulted in a \$9,821,961 per QALY.

Table 21. Deterministic sensitivity for BEV plus the SOC arm inputs on the resulting ICUR

Category	Low	High
Base Case	\$8,393,212	
BEV AE Costs	\$8,390,094	\$8,396,330
BEV Background Costs	\$8,323,902	\$8,462,522
BEV Drug Costs	\$6,964,463	\$9,821,961
BEV Progression Free to Progression Free Transition Probability	-\$1,223,601	\$853,904
BEV Progression to Progression Transition Probability	\$13,339,946	\$6,044,459
BEV QoL	\$44,537,392	\$4,633,174

Decomposing the ICUR into its incremental effectiveness and incremental cost components, one can see that lowering the probability of remaining in the progression free state by 5%, in the BEV plus the SOC arm, strongly affects the incremental effectiveness. By lowering the probability by 5%, the patients receiving BEV plus the SOC remain in the progression free state for a shorter period than the SOC arm, therefore reducing the treatment's effectiveness and resulting in a negative incremental effectiveness, -0.2345. Similarly, altering the QoL of those receiving BEV plus the SOC had a large effect on the incremental effectiveness. Decreasing the progression free state utility by 5% reduces the incremental effectiveness to 0.0097 QALY.

Similarly, the incremental cost component of the ICUR is heavily affected altering the probability of remaining in the progression free state. Decreasing the probability of remaining in the progression free state by 5% decreases the incremental costs to \$286,892, while increasing the probability by 5% increases the incremental costs to \$586,967. The second largest impact on incremental costs is caused by the drug cost of BEV. Decreasing the drug costs of BEV by 20% decreases the incremental cost to \$359,556. Increasing the drug costs of BEV by 20% increase the incremental costs to \$507,081.

Each protocol cost component was investigated for its impact on the overall costs on the five year ICER by changing each cost component to zero cost and calculating the ICER (Table 22). As one can see, the difference in ICER is nominal if present. As all patients require an excision or biopsy, then, as expected, the ICER without the excision or biopsy cost remains the same as the base case.

Table 22. One way sensitivity on protocol cost components for their effect on the ICER

Cost Group	Cost Component	ICER
Base Case		\$8,393,212
Protocol Cost	Excision/Biopsy	\$8,393,212
	Pharmacotherapy	\$7,908,078
	Administration	
	Radiation	\$8,391,432

As the survival curves were projected to a five year horizon, sensitivity was performed on the effect of the projection method. While the best fit projected curve at the five year horizon resulted in an estimated ICUR of \$8,393,212 per QALY, a constant slope after 30 months – last month of RCT contributed survival data – resulted in an estimated ICUR of

\$10,545,883 per QALY. While the best fit projected ICUR is lower than the constant slope ICUR, neither were cost-effective.

5.3. Probabilistic Sensitivity Analysis

For the probabilistic sensitivity analysis, all distributions were simultaneously sampled. The expected cumulative cost and QALY for the BEV plus the SOC is \$633,318 and 1.14 QALY. The expected cumulative costs and QALY for the SOC arm is \$206,501 and 1.12 QALY. The expected ICER comparing the two arms is 421,340,850 per QALY. The difference between the base case and the expected probabilistic sensitivity ICUR is due to the small difference in QALY. As the incremental difference between the two arms is already small, any changes in difference will have exponential effects on the ICUR.

The incremental cost-effectiveness scatter plot was constructed from 1000 simulation results (Figure 25). The plot compared BEV plus the SOC to the SOC arms. The majority of simulations (65.8%) resulted in a positive incremental effectiveness however, a considerable number of trials experienced negative effects by receiving BEV plus the SOC. Overall, BEV plus the SOC was well outside the willingness to pay (WTP) of \$132,264, and could not be justified as a cost-effective first line treatment for GBM.

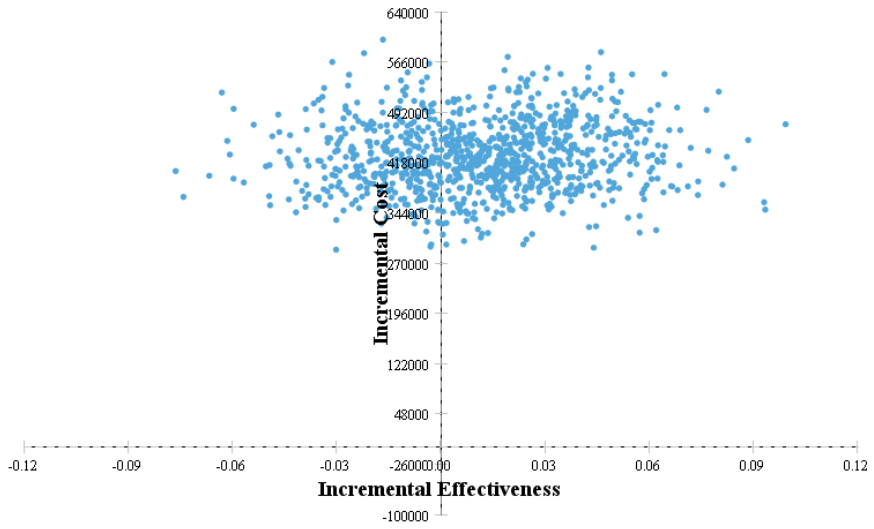


Figure 25. Probabilistic scatter plot of incremental cost-effectiveness of BEV plus the SOC compared to the SOC

A cost-effectiveness acceptability curve (CEAC) was constructed to identify the percentage of simulated ICUR values would meet the WTP when varying the WTP value (Figure 26) [108, 113, 124]. Even at a WTP of \$250,000 per QALY, none of the BEV plus the SOC arm simulations were cost-effective. At a WTP threshold of \$4,000,000 per QALY, a few simulations of BEV plus the SOC become cost-effective.

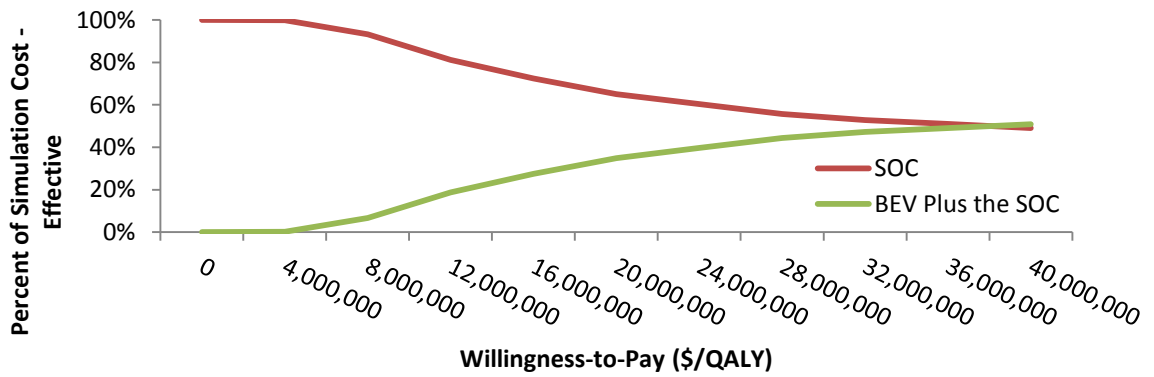


Figure 26. Probability that BEV plus the SOC or the SOC are cost-effective with variable WTP

Chapter 6

6. Discussion & Conclusions

6.1. Summary

This study modeled the treatment for first -line GBM using a Markov model with three states: progression free, progression, and death. This model was designed after clinical practice and clinical trial reported outcomes. Three general inputs were used to populate the model: survival probabilities, costs, and QoL metrics.

The survival probabilities derived from two clinical trials, the AVAglio and RTOG 0825 RCTs, where published survival curves were combined to determine the pooled survival curves [16, 17]. To avoid relying on the Cox-proportional hazards assumption, the survival outcomes from the trials were reverse engineered and combined into a single survival curve. A parametric model was applied to the curve to project the survival probabilities past the clinical trial's duration. Probabilities from the clinical trials were used until 30 months, after which probabilities of survival were estimated from the parametric models.

Cost were estimated from both the clinical trial data and Ontario health records. The event rates for the SOC arm were derived from Ontario health records, however, as no patient in Ontario has received BEV plus the SOC for first line GBM therapy, clinical trial data was used to estimate the BEV plus the SOC arm event rates. Costs for each event were extracted from the Ontario health records. In Ontario, ODB has issued a limited use code for TMZ reimbursement. This indicates that TMZ can only be used for certain indications. While TMZ is explicitly not funded for metastatic melanoma, it has complete public funding for newly diagnosed GBM, along with other brain cancer indications. Therefore, the health records used to elicit the cost of TMZ would properly capture its cost.

Both the AVAglio and RTOG 0825 clinical trials investigated the effect of BEV plus the SOC on QoL metrics. However, the results from each trial conflicted. Therefore, the same QoL metrics were used in both arms. These metrics were estimated using scenarios from GBM patients by a panel familiarized with the Standard Gamble method [44].

The base case found that BEV plus the SOC for first-line GBM therapy had an incremental cost-effectiveness ratio of \$8,393,212 per QALY. The largest component of the incremental cost was BEV drug costs.

From deterministic sensitivity analysis, the most sensitive parameter in calculating the ICUR is the probability to remain in the progression free state. Following, is the QoL metric, which also had a material impact on the expected ICUR. With respect to costs, the ICUR was most sensitive to the drug costs of BEV. Probabilistic sensitivity showed that at current treatment costs and effectiveness, the WTP threshold would need to be very high to find BEV plus the SOC cost-effective.

6.2. Discussion

From this analysis we can conclude that BEV plus the SOC is not cost-effective as a first-line therapy for GBM when compared to the SOC alone. In Ontario, no patients received BEV for first-line therapy, however, it is prescribed as a salvage or second-line treatment.

In general, there are three ways to show cost-effectiveness: increase QoL, increase survival, or decrease costs. The hope was that either overall survival was increased by BEV plus the SOC, or that as progression free survival is increased, and that QoL is

higher in the progression free state. Therefore, the overall QoL for BEV would outweigh the cost and show a cost-effective alternative to the SOC. Two large multicenter RCTs investigated the use of BEV plus the SOC as a first-line treatment, with evidence surfacing that progression free survival is increased. Unfortunately for patients, both clinical trials did not show an overall survival benefit. Moreover, the mild increase in QoL due to a longer progression free survival, did not outweigh the incremental costs. Even so, the QoL of patients on BEV plus the SOC is currently in question as the two RCTs investigating BEV found conflicting evidence on the treatment's QoL effect.

Going forward, future research on the QoL of patients receiving BEV plus the SOC is necessary to determine if overall QoL is increased or decreased. As the ICUR is sensitive to QoL, it is feasible that BEV plus the SOC can be cost-effective. This however, would require general consensus of the metrics and methods used to measure QoL. Once agreed upon, a utility value can be estimated.

It should be noted that Japan has added BEV and SOC to its SOC for newly diagnosed GBM [125]. The health authorities of Japan made this decision as they recognized the benefit of a longer progression free state and the possible increase in QoL for those on BEV and the SOC.

The simple solution towards proving cost-effectiveness would be to decrease the costs of BEV. Lowering the price of the drug, however, would not occur as BEV is currently used as a first-line treatment in metastatic colorectal cancer, and an option for locally advanced metastatic or recurrent non-small cell lung cancer, and platinum-sensitive recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer [69]. If the manufacture of BEV were to lower their selling price of BEV, they would forgo the revenue generated from the other indications, for the smaller GBM indication. To achieve drug coverage for BEV while maintaining the manufacturer's revenue stream, drug insurers, such as ODB,

and the manufacturer can engage in a product listing agreement (PLA). PLAs are confidential purchasing agreements between payer and drug manufacturers outlining the reimbursed price of a drug for a specific indication, line-of-therapy, or duration [126].

However, it should be noted that no phase 1 clinical trials were performed for BEV plus the SOC in first-line GBM treatment. The optimal dose of a drug is determined in part by a phase 1 RCT. Currently, dosing is determined by prior experience [17] and therefore, it is possible that the dose required to treat GBM with BEV plus the SOC can be reduced, thereby reducing the overall costs. Moreover, it is conceivable that reducing the dosing of BEV will have an effect on reducing the AEs. This would not only decrease the costs associated with the AEs, but could increase the QoL.

Future research on genetic markers that correlate with a positive and significant improvement in survival when identified and treated with BEV and the SOC could be used to show cost-effectiveness of the new treatment and increase QoL. Currently, all genetic markers tested in the AVAglio and RTOG 0825 trials did not correlate with better survival for patients receiving BEV and the SOC compared to the SOC [16, 17].

Overall, BEV plus the SOC is not cost-effective for first-line GBM. However, further research is required on the QoL for those on the treatment and the optimal dosing, which can influence the ICUR and show cost-effectiveness. Effort, though, should be placed on increasing the survival of GBM patients, such as identifying genetic markers that correlate with better prognostic outcomes, as no major increase in survival due to treatment has occurred since the approval of TMZ for GBM.

6.3. Strengths

To our knowledge, this is the first study on the cost-effectiveness of BEV plus the SOC where both clinical trial results are incorporated and real-world costs and distributions are used. A prior study was recently published modeling the cost-effectiveness of BEV plus the SOC compared to SOC for first-line GBM therapy [123]. This study only used the AVAglio study, assumed proportional hazards, and drew its costs from published sources. While all these values were stated in the publication and are valid, this study builds upon prior work by incorporating both the AVAglio and RTOG 0825 clinical trial results and reverse engineering the survival curves to find the survival of both studies together thereby avoiding the Cox-proportional hazards assumption.

Moreover, the prior study assumed a uniform probability of AEs. While also valid, it has been shown that the majority of costs are incurred near diagnosis and death [127]. As the median survival for those diagnosed with GBM is not very long and the AEs are quite rare, the assumption of uniform AEs may not have a large impact. However, this study incorporates real-world AE distributions, which occur mostly near diagnosis when the majority of patients are alive. This increases the accuracy of incurred costs due to AEs.

Another study strength is that costs and their distributions are those observed in real-world Ontario practice. As opposed to using costs from a literature search, this study implemented inclusion and exclusion criteria that mirrored those from the published RCTs. Therefore, costs should be similar with those published in cost-effectiveness studies run in parallel with an RCT.

The largest discrepancy between the inputs of the prior study and this study are the drug costs of BEV. The published study used BEV costs from IMS Brogan [128]. These costs seem to differ from those found in the Ontario NDFP database. When the BEV costs

from the prior study are used in lieu of the NDFP BEV costs, the model used for this study produced an expected ICUR that is very similar to the prior study's ICUR – \$680,533 per QALY vs. \$607,966 per QALY. The benefit of using the NDFP prices is that these are costs incurred from the Ontario healthcare perspective as opposed to relying on the official list prices, which are not necessarily incurred by the Ontario healthcare system.

6.4. Limitations

We recognize that there are several limitations to this study. From our perspective, the largest limitation to this study is that no Ontario patient has received BEV plus the SOC for first-line GBM. Therefore, the survival and AE distributions are derived from RCT proxy sources. While RCTs are an excellent source for survival probabilities, they may not represent real-world treatment patterns. Rather, patients in RCTs may be under increased observation, and, as a consequence, receive improved healthcare. This could increase the survival time of a patient within a RCT compared to real-world survival. The effect on this study may be that the median survival is longer than what would be observed in the real-world. However, this method is commonly used in cost-effectiveness analysis as there a few, or sometimes no, alternatives available and a decision on whether to add a therapy to the SOC needs to be made [123, 129, 130].

As real-world data is not available for the BEV and SOC arm, fatal AEs may not be properly captured and incorporated into this study. A paper published by Wu et al. found, using a meta-analysis, that BEV in cancer patients was statistically associated with increased fatal AEs [131]. The publication noted that the use of taxanes or platinum with BEV showed stronger association with the fatal AEs. As BEV is not used to treat newly diagnosed GBM in the real-world, the AEs, fatalities, and costs associated were not directly captured in this study. However, some of these costs should be incorporated into this study. If a patient died during the RTOG 0825 and AVAglio trials from BEV, it

would have been captured in the overall survival and reflected in this analysis in the survival, cost, and QALY metrics. Additionally, all AEs from the RCTs were quantified and dollarized; therefore, if the BEV arm had more AEs, then the increase would be captured and included in this study in the cost metrics.

Additionally, because this study used published survival curves, the survival estimates could only span as long as those published. In order to extend the study's timespan, a parametric curve was fit to the published curves and converted to transition probabilities. The assumption is that past distribution of the survival curves matched to the parametric curve will continue with the same distribution as the projected parametric curve.

Similarly, AE distributions for the BEV plus the SOC arm were estimated using the real-world SOC AE distributions and the AE's relative risk from the clinical trials. As no patients in Ontario received the treatment, it was not possible to capture the true AE distribution for GBM patients on first-line therapy.

From a QoL perspective, the study assumed a constant utility value during the progression free concurrent treatment phase, and a separate, albeit constant, utility value during the progression free maintenance phase. In the transition from concurrent to maintenance treatment, the treatment guidelines used indicate a several week chemotherapy treatment break. The absence of chemotherapy treatment can have either a positive or a possible negative effect on QoL; however, this possible change in utility has not been reflected in the analysis. Ideally, utility values could be established alongside treatment as observed in real-world practice to establish a longitudinal array of utility values, and therefore not have to make assumptions on utility increases or decreases over time and by health state. For practical purposes, this is not possible, and therefore in this analysis we assumed a constant utility during the progression free concurrent and progression free maintenance phase.

6.5. Conclusion

This study evaluated the cost-effectiveness of BEV plus the SOC compared to the SOC for newly diagnosed GBM patients using Ontario health records, published RCT survival curves, and published utility analysis. In the base case scenario, BEV plus the SOC was found not to be more cost-effective than the SOC. The ICUR values for BEV plus the SOC is extremely high: \$8,393,212 per QALY. The high ICUR was driven by high BEV costs and a very low incremental benefit. Deterministic sensitivity analysis found the ICUR is most sensitive to increased probability of remaining within the progression free survival state. Going forward, future research should focus on methods to increase the overall survival and progression free survival. As BEV has shown to have positive effects on progression free survival, the drug may have a place within the SOC if costs can be contained. This economic analysis will help decision makers guide policy into improving GBM patients' lives, and improve the overall healthcare system.

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Appendix

Table 23. Patient Diagnosis Exclusion Codes

OHIP Codes	ICD-10 Codes
Excluded if diagnosis within 12 month of treatment index date	
I500	
Excluded if diagnosis within six month of treatment index date	
420, 428, 432, 435, 436	I64, I63, I62, I61, I60, I213, I212, I211, I210, I200, G45, B24, B23, B20, B22
Excluded if diagnosis within 14 days of treatment index date	
280, 281, 282, 283, 284, 285, 287, 288, 401, 402, 403, 410, 413, 571, 573, 584, 585	P610, N19, N18, N17, K778, K770, K77, K769, K768, K767, K766, K765, K764, K763, K762, K761, K760, K76, K759, K758, K754, K753, K752, K751, K750, K75, K746, K745, K744, K743, K742, K741, K740, K74, K739, K738, K732, K731, K730, K73, K729, K721, K720, K72, K719, K718, K717, K716, K715, K714, K713, K712, K711, K710, K71, K709, K704, K703, K702, K701, K700, K70, I21, I20, I15, I13, I12, I11, I10, D70, D696, D695, D694, D693, D693, D64, D63, D62, D61, D60, D59, D58, D57, D56, D55, D53, D52, D51, D50, M311, D696, D695, D695, D694, D593, D65
Excluded if diagnosis within seven days of treatment index date	
286, 427, 441, 496	R17, J44, I72, I71, I49, I48, I47, D68, D67, D65, D66

Table 24. Procedure and Diagnosis Cost Codes

Group	OHIP Codes	ICD 10 Codes	Procedure Codes
Protocol costs			
Excision			1AA87, 1AB87,1AC87, 1AE87, 1AF87, 1AG87, 1AJ87, 1AK87, 1AN87
Pharmacotherapy			1AA35, 1AB35, 1AE35, 1AN35, 1ZZ35
Radiation			1AC27, 1AE27
Biopsy			2AA71, 2AC71, 2AE71, 2AF71, 2AG71, 2AJ71, 2AK71, 2AN71
Adverse event costs			
Abscesses fistulae	285, 284, 283, 282, 280, 281		
Anemia		R430, P612, D649, D64, D630, D63, D62, D61, D60, D59, D58, D57, D56, D55, D539, D53, D52, D50, D51	

Table 25 Continued. Procedure and Diagnosis Cost Codes

Group	OHIP Codes	ICD 10 Codes	Procedure Codes
Arterial thromboembolism		I26, I74	
Bleeding	627, 569, 626	R58, R31, R048, R042, P26, N950, N938, N930, N93, N923, N92, N02, K922, K920, K5520, I859, I850	
Cerebral hemorrhage		S069, S068, S067, S066, S065, S064, S063, S062, P101, I62, I61, I60	
Congestive heart failure	428	I500	
Fatigue	795	T676, R53, G933, M484	

Table 26 Continued. Procedure and Diagnosis Cost Codes

Group	OHIP Codes	ICD 10 Codes	Procedure Codes
Gastrointestinal perforation		T818, N82, N640, N360, N321, M251, K316, K114, J950, J860, I772, I770, I671, I280, I254, H831, H701, H046, N321, K833, K823, K632, K60, K316, K383	
Hemorrhage	666, 640, 532, 531, 287, 432	S064, R58, R31, R048, R042, P26, N938, N93, N92, N02, K922, K920, I62, I619, I618, I61, I608, I60, H431, H113, H356	
Hypertension	437, 403, 402, 362, 401'	P292, O16, K766, I959, I958, I95, I159, I1581, I158, I152, I151, I150, I15, I139, I132, I131, I13, I129, I120, I12, I119, I11, I101, I10, I100	

Table 27 Continued. Procedure and Diagnosis Cost Codes

Group	OHIP Codes	ICD 10 Codes	Procedure Codes
Leukopenia	288	C959, D70	
Lymphopenia	288	D728	
Mucocutaneous bleeding	627, 569, 626, 666, 640, 532, 531, 287, 432, 627, 569, 626, 786	R042, R58	
Nausea and vomiting		R118, R11, R113	
Neutropenia	288	P615, D70, D700	
Proteinuria	791	R80, O122, O12103, O121, N391, N392	
Thrombocytopenia	287	P610, M311, D696, D695, D694, D6938, D693, D593, D65	
Thromboembolic disease	452, 451	I82, I81, I26, I80, I74	
Venous thromboembolic	452, 451	I82, I80, I81	
Visceral perforation	569	K631, S369	
Wound dehiscence	998	S061, T813	

Table 28 Continued. Procedure and Diagnosis Cost Codes

Group	OHIP Codes	ICD 10 Codes	Procedure Codes
Wound healing complications	998	T813, T018, S061, T010	

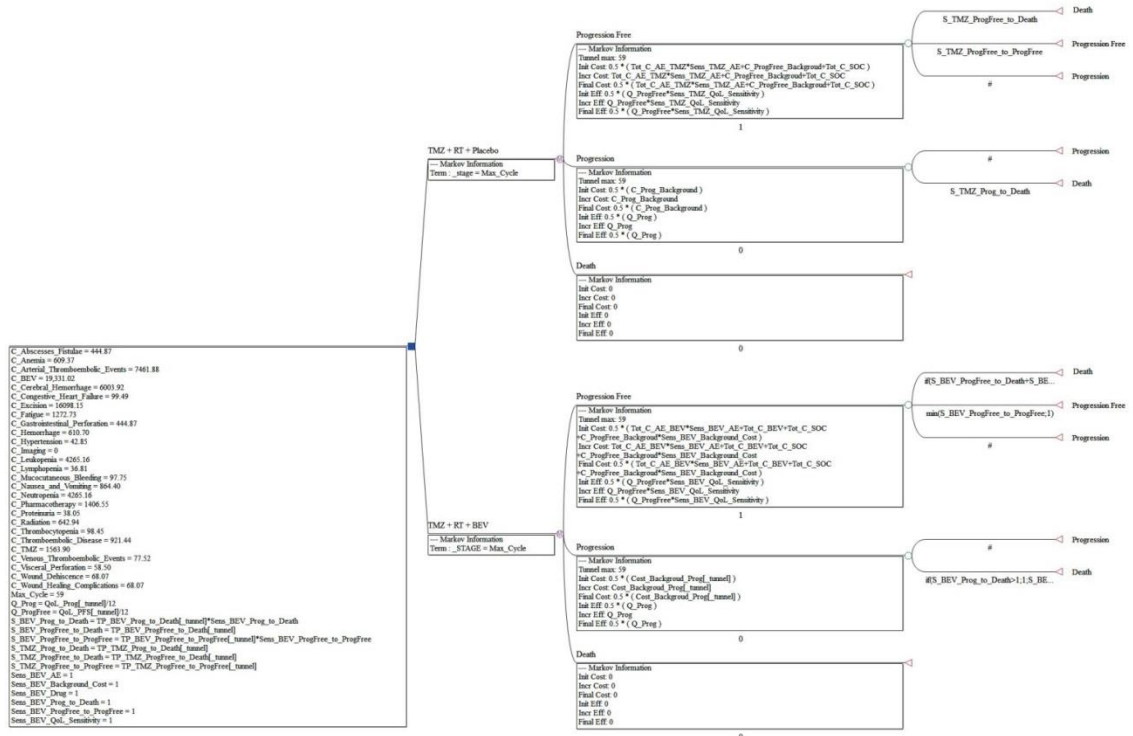


Figure 27. Full TreeAge model with all variables listed

A. Economic Evaluation

Economic evaluation is a mathematical framework integrating outcomes, risks, and costs of a medical or public health intervention [132]. The goal is to develop a method to holistically compare two or more options and choose the best one, however “best” is defined [113, 132, 133]. Healthcare resources are limited, and therefore efficiency usually defines the best option [132]. Outcomes and risks can be thought of as the clinical component of the framework, while costs represent the resource. Most interventions produce a benefit at some cost. The economic evaluation framework provides a method to compare the interventions. The framework is composed of two elements: interventions and health states. Interventions can be screening tests, treatments, or preventative measures: any action that can be deemed as a choice [133]. Health states are discrete conditions a patient can experience along the path from sickness to either health or death [133].

For example, a patient afflicted with a hypothetical illness can be presented with the following options: medication or no medication. These options represent the available interventions for the illness. By choosing an option, a patient can progress from several health states such as sick to healthy. As the patient passes through the health states, costs are incurred as are clinical outcomes: survival QoL. Economic evaluation brings together all components of the journey to compare the two interventions [113].

A.1.1. Cost-Consequence Analysis

Cost-consequence analysis is the simplest form of comparing two or more interventions. All the information for each intervention would be listed, and the evaluator would be left to synthesize and determine the best option [113].

A.1.2. Cost-Minimization Analysis

Cost-minimization analysis takes the information gathered and listed by a cost-consequence analysis and calculates the difference in cost between a base options and various alternatives [113]. The implicit assumption is that the benefit of each option are equivalent or unimportant [113]. This type of analysis provides further structure compared to a cost-consequence analysis so that an evaluator can make an informed decision.

A.1.3. Cost-Effectiveness Analysis

Once the differential in costs is calculated between two interventions, the next step would be to incorporate the differing benefits from each intervention. The cost-effectiveness analysis requires the calculation of a ratio between the differential in costs divided by the

differential in benefit or effectiveness. The ratio is termed the incremental cost-effectiveness ratio (ICER) and is listed in Equation 4.

Equation 4. Formula used to calculate the incremental cost-effectiveness ratio (ICER)

$$ICER = \frac{Cost_B - Cost_A}{Effect_B - Effect_A} = \frac{\Delta Cost}{\Delta Effect} \quad (4)$$

As the costs of intervention B increases, the numerator increases. Therefore, the ratio increases in absolute value. If, however, the more expensive intervention B provides several more time the benefit than intervention A, the ratio can decrease in absolute value. Therefore, the ICER is dependent on both the additional costs and benefits of an alternative intervention. The willingness to pay is the maximum dollar per effect a payer is willing to pay per unit of benefit (e.g. per life year (LY) or quality adjusted life year (QALY)). If the ICER is higher than the willingness to pay, that is the incremental cost per incremental benefit is more than the maximum cost someone is willing to pay for the additional benefit, the new intervention can be rejected [113, 134].

A.1.4. Cost-Utility Analysis

The cost-utility analysis takes a simple concept of QoL and incorporates it into the ICER, termed the ICUR. Imagine that a patient's QoL can be measured between the bounds of 0 and 1, where 0 is no QoL and 1 is full QoL. The effect of an intervention can therefore be seen as how long a patient lives and the QoL during that life. The denominator can therefore incorporate the preference of a short life but high QoL intervention, compared to a long life, by poor QoL intervention [113]. As one can imagine, QoL can be very difficult to measure and preference can be dependent of the patient receiving the treatment.

A.1.5. Willingness to Pay

Once the incremental cost-benefit ratio is calculated between the two interventions, a decision on whether the new intervention is beneficial over the base intervention. A cost-effectiveness plane typically is used to explain illustratively the cost-benefit of a new intervention over the standard of case located at the x-axis and y-axis intercept (Figure 28).

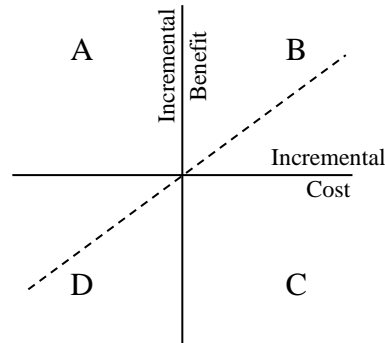


Figure 28. Cost-effectiveness plane with the willingness to pay line and four quadrants

The x-axis represents the incremental cost of the new intervention compared to the standard of care – it is the numerator of the ICER. The y-axis is the incremental benefit of the new intervention compared to the SOC – it is the denominator of the ICER.

Therefore, if the ICER is positive, either the numerator and denominator are positive, or both are negative. Similarly, if the ICER is negative, either the numerator or denominator is negative. These four scenarios can be outlined as plot in one of the four quadrants in the cost-effectiveness plane.

The base scenario is plotted at the x-axis and y-axis intercept. If the new intervention has a higher benefit, but lower cost, it has a negative ICER and is plotted in quadrant A. This scenario would be ideal, with a better outcome with lower costs, and would be accepted as cost-effective. If the new intervention has a higher benefit and a higher cost, it would be plotted in quadrant B. If the new intervention has a higher cost and lower incremental

benefit, it would be plotted in quadrant C, while a new intervention with a lower cost and lower benefit would be plotted in quadrant D.

While a decision to accept a new intervention with an incremental cost/benefit in either quadrant A or C can be easily made, interventions in quadrant B and D are more difficult. A quadrant B new intervention implicitly states that at a higher cost, a better outcome is possible. However, financial resources are limited and therefore a decision needs to be made to decide how much benefit is required for each incremental dollar. The WTP is used to illustrate how much cost can be bore for each additional benefit. An intervention above the WTP line will provide more benefit per dollar than an intervention below the line. The slope of the line differs by country and by treatment area, but the WHO recommends a WTP line of one to three times the gross domestic product per capita (GDPC) per benefit [135]. Therefore, a new intervention above the WTP line can be said to provide enough benefit to justify the cost, while a new intervention below the line cannot. This study will use a WTP threshold of three times the 2014 GDPC as reported by the World Bank: \$132,264 [98].

B. Decision Analytic Modelling

To calculate the total costs and effects of each intervention, several mathematical methods can be used. Broadly, there is cohort based modeling and patient level modeling. Cohort modeling looks at the costs incurred by a population as they progress through the health states, while patient level modeling looks at the costs incurred by a patient as they progress through the health states. Thousands of patient journeys can be simulated, incorporating various patient characteristics, comorbidities, and event probabilities, to calculate the overall costs and effects of each intervention. Moreover, patient level modeling incorporates “memory” into the model so that future event probabilities can be dependent on prior events [113].

Once a cohort or patient level based model is chosen, an analytical framework to evaluate the overall costs and effectiveness of each evaluated intervention must be chosen.

B.1.1. Decision Tree Model

A decision tree model calculates the expected costs and outcomes of an intervention, given event probabilities and costs. A decision tree is typically used when an intervention is a one-time event, such as surgery, and the procedure is evaluated over a set period of time [108]. There are three principal components to a decision tree model:

- The square decision node – represents a decision between the two or more compared interventions.
- The circle probability node – represents the probability that a patient will be in a particular health state, such as survival and death.
- The triangle expected value node – represents the end of a scenario into a health state. The incurred costs and benefits are calculated until this point.

The decision tree models a series of consequences, using event probabilities, based on a past decision. The final calculation a decision tree provides the expected value for each possible decision. For example, choosing intervention A versus intervention B may change the probability of a patient surviving an illness. The expected cost per benefit for intervention A and intervention B to make a decision can then be calculated. However, a decision tree is not adept at modeling recursive events and incorporating time into the model; instead, a decision tree will calculate the expected value for a disease within a period. Overall, decision trees are best at modeling treatment of an acute disease or one-time event within a specified period [136].

B.1.2. Markov Model

Markov models build onto decision tree models by incorporating a time or cycle component. A Markov model is typically used when an intervention has a time

component, like treating cancer. While a several decision trees can be used to incorporate time, like a Markov model, at a certain point the decision tree model will become unwieldy and difficult to follow [108]. Markov models are recursive decision trees that track the probability a patient is in a finite number of possible health states at a given time. The probabilities that a patient will move from one health state to another, called transition probabilities, are then used to calculate the distribution of patients in each health state for the next time period. This gives Markov models the advantage over decision tree analysis to accurately discount expected values and track disease progression through its various states at any period. Markov models are therefore best suited to model chronic disease or disease progression that is time dependent. Advanced Markov models have the ability to incorporate the length of time a patient is within a health state and attributes the correct transition probability to that patient indicating that the probability of changing states is dependent on how long one was in that state on other time based factors [108].

There are two components to a Markov model:

- Cycles – Cycles refer to the number of fixed periods that an intervention is being evaluated. At the end of a cycle, a patient can remain in the health state they started the cycle in or change health states.
- Transition probabilities – Transition probabilities refer to the probability that a patient will remain in a health state by the end of the cycle period. If a patient has a theoretical 50% chance of surviving a health state within a cycle, and 100 patients are in that health state, then by the end of the first cycle 50 patients will have survived. By the end of the second cycle, 25 patients will have survived, etc.

B.1.3. Microsimulation Model

Microsimulation models build upon the Markov model, but allow for variability around the transition probabilities, costs, and benefits [113]. That is to say, we would expect that

on average a patient would remain in a state; however, some patients would remain in that state for longer and shorter periods. By analyzing the paths a simulated group of patients transition through, not only can the expected cost and benefit of an intervention be evaluated, but so can the variability [108, 113].

Curriculum Vitae

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