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# Preliminary Economic Evaluation of Brentuximab Vedotin in Relapsed and Refractory Hodgkin Lymphoma: An "Early Look" Model Based on Phase II Results

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

# PRELIMINARY ECONOMIC EVALUATION OF BRENTUXIMAB VEDOTIN IN RELAPSED AND REFRACTORY HODGKIN LYMPHOMA: AN "EARLY LOOK" MODEL BASED ON PHASE II RESULTS

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## Abstract

We conducted a cost-effectiveness analysis of brentuximab vedotin for the treatment of relapsed and refractory Hodgkin Lymphoma (HL) from health care system perspective in Canada. We developed a Markov decision analytical model to simulate lifetime costs and benefits and parameterized the model using brentuximab phase II clinical trial and cd-link data which is a linked datasets of cancer registry with administrative databases of Ontario, Canada. In the base case scenario, brentuximab treatment led to an increase of 0.352 Quality Adjusted Life Years (QALYs) per person and $108,500 per person, which resulted in incremental cost effectiveness ratio (ICER) of $308,532 per QALYs gained. The ICER was sensitive to hazard ratio, cost per dose of brentuximab and utility values. In conclusion, brentuximab has an ICER higher than $100,000 per QALY threshold that is often classified as having "weak evidence for adoption and appropriate utilization" in Canada according best available information so far. The substantial reduction (e.g., 72%) in the cost of unit dose of brentuximab can reduce ICER dramatically and make the drug cost effective.

## Keywords

Cost-effectiveness, Hodgkin Lymphoma, brentuximab, phase II trial, targeted therapy, Canada

# Dedication

This thesis is dedicated to cancer research.

## Acknowledgments

First and foremost, I would like to extend my sincere gratitude to my supervisor, Dr. Gregory Zaric and co-supervisors Dr. Mehmet Begen and Dr. Joy Mangel for their continuous support, guidance and assistance over the course of my thesis project.

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## Glossary of Terms

**Autologous Stem Cell Transplantation**: A procedure in which blood-forming stem cells (cells from which all blood cells develop) are removed, stored, and later given back to the same person.

**Allogeneic Stem Cell Transplantation**: A procedure in which a person receives blood-forming stem cells (cells from which all blood cells develop) from a genetically similar, but not identical, donor. This is often a sister or brother, but could be an unrelated donor.

**Bulky Disease:** Bulky disease describes an area of lymphoma that is greater than 10 cm (about 4 inches) in size or the disease takes up more than a third of the chest cavity at a generally accepted level of the spine (thoracic vertebrae 5-6) that is seen with a chest x-ray.

**Hematopoietic:** pertaining to the formation of blood or blood cells.

**Hematological Malignancy:** A cancer of the blood or bone marrow, such as leukemia or lymphoma.

**Karnofsky Performance Score (KPS):** A standard way of measuring the ability of cancer patients to perform ordinary tasks. The Karnofsky performance scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.

**Medical Technology**: Healthcare products, interventions and procedures used to promote health, prevent, diagnose and treat disease.

**Monoclonal Antibody:** A type of protein made in the laboratory that can bind to substances in the body, including tumor cells.

**Neoplastic Cells:** a cell that is part of tumor.

**Orphan Drug:** A pharmaceutical agent intended to treat rare disease.

**Positive Predictive Value:** The probability that a person with a positive test result has the disease.

**Risk Adapted Therapy:** Treatment that is generally based on risk stratification. Risk depends on stage of disease, presence/absence of bulky disease and response to therapy.

# List of Abbreviations

ABMT: Autologous Bone Marrow Transplantation

ADC: Antibody Drug Conjugate

AE: Adverse Reaction

ALCL: Anaplastic Large Cell Lymphoma

ASCT: Autologous Stem Cell Transplantation

BMI: Body Mass Index

CEA: Cost-Effectiveness Analysis

CHL: Classical Hodgkin Lymphoma

CMT: Combined Modality Therapy

CT: Chemotherapy

EFS: Event Free Survival

EVPI: Expected Value of Perfect Information

FFTF: Freedom From Treatment Failure

FF2F: Freedom From Second Failure

FFS: Failure Free Survival

HDCT: High Dose Chemotherapy

HL: Hodgkin Lymphoma

ICER: Incremental Cost-Effectiveness Ratio

NLPHL: Nodular Lymphocyte Predominant Hodgkin Lymphoma

OS: Overall Survival

PBSCT: Peripheral Blood Stem Cell Transplantation

PFS: Progression Free Survival

QALY: Quality Adjusted Life Years

RCT: Randomized Controlled Trial

RFS: Relapse Free Survival

RT: Radiotherapy

SCT: Stem Cell Transplantation

SoC: Standard of Care

VOI: Value of Information

WHO: World Health Organization

WTP: Willingness to Pay

# Chapter 1

## 1 Introduction

Hodgkin Lymphoma (HL) is a rare type of cancer with an annual rate of 3 per 100,000 in Canada[1]. In 2010, 960 patients were diagnosed with HL and 116 patients died in Canada[1]. The conventional treatment options for HL include chemotherapy, radiotherapy and hematopoietic stem cell transplantation. Although survival outcomes for the majority of patients are promising, a significant proportion of the population cannot be cured with standard treatment regimens [2-4]. Management of disease after second line treatment becomes more difficult for medical specialists due to lack of guidelines and clinically strong studies.

Like in many cancer centers around the world, in Ontario cancer centers, the standard of care for second line treatment of HL is high dose chemotherapy plus autologous stem cell transplantation (ASCT). It has been shown that 50% of patients relapse after ASCT [5] and prognosis tends to be very poor with median survival less than one year for these patients [6, 7]. Currently, treating these patients remains a therapeutic challenge. The available treatment options are severely limited. Furthermore, these treatment options were tested in non-randomized setting and toxicity and treatment related mortality rates are higher, making them less attractive for the hematology community and patients.

The standard of care treatment options in the post-autologous SCT period include allogeneic stem cell transplantation, second ASCT, standard dose treatments and single

agents which are ultimately palliative. The reported survival benefits of these therapies are minimal with median survival in the range of 6 and 30 months [8-11]. In the last couple years, there have been attempts to develop new agents and new antibody therapeutic agents for the treatment of relapsed HL that resulted in minimal or no antitumor activity [12, 13].

To gain entry into the market, pharmaceuticals are typically evaluated through a series of clinical trials beginning with phase I through to phase III randomized controlled trials that are required by regulatory bodies in order to get definitive results regarding the efficacy and safety of the new intervention. However, in the case of drugs thought to fill unmet medical need, results from phase II trials are considered sufficient evidence to obtain accelerated market approval with a condition that post marketing clinical trials must be conducted to verify the current clinical benefit. Health care payers decide whether or not to include these new and expensive therapies to drug formularies upon market approval. Thus, economic evaluation of such drugs at an early stage would yield interesting results to healthcare payers in light of the existing state of limited information.

Brentuximab vedotin (Adcetris), being an orphan drug, was granted accelerated approval recently from the FDA based on phase II trial results for the treatment of HL after ASCT or two prior multi agent chemotherapy regimen failures. Initial findings were promising and trial showed that objective response rate was 75% with a median progression free survival (PFS) of 5.6 months [14].

In this study we aim to evaluate cost-effectiveness of brentuximab from the Canadian healthcare payer perspective based on phase II trial results. We developed a decision analytic model and used cancer registry and administrative databases of Ontario to populate the model. This study has several objectives. First, we seek to establish the cost-effectiveness of brentuximab versus standard of care. Second we develop an "early look" model that will project lifetime costs and benefits. Finally, as Canadian pricing is not available, we determine the conditions under which brentuximab would be cost effective by conducting a threshold analysis. The remainder of the thesis is organized as follows: Chapter 2 summarizes literature review. Chapter 3 enumerates primary and secondary research questions. In chapter 4 we explain the materials and methods required to conduct cost-effectiveness analysis. We report the results in chapter 5 and conclude in chapters 6 and 7.

# Chapter 2

## 2 Literature Review

### 2.1 Hodgkin Lymphoma

Hodgkin's disease is a cancer of the lymph tissue found in the lymphatic system which helps to fight against infectious diseases. The lymphatic system of the human body circulates lymph (fluid that carries white blood cells by means of lymph nodes and lymphatic vessels). There are hundreds of lymph nodes in the human body. The lymph nodes act as a filter and are clustered around certain parts of body such as the neck, underarm, chest, abdomen and groin. As lymph passes through, the lymph nodes filter out bacteria and unwanted cells including cancer cells. When a hematological malignancy occurs, the lymph nodes start to grow abnormally. These abnormal cells are called Reed-Sternberg cells which are the markers of HL. Since the lymph nodes are spread throughout the body, cancer can initiate from anywhere inside the body.

#### 2.1.1 History and Disease Classification

This rare phenomenon was first explained by British doctor Thomas Hodgkin in 1832 [15]. He described seven cases in his classic paper that forms the basis of HL disease to date. Two decades after Thomas Hodgkin described seven cases, numbers of additional cases with similar pathological traits were found. Subsequently, this disorder came to be known as Hodgkin disease [16]. Once the relationship of disease with lymphadenopathy (enlargement of lymph nodes) and the lymphatic system was revealed, it started to be known as HL [17].

Diagnosis of the disease is established by physical exam, blood tests, chest x-rays and biopsy. In general, patients diagnosed with HL may be treated by one or more of the following treatment options: chemotherapy, radiotherapy and stem cell transplantation. Selection of treatment depends on several factors such as patient characteristics and natural history of disease, e.g., cancer stage. In recent years, new treatment strategies have been developed and many more clinical trials across the globe are investigating variety of novel medical technologies that have potential to prevent and cure the HL [18].

According to a recent World Health Organization (WHO) classification of tumors, HL is divided into two sub-groups based on clinical, biologic and pathologic features: Classical Hodgkin Lymphoma (CHL) and Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) [17]. Classical Hodgkin Lymphoma is further subdivided into four subtypes with distinctive clinical features: Nodular sclerosis, lymphocyte predominance, mixed cellularity and lymphocyte depleted [17, 19, 20]. NLPHL type is rare in practice and comprises only 5% of HL cases [21].

### 2.1.2 Natural History of Disease

The biological markers of CHL malignant cells are mononuclear or multinuclear large and abnormal cells known as Hodgkin Reed-Sternberg cells (HRS) or their variants [19]. The marker of NLPHL is lobulated nuclei cells known as lymphocytic and histiocytic (L&H; also known as popcorn cells) [19, 22]. B-cells are a type of white blood cells (lymphocytes) that fight against the infections. Studies have shown that HRS cells and L&H cells are derived from germinal center B-cells [16, 21]. However, they do not

possess B-cell ancestry [23, 24]. Malignant cells HRS and L&H constitute only 1% of the total cells in the tumor, making the diagnosis and identification of HL difficult [21]. But, advances in understanding of neoplasms have made it easier to accurately classify the subtypes of HL [25]. The only common feature between CHL and NLPHL is the low number of neoplastic cells [24].

HL usually presents as a lymphadenopathy (swollen lymph nodes) which in turn may reveal mass lesion, can be detected by imaging procedures or symptoms (e.g., fever, fatigue). Each of the two major subtypes of HL has a unique group of symptoms and natural history [26]. For instance, a common clinical manifestation of the CHL is painless lymphadenopathy. NLPHL has a different natural history, e.g., indolent disease course which is different from that of CHL. The pattern in which the disease (both types) spreads throughout the body plays a critical role in effective diagnosis and treatment selection.

HL initiates at a single site (lymph node) and progresses to adjacent lymph nodes with the aid of lymphatic vessels. Late in the course of disease it disseminates to distant sites and organs. It spreads in a predictable manner, starting mostly in supradiaphragmatic (above the diaphragm) nodes (90%) and less often in infradiaphragmatic (below the diaphragm) nodes (10%) [26]. Extranodal (affecting other organs) spread of HL can happen in two ways: localized (direct invasion) and distant (hematogenous dissemination). Localized spread affects organs nearby cancerous lymph nodes (e.g., thyroid, skin). In distant spread of HL organs such as the spleen, liver, lung, bone marrow

or bone are involved. The symptoms of HL can be grouped as localized symptoms (e.g., cough, chest pain, bone pain, abdominal swelling), non-specific constitutional or organ related (e.g., fever, night sweats, weight loss, fatigue) and lab abnormalities. Patients with NLPHL rarely experience constitutional symptoms such as fever, weight loss, night sweats [19].

### 2.1.3 Prevalence and Incidence of Hodgkin Lymphoma

HL accounts for approximately 10% of all lymphomas and approximately 0.6 % of all cancers diagnosed in the world annually [22]. The global incidence of HL for both males and females varies with continents and geographical regions. According to 2008 International Agency for Research on Cancer (IARC) statistics, incidence was highest in Southern Europe, followed by North America and lowest in East Asia[27]. The age standardized incidence rates in North America was 2.6 (per 100,000) for men and 2.2 (per 100,000) for women [27].

The US National Cancer Institute estimated that 8830 new HL cases occurred in United States and 1300 of the prevalent cases died from this disorder in 2011 [28]. In 2010, the Canadian Cancer Society (CCS) estimated the incidence rate of HL to be 3 (per 100,000) for both men and women in Canada[1]. According to CCS, 960 new cases were diagnosed with HL and 116 of the cases died in 2010. Furthermore, CCS estimated the annual percentage of change in age standardized incidence rates to be 0.2% for men and 0.4% for women based on data from 1997 to 2006.

### 2.1.4 Epidemiology and Risk factors of Hodgkin Lymphoma

Despite advances in medical sciences and technologies, the etiology of HL is not conclusive. The main known risk factors of HL are age, gender, socioeconomic status, race and ethnicity, family history and certain viruses such as human immunodeficiency virus (HIV) and Epstein - Barr virus (EBV) [29] that will be described in more detail below.

**HIV and EBV:** There have been prospective cohort or registry match studies conducted on HIV patients around the world. A recent prospective cohort study showed that the risk of developing HL among the HIV infected patients is higher than that of general population [30]. The study reported that standardized rate ratio (SRR) was 14.7 (95% CI: 11.6 to 18.2). Two systematic reviews have indicated that the risk of developing HL among the HIV infected population is approximately 8 to 15 times more than for the general population [31, 32].

Some other studies have shown that there is a positive association between EBV status and HL [33]. However, the true relationship between EBV and HL is still unclear [34] and the direct versus indirect effect of EBV on Hodgkin disease remains questionable. A prospective study from Brazil showed that prevalence of EBV is more apparent in HIV positive (100% versus 29%) and advanced stage (63% versus 9%) HL diagnosed patients. In general it has been shown that EBV is associated with between 20% and 50% of HL cases in North America [35, 36].

**Age:** One of the unique characteristics of the HL is that it has a bimodal age distribution [37-39]. The incidence is small among children, followed by a sharp increase in teenagers which reaches a peak at 25 years of age. Thereafter, incidence falls between the ages of 25 and 70 and then increases again after the age of 70, peaking in the late 70s. This variation can be explained by different pathogenesis of the disease in the two separate populations [40].

**Gender:** HL incidence is higher among males than among females [41]. Some researchers explained this phenomenon by the role of reproductive factors and sex hormones [42]. According to 2010 CCS statistics, 540 males and 420 females were diagnosed with HL cancer [1]. Furthermore, according to US National Cancer Institute SEER (Surveillance Epidemiology and End Results) estimates, males on average were 1.22 to 1.25 times more likely to develop a HL cancer than females [43].

**Socioeconomic Status (SES):** HL incidence may vary with socioeconomic status. Age specific incidence rates from one study were highest in high socioeconomic group across the all ages [44]. Using SEER data Glaser et al. (1987) showed that HL incidence was positively associated with community level socioeconomic status [45].

**Race/Ethnicity:** Disease incidence varies with race and ethnicity (Table 2-1). A Canadian case control study showed that HL incidence is higher among people of Eastern and Western European descent [46]. Blacks tend be less susceptible than whites and this might be partially explained by genetic factors or socioeconomic status [47]. According

to 2004-2008 US National Cancer Institute statistics data, incidence rates were highest among whites (3.3 per 100,000 men and 2.8 per 100,000 women) and lowest among the Asian/Pacific Islander (1.5 per 100,000 men and 1.1 per 100,000 women)[43].

**Table 2-1:** Incidence by Race

| | Incidence (per 100,000) | |
|---|---|---|
| **Race/Ethnicity** | **Males** | **Females** |
| All | 3.1 | 2.6 |
| White | 3.3 | 2.8 |
| Black | 3.2 | 2.4 |
| Asian/Pacific Islander | 1.5 | 1.1 |
| American Indian/Alaska Native | 1.0 | N/A |
| Hispanic | 2.7 | 2.2 |

**Source:** 2004-2008 SEER data [43]

**Family History:** Genetic susceptibility is an important predictor of HL. The risk of developing disease increases threefold if a first degree relative (e.g., parent, sibling, offspring) has the disease [22]. Risk is especially higher in twins and siblings but lower in older parents.

A familial risk study conducted using cancer registry data from Sweden and Denmark, has shown that the relative risks of HL in relatives of HL patients were 3.47 (95% CI: 1.77- 6.80) in Sweden and 2.55 (95% CI: 1.55-6.05) in Denmark [48].

**Smoking:** Several studies indicated being a current or former smoker is positively associated with risk of HL [49, 50]. However, other studies showed no association or inverse association [51, 52].

**BMI:** The effect of BMI is not conclusive. In a Swedish cohort study relative risk of HL was 3.3 (1.4-6.5) among the obese men (BMI > 30 kg/$m^2$) and 0.9 (0.3-2.4) among obese women (BMI>28.6 kg/$m^2$) [53]. However, a Scandinavian case control study showed that there was no association between obesity and risk of HL [54].

**Occupation:** It has been shown that certain occupation exposures can also play a role in the development of HL [55, 56]. These studies showed that several environmental exposures such as uranium ionizing radiation and gasoline station occupation are associated with increased risk of HL.

### 2.1.5 Diagnosis of Relapsed and Refractory Hodgkin Lymphoma

Initial evaluation of patient starts with physical examination for swollen lymph nodes, presence or absence of systemic symptoms (e.g., fever, night sweats, and weight loss) and any history of past malignancy. About one third of patients develop systemic symptoms and these symptoms are associated with poor prognosis [19, 57]. Definitive diagnosis of HL is established either by excisional (entire lymph node) or incisional (part of a lymph node) biopsy. In addition, blood tests are conducted to count the number of blood cells which may provide supportive evidence for cancer. Finally, imaging tests (e.g., CT, PET) shows swollen lymph nodes and allows determining the tumor burden. Once diagnosis of disease is established, clinical stage of HL is determined in order to determine appropriate treatment strategy.

Clinical staging of HL is an important factor that measures the burden of disease and prognosis prediction. In 1971, the Ann Arbor Staging system was introduced [58] and later in 1989 the Cotswolds modification of the Ann Arbor staging system was introduced [59]. This is still used for staging of Hodgkin cancer (Table 2-2).

**Table 2-2 :** Staging System

| Stage | Definition |
|---|---|
| I | Involvement of a single lymph node region (I) or single extralymphatic site (Ie) |
| II | Involvement of two or more lymph node regions on the same side of the diaphragm (II) or of one lymph node region and a contiguous extralymphatic site (IIe) |
| III | Involvement of lymph node regions on both sides of the diaphragm, which may include the spleen (IIIs) and/or limited contiguous extralymphatic organ or site (IIIe, IIIes) |
| IV | Widespread involvement of one or more extralymphatic organs |

The absence of systemic symptoms is represented by adding 'A' to the stage; the presence of systemic symptoms is represented by adding 'B' to the stage. Bulky disease is denoted by 'X'. The subscript 'E' is used if limited extranodal extension is documented. 'S' means disease has spread to the spleen.

Diagnosed patients are placed into one of four stages (I-II-III-IV) based upon number of lymph nodes involved, presence or absence of systemic symptoms (e.g., weight loss, night sweats and fever), bulky disease and extranodal involvement. Patients with stage I and II are further classified as favorable and unfavorable prognosis based on presence or absence of specific clinical features.

According to the German Hodgkin Lymphoma Study Group (GHSG) unfavorable prognosis is defined as if one of these criteria is met: large mediastinal mass, extranodal disease, higher erythrocyte sedimentation rate and at least 3 sites involved. The European Organization for Research and Treatment of Cancer (EORTC) definition is similar and it

includes age of 50 years old instead of extranodal disease and at least 4 sites involved instead of 3. The adverse prognostic factors for advanced HL are age of 45 years or older, stage IV disease, male sex, white blood cells count (at least 15,000 per $m^3$), lymphocyte count (less than 600 per $m^3$), albumin level (less than 4 g per dl) and hemoglobin level (less than 10.5 g per dl) and patients with at least 5 of the factors had 5-year overall survival (OS) of 56% versus 89% for patients with none of these factors [60]. More than 80% of patients of patients less than 60 years old diagnosed with HL for the first time are cured from HL [19]. At least 50% of recurrent HL cases happen during first 1 to 2 years and up to 90% of recurrent HL cases seen after 5 years of the completion of primary therapy [26].

The US National Comprehensive Cancer Network (NCCN) guidelines are frequently used for diagnostic workup [61]. According to NCCN v3.2011 guidelines, an integrated PET-CT or a PET with diagnostic CT is recommended as the standard of surveillance imaging. Chest x-ray or CT every 6-12 months (during first 2-5 years) and CT abdominal every 6-12 months (during first 2-3 years) are follow up recommendations after the primary treatment [62], although some studies showed that serial imaging has limited value in detecting the recurrence of HL [63, 64].

Re-biopsy is suggested for all patients to establish recurrence of the HL. However clinical researchers recommend use of the repetitive biopsy only in certain conditions such as unclear primary diagnosis, late relapse or possible alternative diagnosis since it is an invasive procedure with possible risk of complications [61].

The popularity of PET scans has risen in the post-treatment period to assess the response to a treatment. The International Harmonization Project in Lymphoma consensus guidelines recommend scanning 6-8 weeks after chemotherapy and 8-12 weeks after radiation [65]. The positive predictive value of the FDG-PET is variable and hence, it is recommended for FDG-PET positive patients to undergo biopsy or serial imaging until disease progresses.

### 2.1.6 Prognostic Factors in Relapsed and Refractory HL

Multivariate analyses have shown that poor performance (measured by the Karnofsky performance score) status at relapse, age > 50 years and primary treatment failure were significant prognostic factors [66]. The 5-year OS was 55% for patients with none of these risk factors versus 0% for patients with all of the risk factors. A study of 422 patients conducted by German Hodgkin Lymphoma Study Group (GHSG) showed that anemia, advanced clinical stage (III-IV) and time to treatment failure (< 12 months) at relapse were significant prognostic factors [67]. Factors such as B-symptoms and age were shown to be predictors of the poor outcome by some studies if not by all [68]. Therefore, further prospective validation is necessary for these determinants. However, time to relapse, advanced stage and poor performance status are shown to be robust predictors and can be utilized in risk adapted treatment approach [61].

## 2.2 Treatment Options

Survival rates of HL patients have improved after the introduction of combined modality therapy (CMT). About 80 to 90% of the patients can be treated with standard

treatment options and the remaining is disease refractory [4]. We described first, second and third line treatment options (Figure 2-1) in detail in the following sections.

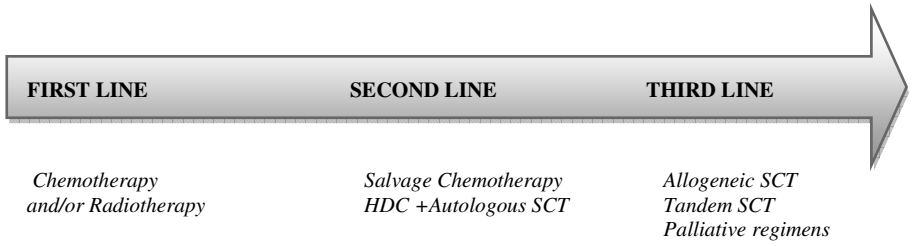



**Figure 2-1:** Treatment Pathway

### 2.2.1 First Line Treatments

In recent years, risk adapted therapies have been extensively used as new first line treatment options and more accurate staging techniques have emerged for HL patients. For favorable early-stage (stages I-IIA) HL patients short term chemotherapy followed by involved-field radiotherapy (IFRT) is considered as standard front line treatment [69, 70]. Combination chemotherapy consists 2 to 4 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by dose of 30 Gy radiotherapy [71]. Commonly adopted regimen for early stage (I and II) unfavorable HL patients is combination chemotherapy with 4 to 6 cycles of chemotherapy regimen followed by IFRT with the dose of 30 Gy [71, 72].

For advanced stage (III-IV) patients, MOPP (mechlorethamine, vincristine (oncovin), procarbazine and prednisone) was the first regimen employed. The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) showed superior results in terms

of efficacy and acceptable toxicity to MOPP and therefore became the standard regimen for advanced HL patients [73]. Currently, the most frequently employed treatment regimen in North America and Europe is eight cycles of ABVD plus consolidative radiotherapy for residual disease [71]. The alternative regimens are Stanford V (mechlorethamine, adriamycin (doxorubicin), vinblastine, vincristine, bleomycin, etoposide, prednisone, G-CSF) and BEACOPP (bleomycin, etoposide, adriamycin (doxorubicin), cyclophosphamide, oncovin (vincristine), procarbazine, prednisone, G-CSF).

### 2.2.2 Second Line Treatments

Although the majority of patients diagnosed with HL attain complete remission after the first line therapy, approximately 15% of early stage HL and up to 50% of advanced stage HL patients relapse following initial therapy [2, 3].

#### 2.2.2.1 Salvage Chemotherapy

Despite the number of regimens available there is no consensus on optimal salvage chemotherapy regimen. Most of these regimens are tested in non-randomized and single arm trials that resulted in overall response rates varying from 69% to 81%. Thus, it is difficult to conclude which regimen is preferable since there is no head to head comparison between regimens. Death rates related to toxicities varied from 0% to 5% among available salvage regimens. According to documented salvage chemotherapy regimens, there appears to be a tradeoff between the toxicity level and higher response rates, since an increase in dose of chemotherapy regimen results in more deaths. The

major observed toxicities in these salvage regimens were grade III-IV neutropenia, thrombocytopenia and vomiting. Dose escalation may result in gains in efficacy, but comes with the cost of toxic effects. The goal of the salvage treatment is an important criteria in selection of the treatment regimen. For instance, if the goal of salvage is to enable patient to proceed to ASCT then regimen must have acceptable level of hematological toxicity so that it does not impair ability for stem cell mobilization. Hence, efficacy must be balanced with toxicity. The key characteristics of salvage chemotherapy regimens are listed in Table 2-3.

**Table 2-3:** Salvage Chemotherapy Regimens

| Salvage Regimen | # of Patients | Age range | CR (%) | PR (%) | Regimen | TRM (%) | Type of Study | Year of Publication | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Dexa-BEAM | 144 | 16-60 | 27 | 78 | dexamethasone and carmustine, etoposide, cytarabine, melphalan | 5 | RCT | 2002 | [74] |
| DHAPq2wk | 102 | 21-64 | 21 | 68 | dexamethasone, cisplatin, cytarabine | 0 | Phase II | 2002 | [75] |
| GDP | 23 | 19-57 | 17 | 52 | gemcitabine, dexamethasone, cisplatin | 0 | Phase II | 2003 | [76] |
| GVD | 91 | 19-83 | 19 | 51 | gemcitabine vinorelbine pegylated liposomal doxorubicin | 0 | Phase I/II | 2006 | [77] |
| ICE | 65 | 12-59 | 26 | 58 | ifosfamide,carboplatin and etoposide | 0 | Prospective Trial | 2001 | [78] |
| IVE | 51 | 16-53 | 61 | NR | ifosfamide, etoposide and epirubicin | 0 | Prospective Trial | 2003 | [79] |
| MINI BEAM | 55 | 15-60 | 51 | 33 | BCNU (carmustine), etoposide, cytarabine and melphalan | 2 | Prospective Trial | 2001 | [80] |
| MINE | 157 | 15-65 | NR | NR | mitoguazone, ifosfamide, vinorelbine etoposide | 5 | Prospective Trial | 2002 | [81] |
| IV | 47 | NR | 45 | 38 | vinorelbine, ifosfamide | NR | NR | 2001 | [82] |

CR: Complete Remission, PR: Partial Remission, TRM: Treatment Related Mortality, NR: Not Reported

#### 2.2.2.2 High Dose Chemotherapy and Autologous Stem Cell Transplantation

To our knowledge there have been two RCTs conducted to examine efficacy of the high dose chemotherapy regimen followed by stem cell transplantation in relapsed and refractory patient population [74, 83]. Therefore, carmustine (BCNU), etopside, cytarabine and melpahalan (BEAM) is considered as a standard high dose regimen in this setting [61] and BEAM regimen followed by ASCT is considered standard of care for patients following the relapse after the first line therapy.

The first clinical trial of high dose chemotherapy (e.g., BEAM) was conducted by British National Lymphoma Investigation (BNLI) by randomizing 40 patients to BEAM followed by stem cell transplantation and to Mini-Beam treatment arms. Patients were followed up for the median length of 34 months. Two patients died due to toxic effects of bone marrow transplantation. Event free survival (EFS) at 3 years was 53% and 10% for Beam plus ABMT and mini-Beam arms respectively. Both EFS and PFS were superior in Beam plus ABMT treatment group ($p=0.025$ and $p=0.005$).

In another trial, GHSG randomized 161 patients to two cycles of Dexa-BEAM (dexamethasone and carmustine, etoposide, cytarabine, and melphalan). Responded (or chemo-sensitive) patients received either two more cycles of Dexa-BEAM or high dose BEAM followed by ASCT. Bone marrow or progenitor cells were harvested after the second cycle of Dexa-BEAM and patients received either autologous bone marrow or peripheral blood proginetor cells transplantation following the high dose chemotherapy.

Median follow up of patients was 39 months. OS at 3 years was 65% for Dexa-Beam and 71% for high dose BEAM followed by ASCT. Freedom from treatment failure (FFTF) at 3 years was 34% for Dexa-BEAM and 55% for high dose Beam followed by ASCT. Difference in OS was not statistically different between treatments (p=0.331). One out of 61 patients (2%) died due to toxic effects of HDCT plus ASCT.

In each of these trials refractory patients were excluded from study. The evidence of efficacy of high dose regimen and ASCT among refractory patients is very limited. Like salvage regimens, there is no one-to one comparison of high dose regimens in randomized control setting. The efficacy and toxicity of the high dose regimens are highly variable. Other reported high dose regimens are CBV (cyclophosphamide, BCNU, VP-16; OS: 45%, FFS: 25% at 4 years), CBVP (cyclophosphamide, BCNU, VP-16, cisplatin; DFS: 39% at 4 years), CCV (cyclophosphamide, CCNU, VP16; OS: 57%, EFS: 52%, FFP: 68% at 3 years), TLI-total lymphoid irradiation with VP16/CY (OS: 81%, EFS: 68%), VP-16 and melphalan (DFS:38.4% at 4 years) and high dose melphalan-HDM (OS:57%, EFS:52% at 5 years) [78, 84-88].

#### 2.2.2.3 Standard Dose Treatments

GHSG reported that salvage radiotherapy (SRT) could be a treatment strategy for subset of relapsed and refractory patients, in particular for those with limited stage late relapses, without B-symptoms and good performance status [89]. GHSG study found that FF2F and OS at 5 years were 28% and 51% respectively. Other studies have reported similar results. For instance, Wirth et al. (1997) reported that 5- year Failure Free

Survival (FFS) and OS of 51 patients receiving salvage radiotherapy were 26% and 57% respectively [90]. Leigh et al. (1993) showed that 28 patients who received salvage radiotherapy in previously un-irradiated areas after failure to combination chemotherapy had 5-year relapse free survival (RFS) of 40% and OS of 63% [91]. Brada et al. (1992) analyzed 44 patients who received salvage radiotherapy after relapsing from chemotherapy and reported that 5-year PFS rate was 38% [92]. In addition, these studies showed that B-symptoms, advanced stage and poor performance status are important predictors of salvage radiotherapy. Moreover, it can be employed as a treatment option if the relapsed area was not previously irradiated.

There is limited data showing effect of conventional dose combined modality therapy as a second line therapy for relapsed and refractory patients. Moreover, these studies were conducted retrospectively. For instance, Bonfante et al. (1997) showed that standard dose chemotherapy can be treatment option for patients in long term complete remission (greater than 12 months) [93]. In their series of 115 patients who were re-treated with MOPP-ABVD, it was reported that 8–year OS was 54% for those in remission greater than 12 months and 28% for those in remission shorter than 12 months.

Likewise, series from Croatia reported outcomes of 65 relapsed and refractory patients who received MOPP followed by radiation as a primary treatment and continued with MOPP and ABVD as a second-line treatment [94]. Out of 65 patients 51% had complete remission, with OS and FFS at 10 years being 21% and 16% respectively. Prognosis was good for patients remaining in remission for more than 12 months versus for patients

remaining in remission for less than 12 months. Thus, it is concluded that conventional dose salvage chemotherapy followed/or not followed by radiotherapy is a treatment option for patients with late relapse and favorable prognosis.

### 2.2.3 Third Line Treatments

Patients who relapse from autologous stem cell transplantation (ASCT) have very limited treatment options and available therapies are ultimately non-curative. Disease recurs in 50% of patients who underwent ASCT [5]. Prognosis for these patients is usually poor with median survival less than a year [6, 7]. More recent study showed that median survival is 26 months after autologous stem cell failure [95].

#### 2.2.3.1 Allogeneic Stem Cell Transplantation

A study explored survival outcomes of cohort of 114 patients who relapsed after autologous stem cell transplantation and underwent myeloablative allogeneic stem cell transplantation [8]. PFS and OS at 3 years were 33% and 25% respectively. Treatment related mortality (TRM) was 22% at the end of follow up. The study concluded that only a small proportion of patients can benefit from allogeneic transplant in particular, patients with Human Leukocyte Antigen (HLA) matched sibling donor and good performance status.

Studies have shown that reduced intensity allogeneic stem cell transplantation (RIC-allo) had much better survival, safety and lower treatment related toxicity than myeloablative allogeneic transplantation [96, 97]. There are several prospective trials

conducted to explore the effect of the reduced intensity regimens fludarabine and melphalan. Peggs et al.(2005) documented that 49 patients, 90% of whom had autologous transplantation before and failed, received fludarabine (150 mg/$m^2$) and melphalan (140 mg/$m^2$) before allogeneic SCT [98]. Treatment related mortality was 16% at 2 years. OS and EFS at 4 years was 56% and 39% respectively. Similarly, Alvarez et al. (2006) reported that reduced intensity regimen resulted in mortality rate of 25% at 1 year and relapse rate of 68%. Furthermore OS at 2 years was 48% in this study [99]. Finally, Armand et al. (2008) estimated that PFS was 22% and OS was 48% at 2 years with treatment related mortality of 25% at 1 year [9].

#### 2.2.3.2 Tandem Autologous Stem Cell Transplantation

Treatment options for the patients relapsing after autologous transplantation are severely limited. Widespread use of allogeneic transplantation is not accepted due to treatment related mortality, lack of donor availability and graft versus host disease. Studies exploring the effect of the second stem cell transplantation are of limited number and most are from single institution.

Recently, a Center for International Blood and Marrow Transplant Research (CIBMTR) study investigated the survival outcomes of patients who underwent second autologous stem cell transplantation [11]. A total of 49 patients (53% Hodgkin Lymphoma versus 47% Non-Hodgkin Lymphoma) patients reported to CIBMTR between 1986 and 2003 that underwent second autologous transplantation. Median follow up of patients were 72 months. OS and PFS at 5 years was 30% and treatment

related mortality (TRM) was 11% at day 100. PFS at 5 years for patients relapsing (<12 months) and (>12 months) after first transplant was 0% and 32% respectively.

#### 2.2.3.3 Palliative Regimens

A minority of patients will be eligible for allogeneic transplantation after autologous graft relapse. These patients, along with those not eligible for stem cell transplantation cannot be cured by standard treatment options. Agents used in non-curative setting include *gemcitabine*, *vinorelbine* and *vinblastine*.

Little et al. (1998) explored the efficacy of vinblastine by retrospective chart reviews of patients who relapsed after transplantation [100]. It has been shown that EFS and OS were 8.3 months and 38.8 months respectively, with median follow up of 20.4 months. The toxicity of the vinblastine was well tolerated and therefore, vinblastine is considered as an effective palliation regimen. Zinzani et al. (2000) investigated gemcitabine on 14 patients in phase II clinical trial [101]. Treatment resulted in overall response rate of 43%. There was no severe toxicity reported other than myelosuppression. Despite the lower sample size and short follow up period gemcitabine is commonly accepted and widely used palliative agent. A study by Devizzi et al. (1994) evaluated vinorelbine on 24 patients and showed that 11 out 22 patients had objective response [10]. The median duration of response was 6 months. The toxicity was mild and largely reversible.

#### 2.2.3.4 Antibody Therapies and Investigational Agents

Rituximab has been shown to be somewhat effective in treatment of classical HL with response of 22% and median duration of 7.8 months [12]. However, it has been shown to be highly effective in the treatment of nodular lymphocyte predominant HL [102]. The response rate was 94% and median PFS was 33 months. Bortezomib was shown to be unsuccessful for the treatment of HL [13, 103]. An anti CD30 monoclonal antibody MDX-60 and SGN-30 had very low antitumor effect [104, 105].

## 2.3 Brentuximab Vedotin (SGN-35)

A monoclonal antibody targets a specific antigen that is present on the surface of cancer cells. Several monoclonal antibodies such as anti CD20 specific rituximab for non-Hodgkin Lymphoma demonstrated clinical success [106]. CD30 is an antigen expressed on the surface of malignant cells of HRS, cells of anaplastic large cell lymphoma (ALCL) and other lymphoid malignancies [107]. First generation of anti CD30 monoclonal antibodies (e.g., SGN-30, MDX-30) was unconjugated and resulted in minimal antitumor activity. This fact enhanced the efforts that yielded the development of conjugated monoclonal antibodies (mAbs). Antibody Drug Conjugate (ADC) treatment approach overcomes some of the limitations caused by systemic chemotherapy. In particular, toxicity is reduced due to targeted attack of conjugated chemo agents. There are 3 key components of ADCs: monoclonal antibody, cytotoxic drug and linker [108]. Recent developments in this field increased number of ADC drugs under the

development. Brentuximab Vedotin for HL, Trastuzumab-DM1 for breast cancer and Inotuzumab ozogamicin for non-Hodgkin lymphoma are some of the examples.

Brentuximab Vedotin (a.k.a SGN-35) is an ADC composed of anti CD30 anitbody cAC10 conjugated with anti-tubulin agent called monomethyl auristatin E (MMAE) by cleavable dipeptide linker [109, 110]. After antibody cAC10 binds with CD30, ADC is rapidly transported into lysosomes and cleavable linker is cleaved, releasing MMAE into the cell. The free potent agent MMAE, after binding with tubulin disrupts the microtubulin network within cell that results in apoptotic death of CD30 positive tumor cells [110]. This drug has been developed by Seattle Genetics Inc. (Bothell, WA) and Millennium: Takedo Oncology Company.

Clinical studies of brentuximab yielded encouraging results from phase I and the pivotal phase II trials [14, 111]. The target population in phase I trial (n=45) were those who relapsed and were refractory to the first line chemotherapy, high dose chemotherapy stem cell transplantation or salvage chemotherapy regimen. The median age of patients included in the trial was 36 years (20 to 87). All of the patients underwent median of 3 previous chemotherapy regimens and 73% had undergone autologous stem cell transplantation. Patients receiving allogeneic stem cell transplantation were not included in phase I study. Brentuximab was administered intravenously every 3 weeks. The treatment was associated with mild to moderate toxicity levels, e.g., fatigue, nausea, diarrhea, neutropenia and peripheral neuropathy. According to dose escalation study maximum acceptable dose of brentuximab vedotin was 1.8 mg/kg. The median duration

of the objective response was at least 9.7 months and median PFS was 5.9 months. Overall, 86% (36 out 42) patients in the trial had a tumor regression.

Results of the pivotal phase II trial were consistent and verified the initial findings from the phase I trial [14]. A total of 102 patients with the median age of 31 years received a brentuximab vedotin at the dose of 1.8 mg/kg every 3 weeks for up to 16 cycles. All of the patients received median of 4 (range: 1 to 13) prior chemotherapy regimens and autologous stem cell transplantation. More than 70% of the patients were primary refractory and in addition 39% of the patients did not respond to the most recent salvage therapy, excluding ASCT. Reported treatment related adverse events were peripheral sensory neuropathy, fatigue, nausea, neutropenia, diarrhea and pyrexia. Observed grade IV treatment-related events were neutropenia, and thrombocytopenia, abdominal pain, and pulmonary embolism. A total of 20% of the patients discontinued the treatment due to treatment related adverse event. Peripheral sensory neuropathy was the main reason for stopping treatment.

In August 2011, US FDA granted fast track approval to brentuximab veotin (Adcetris) at the dose level of 1.8 mg/kg for two indications: for patients with HL that failed after autologous stem cell transplant (ASCT) and for patients (not eligible for ASCT) who failed at least two prior multi agent chemotherapy regimens. In other words the new drug will be prescribed to patients only after the second relapse (Figure 2-1). Brentuximab Vedotin is also being clinically tested in a randomized setting and in combination with

multi agent chemotherapy regimen ABVD for potential use in the frontline treatment portfolio.

## 2.4 Economic Evaluation and Cost-Effectiveness Analysis

The goal of the economic evaluation is to prioritize resource allocation by assessing the value for money of alternative healthcare programs [112]. There are several different types of economic evaluation. Cost effectiveness analysis (CEA) is among the most common type of economic analysis [113]. CEA compares alternatives with the same health outcome measure (e.g., life years gained, lives saved). The outcome measure in CEA is presented in the form of a ratio called the incremental cost-effectiveness ratio (ICER). The ICER provides incremental cost per additional unit of health benefit (e.g., life years saved) by adopting a new health technology under the consideration.

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

The perspective taken in economic analysis is important and different viewpoints may yield different results. Common viewpoints include that of the patient, hospital/clinic, healthcare system or society. Most guidelines advocate a societal perspective[114], but in practice many CEA analyses are done from health system perspective [115, 116].

### 2.4.1 Interpretation of the ICER and Value Judgment

If the denominator of the ICER is negative and numerator is positive then the new technology is more costly and less effective than comparator and hence, it should not be

adopted. If the denominator of the ICER is positive and numerator is negative, then the new technology is less costly and more effective than comparator and the proposed medical technologies should be adopted. One faces a challenging decision when new strategy results in both higher costs and higher effectiveness (or less effective and less costly). The decision then becomes is to whether additional benefit in health outcome is worth paying (e.g., value judgment).

There are a number of ways to decide whether the ICER for the given treatment option is cost effective and hence, treatment should be adopted. One approach is the league table approach which is the list of cost per QALY values in the increasing order for all interventions and treatments with the lowest cost per QALY are selected until budget is exhausted [117]. It helps the decision makers to compare the ICER of the new technology to previously approved interventions to make a judgment whether it shows good value for money.

However, this approach is rarely used in practice since there is a variation in methodology of the source studies in the league table [112] and some decision making guidelines is used to assist decision. A willingness to pay (WTP) threshold is used in some countries. In the UK, medical technologies that cost less than £30,000/QALY are considered to be cost-effective [118]. In Canada, interventions with ICERs smaller than $20,000/QALY are often classified as having “strong evidence for adoption and appropriate utilization” and those with ICER greater than $100,000/QALY are classified as having “weak evidence for adoption and appropriate utilization”[119].

### 2.4.2 Quality Adjusted Life Years

The quality adjusted life year (QALY) is defined as measure of a person's length of life weighted by a valuation of their health-related quality of life [113, 120]. It takes into account quality and quantity of life generated by new treatment and is the arithmetic product of life expectancy and measure of quality of life. QALY places different utility weights (continuous measure varying between 0 and 1) to different health states. A year of perfect health is represented by 1. Any value less than 1 represents non-perfect health status and death is considered to be equivalent to 0.

### 2.4.3 Decision Analytic Models

Decision analytic modeling has been extensively used for clinical and epidemiological applications. It is widely utilized to compare competing alternatives with respect to costs, life years, QALYs and to estimate ICER. The most commonly used models include decision trees and Markov models, as well as combination of these.

### 2.4.4 Markov Models

In most cases, data are obtained from randomized clinical trials. However, one of the limitations of the clinical trial is relatively short follow up period. Use of Markov model is necessary to project long term impact of the new therapy and to avoid difficulties of recursive decision tree model. Markov model was introduced in 1983 to the medical decision makers and has been extensively used in therapeutic decision making since its introduction [121, 122]. Markov models simplified the modeling of stochastic (probabilistic) events that may occur repeatedly and over the long time horizon (time

frame). Clinical events of interest with ongoing risk are modeled as a Markov process. The underlying assumption of the Markov process is that it is sufficient to know the present health state of the patient in order to project entire path of the future health states. In other words prognosis of all patients in a state X is same regardless of their disease history. It is also assumed that patient is in one of the finite number of health states at a given point in time. Markov process evolves as patient transitions from one state to another. The finite time horizon is divided into equal discrete time intervals known as cycles which can be of any (day, week, month, and year) length. The probability of transitioning from one state to another in a given cycle is known as the transition probability, which is a time variant in real life. There is a cost and utility (expressed in quality of life weights) reward for being in each state in a given cycle. Total cost (or utility) per cycle is calculated by summing the multiplication of probability of being in a given state with the cost (or utility) of being in that state across all states. The ICER is estimated by dividing incremental total cost by incremental total effectiveness at the end of time horizon.

## 2.5 Economic Evaluation of HL Technologies

The number of studies that conducted economic analysis of HL treatments and technologies is very limited. Moreover, most of these studies are conducted in a European setting.

### 2.5.1 Treatments

Norum et al. (1995) conducted a cost-utility analysis using a data of 55 HL patients from a Norwegian hospital setting. Total treatment costs included cost of medication, treatment, hospital stay, hotel stay, radiotherapy and etc. EuroQol questionnaires and Visual Analogue Scale (VAS) instruments were used to measure quality of life. Estimated total cost varied between £7905 and £29,837 depending on disease stage. Total healthcare costs were higher in advanced staged disease (P=0.0006) because of increased number of relapses. Mean treatment cost for relapsed and non-relapsed patients were £27929 and £8210 respectively. Quality of life scores did not differ much with disease stage. Overall cost per QALY ranged from £795 to £1803 depending on assumptions about indirect benefit and discount rate utilized.

Another study was conducted in a UK setting explored the cost effectiveness of high dose chemotherapy in relapsed and refractory Hodgkin and non-Hodgkin Lymphoma patients [123]. The baseline ICER was £12,800 and £17,600 per life year gained. Sensitivity analyses showed that HDC is cost effective at varying marginal cost and benefit levels. In particular, for the marginal benefit of 0.8 life years gained and for the marginal costs of between £10,000 and £16,000, high dose chemotherapy is cost effective and is below the accepted UK cost effectiveness threshold.

The study by van Agthoven et al. (2001) conducted cost effectiveness analysis by comparing costs and quality of life of PBSCT and ABMT for relapsed and refractory Hodgkin and non-Hodgkin Lymphoma [124] in a Dutch setting. A cohort of patients (91

transplanted) data registered in phase 3 randomized control trial was used to estimate costs and quality of life (QoL). Costs were estimated from institutional perspective and health related quality of life was estimated by SF-36, EuroQol and Rotterdam Symptom Checklist instruments in pre and post transplantation period. This study found that PBSCT results in both favorable costs and quality of life scores. Total costs per patients for PBSCT and ABMT treatment arms for the entire treatment were €33742 and €39610 respectively.

Verenga et al. (2001) conducted an economic analysis comparing the PBSCT and ABMT treatment using the Hovon 22 study from Netherlands [125]. Data from cohort of 204 patients with relapsed and progressive lymphoma (Hodgkin and Non-Hodgkin) that were in randomized phase 3 trial was used to conduct an economic analysis. Direct (personnel, materials, disposables, equipment, laundry and regular nutrition) and overhead costs were estimated from financial databases of two hospitals. Similar to van Agthoven et al's findings, PBSCT had resulted in favorable costs and quality of life scores. Average total cost per patient was estimated as $13 954 (range: $4913 to $29 532) for PSCT and $17 668 (range: $10 170 to 44 082) for ABMT. The SF-36 and EuroQol scores did not significantly differ for the treatments, whereas on the RSCL scores PSCT patient quality of life was superior to that of ABMT.

A group of researchers studied the cost effectiveness of different treatment options for early stage HL patients [126]. Decision-analytic model was used to estimate lifetime costs and benefits. For pathologically confirmed stage I and II patients, ICER of

laparotomy staging and tailored treatment compared with mantle and para-aortic-splenic (MPA) radiation therapy was $24,100/QALY and that of combined modality therapy (CMT) compared with laparotomy was $61,700/QALY.

### 2.5.2 Imaging and Diagnostics

Dryver et al. (2003) explored the breakdown of follow up costs and the role of routine follow up imaging among HL patients and reported that cost per true indication of relapse was $6000 and moreover, routine follow up tests were accountable for 84% of the total follow up costs [64].

Guadagnolo et al. (2006) conducted a cost effectiveness analysis of the CT computerized tomography (CT) in the routine follow up of patients in the post primary treatment period [127]. They compared 3 strategies such as annual CT for 10 years, annual CT for 5 years and follow up with non-CT modalities. The study showed that for early stage patients routine follow up with CT was associated with increased costs and reduced QALYs and for advanced stage patients ICER was well above the accepted threshold. Moreover, results were robust to the most of the variables. Overall, annual CT scan resulted in minimal survival benefit and CT was not recommended for routine use in diagnostic follow up.

## 2.6 Summary

The number of treatment options for HL patients in the post ASCT failure period is limited. ASCT therapy cannot cure approximately half of the patients. The prognosis for

these patients is poor. Newly developed antibody drug conjugate brentuximab vedotin was approved for the use in US based upon phase II clinical trial. Initial findings showed that brentuximab can potentially be superior to existing treatment options. Economic evaluation of the drug has not yet been established.

# Chapter 3

## 3 Research Questions & Hypothesis

### 3.1 Primary research question

To assess the potential cost effectiveness of *brentuximab vedotin* versus the *standard of care* in HL population failing ASCT, from a healthcare payer perspective in a Canada.

### 3.2 Secondary research questions

1. To develop an "early look" model that will let us to project life time costs and benefits for patients who relapsed for the second time.

2. To identify the conditions under which this treatment will or will not be cost effective, as Canadian pricing is not yet available.

# Chapter 4

## 4 Methods

### 4.1 Description of Model

We developed a Markov decision analytic model to project lifetime clinical and economic consequences of HL patients who received third line treatment. The model starts with a clinical decision to treat with brentuximab versus standard of care and it consists of two distinct Markov models, namely model M1 for *brentuximab vedotin* and model M2 for *standard of care* treatment options (Figure 4-1).

The decision analytic model was developed using software TreeAge Pro Suite 2009 (TreeAge Software, Inc. Williamstown, MA). We ran the model for lifetime horizon. The model M1 simulates lifetime costs and benefits of patients receiving *brentuximab* treatment and includes four health states: (1) Patient shows improvement or remains stable, (2) patient develops treatment related serious adverse event which prevents him/her to continue treatment, (3) patient's disease progresses (4) patient dies from HL cancer or from other causes (Figure 4-2). We assumed that peripheral sensory neuropathy is the only adverse reaction that stops patient from continuing treatment. The model M2 simulates the lifetime economic and clinical outcomes of patients on *standard of care* option and includes three distinct health states: (1) Patient is free from treatment failure (FFTF), (2) patient's disease progresses, (3) patient dies from HL cancer or other reasons (Figure 4-3).

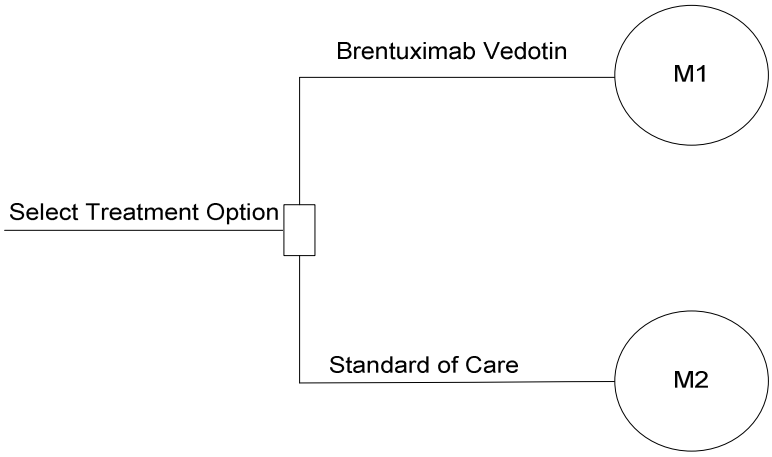



**Figure 4-1:** Decision Tree

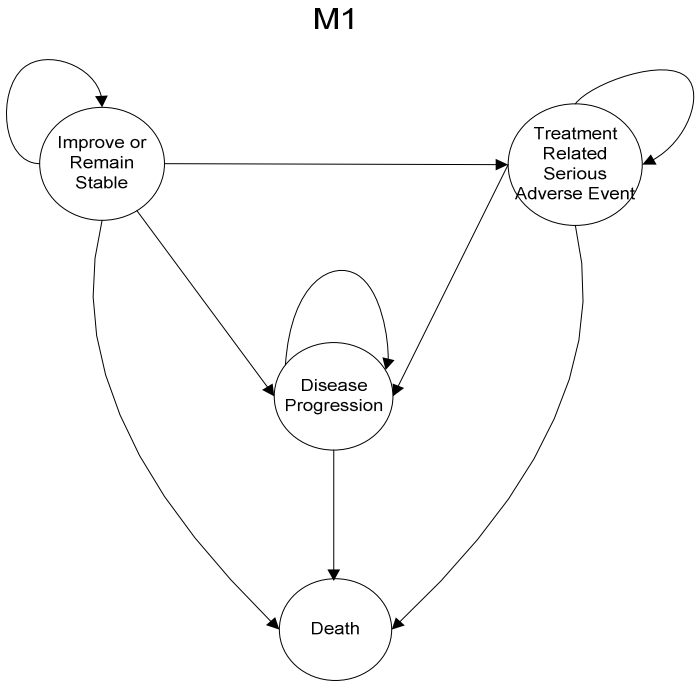



**Figure 4-2:** Markov model M1 (brentuximab)

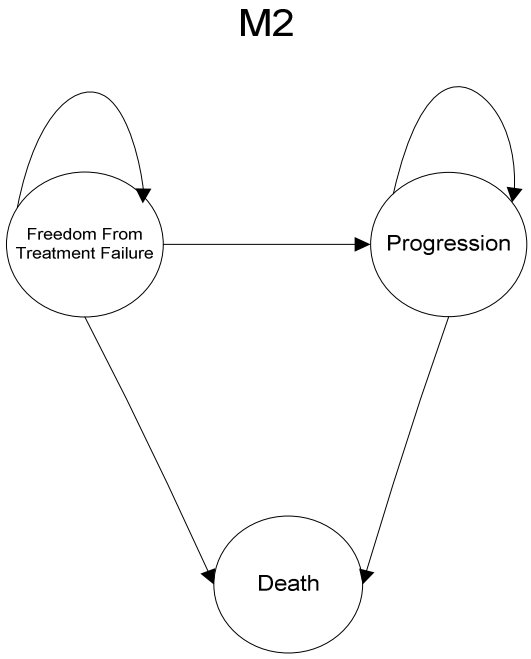



**Figure 4-3:** Markov model M2 (standard of care)

## 4.2 Data Sources

i) Description of Source:

The models were populated using *brentuximab* phase II clinical trial and administrative data from cd-link which is cancer data linkage ('cd-link') program that includes datasets relevant to cancers such as cancer registry and administrative databases of Ontario.

The study was approved by the Research Ethics Board (REB) at the University of Western Ontario. A data request was submitted to cd-link in August 2011. We requested data for all patients diagnosed with HL (ICD-9 diagnosis code: 201) between January 1, 2000 and December 31, 2006 along with follow up data until 31 March 2011. HL patients

are selected from Ontario cancer registry and linked to CIHI Discharge Abstract Database (CIHI-DAD), Ontario Health Insurance Plan (OHIP) and Ontario Drug Benefit (ODB) databases to estimate healthcare utilization, cost and transition probabilities (Figure 4-4). The CIHI-DAD database includes the hospitalization abstracts, OHIP keeps track of physician claims and ODB records the drug benefit claims. The cd-link data of patients are de-identified and made anonymous before being released to researchers. The National Ambulatory Care Reporting System (NACRS), Continuing Care Reporting System (CCRS), CytoBase (cervical screening), Home Care Database (HCD)/Ontario Home Care Administrative System (OHCAS), National Rehabilitation Reporting System (NRS), Ontario Breast Screening Program (OBSP) and Registered Persons Data Base (RPDB) are other available datasets through cd-link program for the researchers. We did not use these datasets in this study.

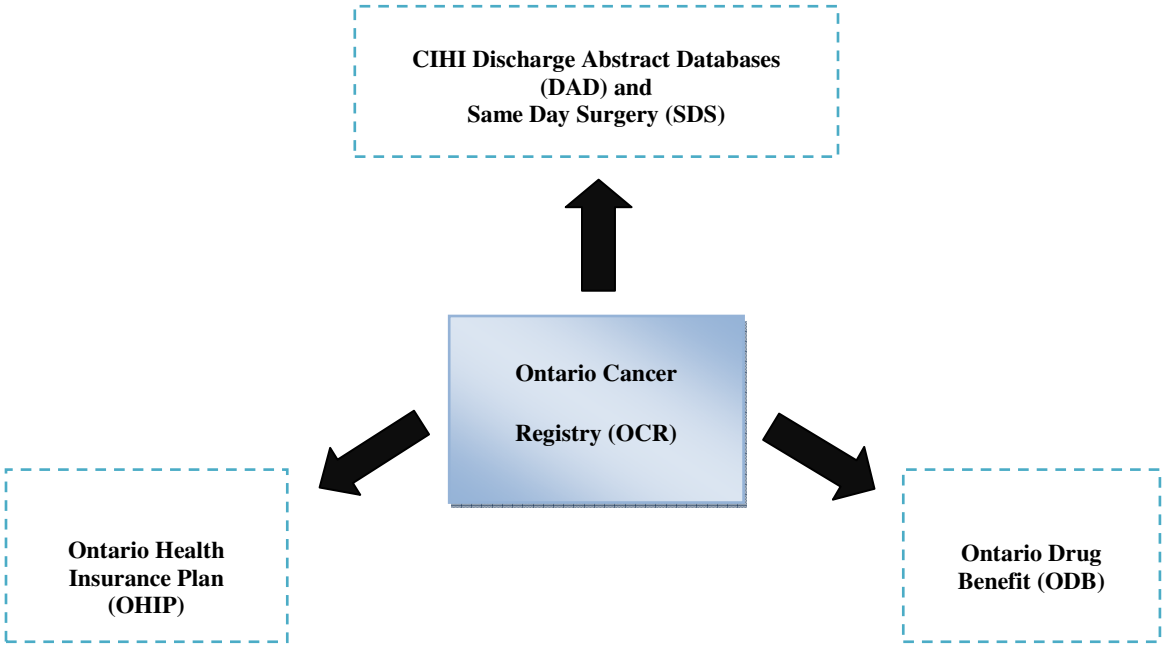



**Figure 4-4:** Data Linkage Project

ii) Cohort of Interest

According to US Food and Drug Administration (FDA) brentuximab is approved for two indications: i) for the treatment of HL after failure of ASCT ii) for the treatment HL after failure of two multi agent chemotherapy regimens in patients who are not ASCT candidates [128]. The phase II trial of brentuximab included patients with autologous SCT failure history and hence we limited our cohort to patients who had ASCT failure.

Each permanent resident of Ontario is covered by the Ontario Health Insurance Plan (OHIP). To identify the cohort of interest we used the OHIP database of physician claim records. This database tracks the medical claims submitted by physicians for the reimbursement of the services provided to the patients. Each medical service has a specific fee for service code that indicates the labor cost of the medical service. Physicians must specify the service and relevant fee code for the service in claim form. The fee codes for chemotherapy, radiotherapy, stem cell transplantation and palliative treatments are summarized in Table 4-1.

**Table 4-1:** OHIP Fee Codes

| Code | Explanation |
|---|---|
| ***Chemotherapy*** | |
| G339 | Single Agent High Dose |
| G345 | Complex single agent or multi agent therapy |
| G359 | Special singe agent or multi agent therapy with major toxicity |
| G381 | Standard chemotherapy (single injection) agents with minor toxicity |
| G281 | Each additional standard chemotherapy agent other than initial agent |
| G390 | Supervision of chemotherapy agent for induction phase of acute leukemia or myeloablative therapy prior to bone marrow transplantation |
| G075 | Test dose once per patient per drug |
| G382 | Supervision of chemotherapy by telephone, monthly |
| G388 | Management of special oral chemotherapy, for malignant disease |
| ***Radiotherapy*** | |
| X305 | Intracavitary 1.st application |
| X306 | Intracavitary repeat application |
| X322 | Treatment Planning, dosage calculation and preparation of device |
| X310 | Level 1 :Simple Treatment Planning |
| X311 | Level 2: Intermediate Treatment Planning |
| X312 | Level 3: Complex Treatment Planning |
| X313 | Level 4: Full 3D Treatment Preparation |
| ***Stem Cell Transplantation*** | |
| Z426 | Bone marrow transplantation, infusion into recipient |
| ***Palliative Care*** | |
| A945 | Special palliative care consultation (family and general practice) |
| C945 | Special palliative care consultation (non-emergency hospital in-patient) |
| C882 | Palliative care per visit, subsequent visit |
| C982 | Palliative care per visit, subsequent visit |
| K023 | Palliative care support per unit |
| W872 | Palliative care (nursing home or home for aged) |
| W972 | Palliative care per visit (nursing home or home for aged) subsequent visit |
| W982 | Palliative care per visit (chronic care or convalescent hospital) |

| W882 | Palliative care per visit (chronic care or convalescent hospital) subsequent visit |
|---|---|

According to the OCR, 2475 patients were diagnosed with HL between January 1, 2000 and December 31, 2006 (Figure 4-5). By linking the data of these patients with the OHIP database, we determined 176 medical claims with fee code Z426 that was associated with stem cell transplantation. The autologous SCT is always a preferred treatment option over allogeneic SCT due to lower treatment toxicity and is approved for second line treatment of HL in Ontario. Given that if one is eligible for SCT he will first undergo autologous SCT after the first relapse. Using service dates of stem cell transplantation procedures, we concluded that 163 patients received autologous SCT as a second line treatment.

Amongst these patients, ones receiving the chemotherapy (with fee codes G075, G281, G339, G345, G359, G381, G382, G388 and G390) or second autologous or allogeneic transplant (with fee code Z426) or radiotherapy (with fee codes X310, X311, X312, X313, X305, X306, X322) in post autologous SCT period were considered as relapsed following the high dose chemotherapy and autologous stem cell transplantation (n=77). The baseline characteristics of the cohort of interest are summarized in Table 4-2.

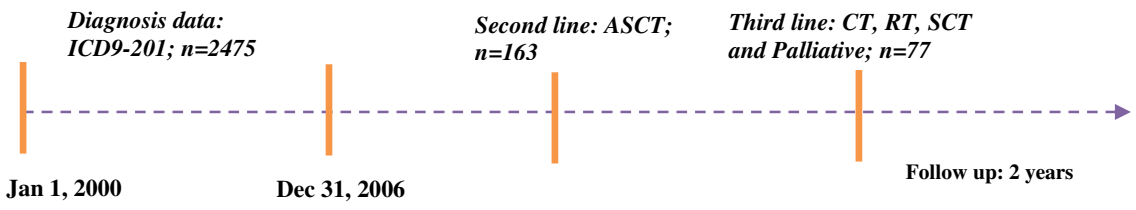



**Figure 4-5:** Schematic representation of steps to capture the cohort

**Table 4-2:** Demographics and Clinical Characteristics of 77 Patients

| Variables | Value (%) |
|---|---|
| *Age-(years)* | |
| < 20 | 17 (22.08) |
| 20-24 | 6 (7.79) |
| 25-29 | 14 (18.18) |
| 30-34 | 7 (9.09) |
| 35-39 | 10 (12.99) |
| 40-49 | 13 (16.88) |
| 50-59 | 7 (9.09) |
| 60-69 | 3 (3.90) |
| *Sex* | |
| Male | 33 (42.86) |
| Female | 44 (57.14) |
| *Time since initial diagnosis (years)* | |
| Median | 1.61 |
| Mean | 2.06 |
| Range | 0.59-7.67 |
| *Previous Therapy* | |
| Chemotherapy | 76 (99) |
| Radiotherapy | 15(20) |
| Transplantation | 77 (100) |
| *Initial Diagnosis Year* | |
| 2000 | 12 (15.58) |
| 2001 | 10 (12.99) |
| 2002 | 15 (19.48) |
| 2003 | 8 (10.39) |
| 2004 | 13 (16.88) |
| 2005 | 10 (12.99) |
| 2006 | 9 (11.69) |
| *Status on 31 March 2011* | |
| Alive | 51 (66.2) |
| Dead | 26 (33.7) |

## 4.3 Survival Analyses & Transition Probabilities

### 4.3.1 Cd-link Data

We followed all patients for 2 years and conducted survival analysis. We obtained PFS (Figure 4-1), OS (Figure 4-7), Progression to Death (Figure 4-8) and FFTF to Death (Figure 4-9) survival curves using the physician claims database. Using physician billing codes we defined the progression endpoint if patient satisfied one or more of the following criteria:

i) If one received chemotherapy after 5 months following the start of third line treatment or difference in service dates of any two consecutive chemotherapy claims is at least 60 days.

ii) If one received radiotherapy (X305, X306, X322, X310, X311, X312, and X313) after the third line treatment.

iii) If one underwent transplantation (Z426) following the third line treatment.

iv) If one received palliative treatment (A945, C882, C945, C982, K023, W982, W882, W872, and W972) in the post third line therapy period.

The above definition of progression is a proxy, since it assumes progression only when there is a treatment change. According to these criteria 40 (out of 77) patients developed progression at the end of follow up period and median PFS was 13 months. According to OHIP database 28 (out of 77) patients did not have any treatment records since start of

third line treatment. OS, Progression to Death and FFTF to Death survival at 2 years were 80%, 76% and 83% respectively.

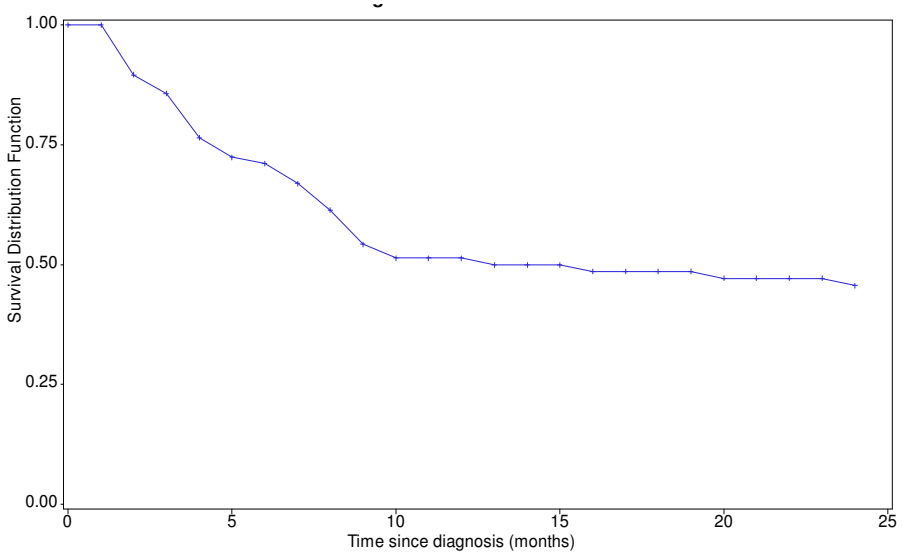



**Figure 4-6:** PFS of 77 patients from cd-link cohort

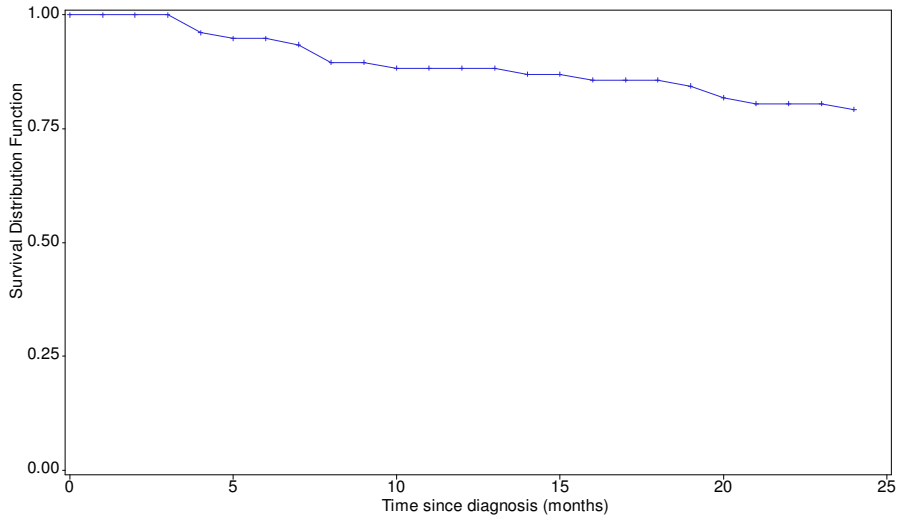



**Figure 4-7:** OS of 77 patients from cd-link cohort

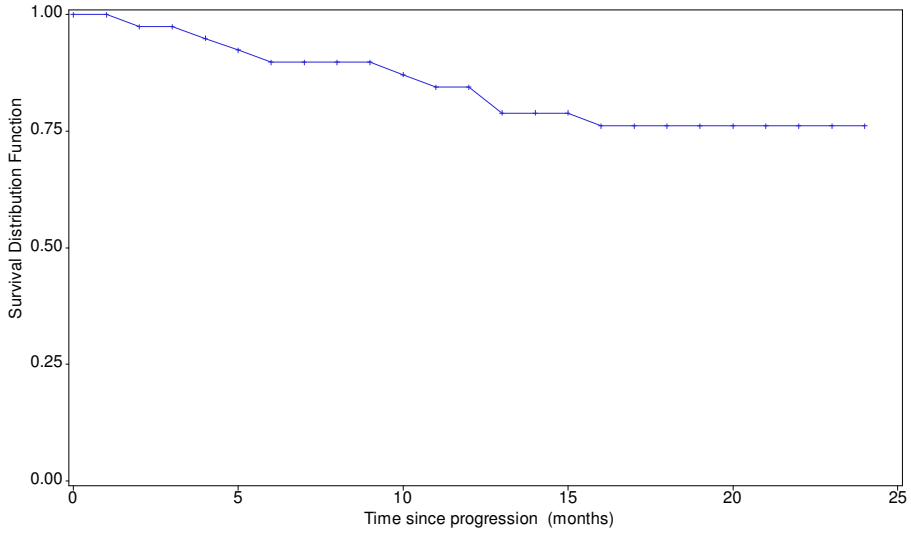



**Figure 4-8:** Progression to Death of 77 patients from cd-link cohort

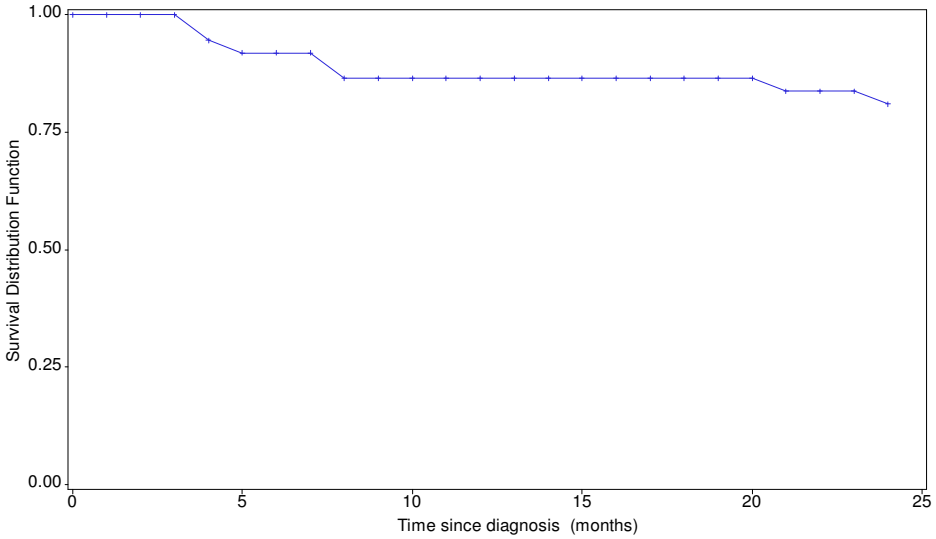



**Figure 4-9:** FFTF to Death based of 77 patients from cd-link cohort

### 4.3.2 Clinical Trial

In phase II clinical trial, the investigators conducted a subgroup analysis in which a subset of patients (n=57) underwent systemic therapy first and then received brentuximab. The response was assessed by CT and PET scans at a specified time intervals. The PFS was measured before and after the brentuximab treatment. The median PFS was 4.1 months for the systemic therapy and 7.8 months for brentuximab that yielded hazard ratio of 0.41. The PFS curves for both clinical cases are reported [14]. For the illustrative purposes all PFS curves are depicted in Figure 4-10.

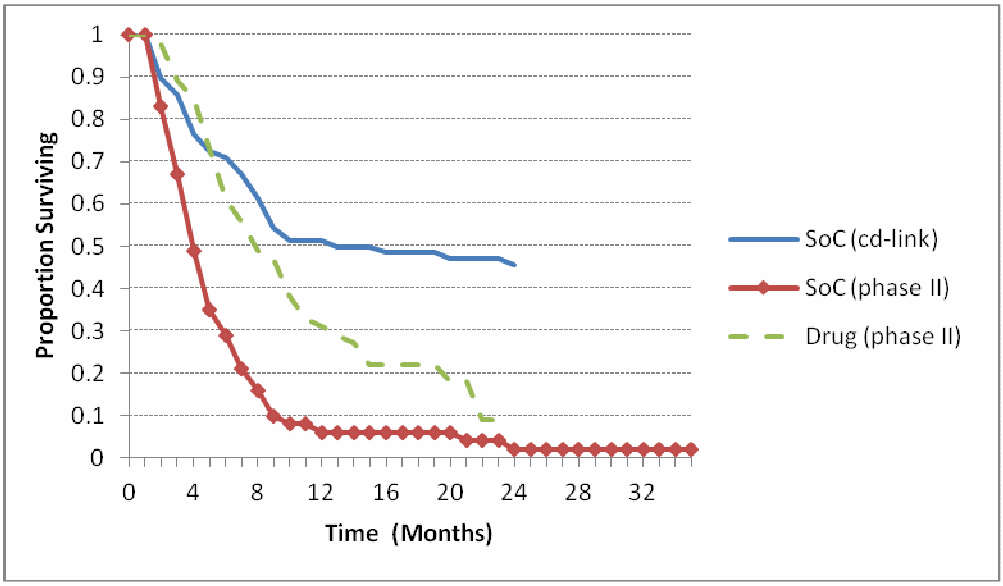



**Figure 4-10**: Illustrative PFS Curves from Phase II trial and cd-link data

### 4.3.3 Transition Probabilities for Markov Models

We fitted parametric Weibull distribution to the patient level data to predict the survival beyond the 24 months follow-up period for patients who developed progression and who were cancer free. To be consistent, we also estimated the survival distribution of patients on standard of care treatment arm (phase II clinical trial) by fitted Weibull distribution. The scale (λ) and shape (k) parameters and parametric survival curve are summarized in Figure 4-11, Figure 4-12 and Figure 4-13.

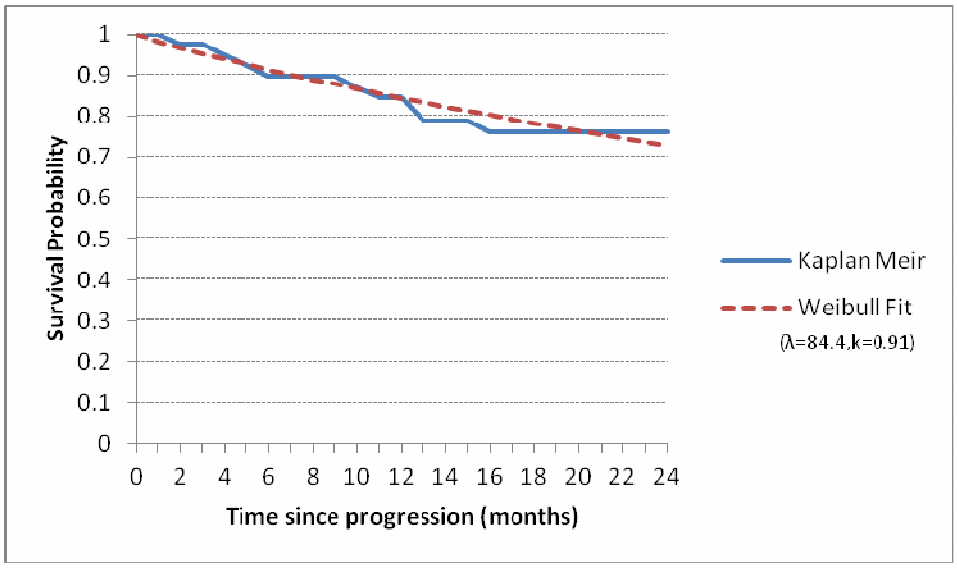



**Figure 4-11:** Comparison of Kaplan-Meir and parametric Weibull survival curve (patients developing progression)

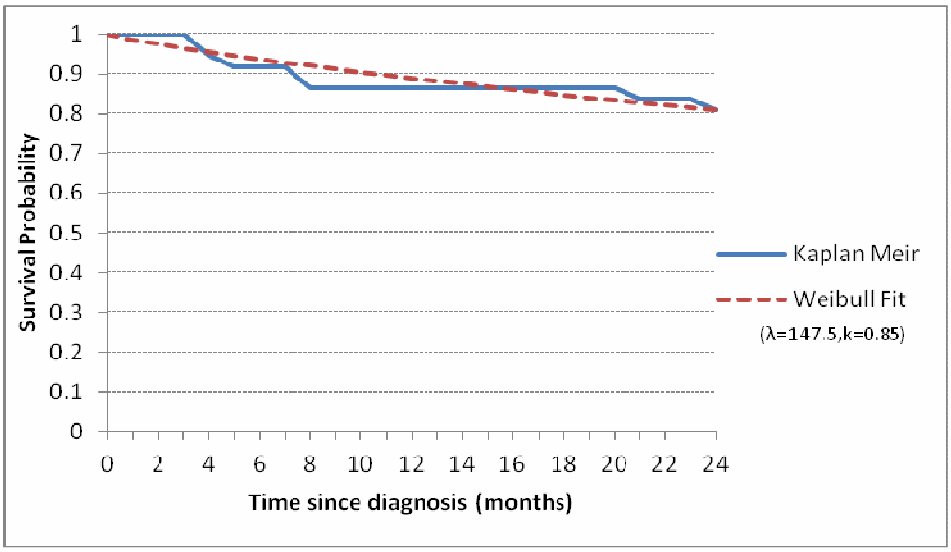



**Figure 4-12:** Comparison of Kaplan-Meir and parametric Weibull survival curve (cancer free patients)

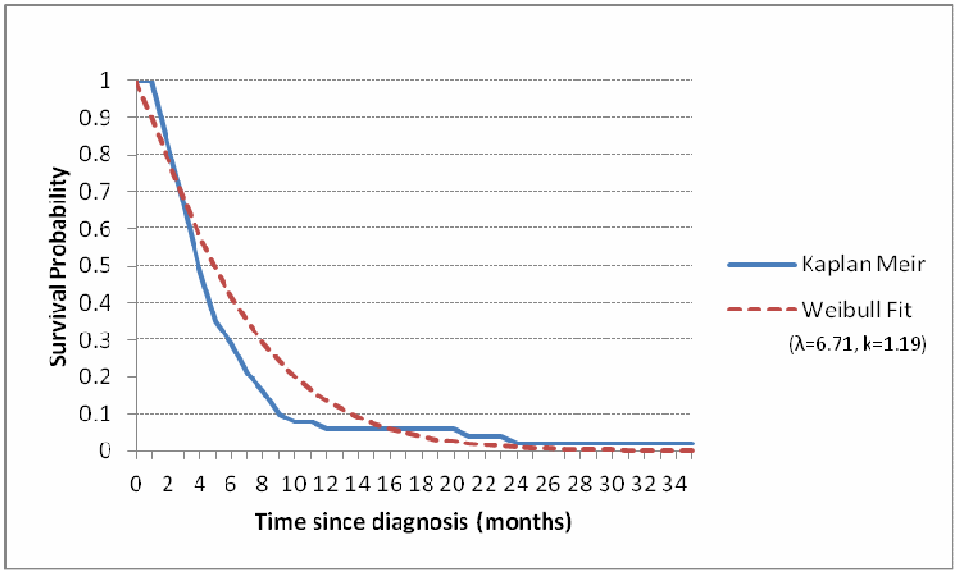



**Figure 4-13:** Comparison of Kaplan-Meir and parametric Weibull survival curve (patients on standard of care treatment in phase II trial)

In the base case scenario, we derived transition probabilities from "FFTF" to "Progression" state in model M2 from parametric Weibull survival curve of patients on standard of care treatment arm in phase II trial (Figure 4-13). We adjusted these transition probabilities for hazard ratio (hr=0.41) reported in clinical trial to estimate transitions from "Improve or Stable" to "Progression" state in model M1. The transition probabilities from "Progression" to "Death" were derived from fitted Weibull survival curve of patients who had progression (Figure 4-11). Similarly, we estimated the transition probabilities from "FFTF" to "Death" in model M2 from fitted Weibull survival curve of cancer-free patients. Since we run the model for lifetime horizon, the transition probabilities beyond the 24 months period were estimated from the predicted survival estimates. We assumed that patients who develop serious adverse reaction stop brentuximab treatment and switch to standard of care treatment and hence follow the same transition probability matrix as for model M2. According to phase II trial of brentuximab none of the patients died from drug related causes. Therefore, we used Ontario gender specific life tables to derive the transition probabilities from "Improve or Stable" to "Death" state in model M1 by accounting for gender distribution in the trial.

## 4.4 Costs

**Standard of Care:** Using Canadian Classification of Interventions (CCI) and OHIP fee codes we sub-classified the hospitalization and physician costs as *relevant* and *other* costs. Relevant costs are the direct costs associated with cancer treatment such as chemotherapy, radiotherapy and transplantation and other costs include costs related to

follow up tests, comorbidities, treatment of toxicities and etc. All costs are adjusted for inflation using health and personal care consumer price index (CPI) reported by Statistics Canada and expressed in 2012 CAD. Monthly average costs per subject for freedom from treatment failure and progression states are summarized in Table 4-3 and Table 4-4. To avoid the impact of monthly variations in costs on the ICER we used smoothing technique, averaging the costs in the first 5 months and in the following months (Table 4-5).

**Hospitalization Cost:** Resource Intensity Weight (RIW) was used to estimate the cost of hospital services. The costs were estimated using RIW from CIHI-DAD database and cost per weighted case (cpwc). After removing four hospital abstracts with missing riw values, a total of 213 hospital abstracts were associated with 58 patients in the cohort. We obtained cost per weighted case (cpwc) data for the fiscal years 2005-2010 from Hospital Financial Performance Indicators annual report released by CIHI.

**Physicians Cost**: Physician labor cost was estimated by medical claims from OHIP database. A total of 25125 physician claims corresponding to all patients were used to estimate the cost.

**Drug Cost:** In Ontario, people with age above 65, long term care residents, those receiving home care and people with limited income are covered by Ontario Drug Benefit (ODB) plan. The patients on standard of care had 3795 drug benefit claims that correspond to 39 patients in the cohort. We assumed that patients who are under 65 years

old and not covered by ODB will experience the average drug costs of patients who are under 65 and covered by ODB.

**Brentuximab:** According to the US FDA brentuximab prescribing information patients receive treatment for maximum of 16 cycles, until patient develops serious adverse reaction or progression. The manufacturer revealed the cost of the brentuximab to be $13,500 US per dose or $4500 US per vial [129]. In the base case scenario we assumed that cost of brentuximab in Canada will be the same as in the US. Knowing that patients in the trial received 10 doses on average, we estimated average monthly cost of the drug to be US $ 18,000. Cost of the administration is estimated from internal costing by London Regional Cancer Program (LRCP) pharmacy. Infusion time cost for a 30 minute is $160 CAD and pharmacy preparation time cost is $35 CAD at LRCP. We assumed that serious adverse reaction, i.e., peripheral sensory neuropathy results in one time consultation visit, but not in hospitalization and these patients stop brentuximab, switch to standard of care as per phase II trial outcomes.

**Table 4-3:** Average Monthly Cost ($, CAD) per Patient in FFTF State (77 patients)

| | Hospitalization Cost | | Physician Cost | | Drug Cost |
|---|---|---|---|---|---|
| Months | Relevant | Other | Relevant | Other | Total |
| 1 | 1511.37 | 257.028 | 659.241 | 390.239 | 188.258 |
| 2 | 43.748 | 968.983 | 47.0449 | 944.373 | 115.311 |
| 3 | 522.46 | 616.601 | 61.7026 | 437.435 | 96.213 |
| 4 | 502.357 | 654.01 | 19.6078 | 289.18 | 92.3373 |
| 5 | 0 | 3593.15 | 10.6438 | 1264.66 | 87.413 |
| 6 | 0 | 239.459 | 295.71 | 364.495 | 105.401 |
| 7 | 199.042 | 254.62 | 32.7648 | 241.362 | 104.029 |
| 8 | 0 | 339.295 | 1.90753 | 223.921 | 135.367 |
| 9 | 0 | 0 | 2.35742 | 113.578 | 98.6971 |
| 10 | 0 | 0 | 0 | 171.731 | 100.89 |
| 11 | 0 | 0 | 0 | 143.102 | 101.085 |
| 12 | 0 | 346.375 | 1.52882 | 1327.38 | 101.158 |
| 13 | 0 | 0 | 0 | 108.224 | 105.543 |
| 14 | 0 | 1078.28 | 0 | 107.07 | 104.787 |
| 15 | 0 | 0 | 0 | 191.569 | 104.873 |
| 16 | 0 | 40.6103 | 0 | 186.064 | 106.825 |
| 17 | 0 | 326.693 | 0 | 229.392 | 106.825 |
| 18 | 0 | 0 | 0 | 95.9656 | 106.825 |
| 19 | 0 | 0 | 0.39686 | 60.3808 | 106.825 |
| 20 | 0 | 0 | 0 | 118.852 | 110.074 |
| 21 | 0 | 0 | 0 | 110.357 | 141.015 |
| 22 | 0 | 0 | 0 | 120.676 | 161.988 |
| 23 | 0 | 0 | 1.71992 | 84.418 | 113.501 |
| 24 | 0 | 0 | 0 | 54.9987 | 124.298 |
| **Total** | 2778.977 | 8715.104 | 1134.6255 | 7379.423 | 2719.538 |

**Table 4-4:** Average Monthly Cost ($, CAD) per Patient in Progression State (40 patients)

| | Hospitalization Cost | | Physician Cost | | Drug Cost |
|---|---|---|---|---|---|
| Months | Relevant | Other | Relevant | Other | Total |
| 1 | 0 | 0 | 4.12782 | 35.0767 | 16.0098 |
| 2 | 0 | 0 | 23.4119 | 68.442 | 96.9649 |
| 3 | 0 | 414.078 | 102.857 | 176.476 | 191.933 |
| 4 | 0 | 209.623 | 25.803 | 336.121 | 159.272 |
| 5 | 0 | 153.718 | 23.6171 | 186.617 | 116.953 |
| 6 | 0 | 710.931 | 9.81618 | 439.341 | 202.486 |
| 7 | 0 | 842.186 | 18.8089 | 327.145 | 67.6588 |
| 8 | 0 | 327.18 | 31.6529 | 621.375 | 460.516 |
| 9 | 0 | 1023.24 | 19.8801 | 311.719 | 251.844 |
| 10 | 0 | 314.671 | 38.4886 | 434.788 | 161.606 |
| 11 | 1292.94 | 1536.16 | 54.1703 | 364.885 | 313.723 |
| 12 | 2801.52 | 0 | 22.6221 | 383.375 | 237.51 |
| 13 | 1022.65 | 0 | 42.0554 | 288.049 | 326.383 |
| 14 | 2635.51 | 241.269 | 85.7865 | 523.51 | 89.9432 |
| 15 | 0 | 999.994 | 23.6528 | 546.882 | 105.047 |
| 16 | 0 | 2012.37 | 15.6217 | 1052.35 | 156.791 |
| 17 | 1302.69 | 0 | 5.04332 | 2200.76 | 122.211 |
| 18 | 0 | 3026.95 | 13.7531 | 408.841 | 181.306 |
| 19 | 0 | 574.306 | 22.4919 | 1825.37 | 193.253 |
| 20 | 0 | 41.4382 | 29.7032 | 414.609 | 224.312 |
| 21 | 0 | 491.273 | 24.0948 | 890.971 | 112.506 |
| 22 | 2443.61 | 710.592 | 209.006 | 1285.14 | 243.247 |
| 23 | 0 | 189.649 | 97.1401 | 774.947 | 529.766 |
| 24 | 0 | 0 | 97.3599 | 1022.2 | 447.904 |
| **Total** | 11498.92 | 13819.628 | 1040.9646 | 14918.99 | 5009.146 |

## 4.5 Health Utilities

We conducted comprehensive review of the literature to determine appropriate quality of life estimates for health states in the Markov models. Available utility data in the published literature is very limited. In the base case scenario we assumed that brentuximab does not improve quality of life and is same for “Improve or Stable” and “FFTF” state. The estimated quality of life for persistent disease is 0.8 after high dose chemotherapy plus autologous stem cell transplantation (SCT) [127]. Therefore, in the base case, we assumed that utility of “Improve or Stable” and “FFTF” is equal to 0.8. We assumed 10% decrease in quality of life when patient relapses after third line treatment [127]. Finally, we assumed that patient developing peripheral sensory neuropathy has quality of life estimate equal to that of patients developing same adverse reaction with metastatic breast cancer [130]. The quality of life of these patients becomes better and increases to 0.8 after resolution of adverse the event. We assumed that resolution time of the adverse reaction is 13.2 weeks for everyone. Baseline model utility estimates are summarized in Table 4-5.

## 4.6 Discounting

We discounted all future costs and benefits at the rate of 5% as per Canadian guidelines[114]. We varied this between 0% and 5% in sensitivity analysis.

## 4.7 Sensitivity Analysis

We conducted one-way deterministic sensitivity analyses with +/- 20% of the baseline value on all of the variables. We also conducted probabilistic sensitivity analyses on key

variables to handle uncertainty around the model parameters. The probabilistic sensitivity analyses were carried out with 1000 Monte Carlo simulations. We used lognormal distribution for cost and beta distribution for probability and utility values respectively. The ranges of the variables in the sensitivity analyses and parameters used in distributions are summarized in Table 4-5. We also conducted value of the information analysis to quantify the cost of uncertainty around baseline ICER.

**Table 4-5:** Model Parameters and Sources

| Variables | Base Case Value | Duration | Ranges tested in Sensitivity | Probability Distribution (Parameter) | Reference |
|---|---|---|---|---|---|
| **Cost ($,CAD)** | | | | Lognormal (μ,σ) | |
| brentuximab | | | | | |
| Cost per dose | $13,500 | Treatment Course | $0-$13,500 | 9.74,0.34 | [129] |
| Infusion Time Cost per month¶ | $213 | Treatment Course | +/-20 % | 5.35,0.17 | LRCP |
| Pharmacy Preparation per month¶ | $47 | Treatment Course | +/-20 % | 3.76,0.42 | LRCP |
| Adverse Reaction¥ | $149 | One Time | +/-20 % | 4.99,0.11 | OHIP |
| **Pre-Progression† (Standard of Care)** | | | | | |
| **Hospitalization Cost** | | | | | CIHI-DAD |
| *During First 5 months* | $1,734 | First 5 months | +/-20 % | 7.46,0.07 | |
| *During following months* | $149 | Following months | +/-20 % | 4.99,0.12 | |
| **Physician Cost** | | | | | OHIP |
| *During First 5 months* | $825 | First 5 months | +/-20 % | 6.71,0.07 | |
| *During following months* | $231 | Following months | +/-20 % | 5.43,0.09 | |
| **Drug Cost** | | | | | ODB |
| *During First 5 months* | $116 | First 5 months | +/-20 % | 4.74,0.13 | |
| *During following months* | $113 | Following months | +/-20 % | 4.72,0.13 | |
| **Post-Progression† (Standard of** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Care)** | | | | | |
| **Hospitalization Cost** | | | | | CIHI-DAD |
| *During First 5 months* | $155 | First 5 months | +/-20 % | 5.02,0.2 | |
| *During following months* | $1,292 | Following months | +/-20 % | 7.16,0.05 | |
| **Physician Cost** | | | | | OHIP |
| *During First 5 months* | $197 | First 5 months | +/-20 % | 5.27,0.14 | |
| *During following months* | $788 | Following months | +/-20 % | 6.66,0.14 | |
| **Drug Cost** | | | | | ODB |
| *During First 5 months* | $116 | First 5 months | +/-20 % | 4.73, 0.23 | |
| *During following months* | $233 | Following months | +/-20 % | 5.44,0.16 | |
| **Health State Utilities** | | | | Beta (r, n)§ | |
| Improve or Stable | 0.8 | Lifetime | 0.6-1 | 80,100 | [127] |
| FFTF | 0.8 | Lifetime | 0.6-1 | 80,100 | [127] |
| Progression | -10% | Lifetime | -5 %-30 % | 72,100 | [127] |
| Adverse Reaction (AE) ‡ | | | | | [130] |
| *During First 13 Weeks* | 0.62 | 13 weeks | +/-20 % | 62,100 | |
| *During following weeks* | 0.8 | Following weeks | +/-20 % | 80,100 | |
| Death | 0 | | | | |
| **Probabilities** | | | | Beta (r, n)§ | |
| Probability of AE | 0.0588 | Lifetime | 0.01-0.2 | 588 , 10000 | [14] |
| FFTF to Death | Varying by month | Lifetime | +/-20 % | Varying by month | OHIP |
| Progression to Death | Varying by month | Lifetime | +/-20 % | Varying by month | OHIP |
| FFTF to Progression | Varying by month | Lifetime | +/-20 % | Varying by month | [14] |

| | | | | | |
|---|---|---|---|---|---|
| Improve or Stable to Progression | Varying by month | Lifetime | +/-20 % | Varying by month | [14] |
| **Discount Rate** | 5% | | 0%-5% | | [114] |

¶ Pharmacist's labor cost is $35 per cycle, Infusion time cost is $160 per cycle

† Cost figures include both relevant and other costs for hospitalization and physician costs category

‡ Peripheral sensory neuropathy is a modeled adverse reaction that stopped treatment continuation

¥ Cost of consultation visit

§ Parameters of Beta distribution are integers.

# Chapter 5

## 5 Results

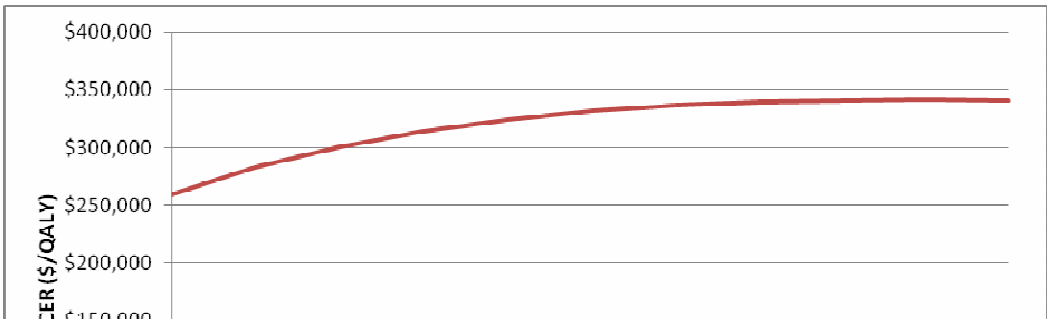
### 5.1 Base Case Scenario

In the base case scenario brentuximab treatment led to an increase of 0.352 QALYs per person and $108,500 per person, which resulted in incremental cost effectiveness ratio (ICER) of $308,532 per QALYs gained.

### 5.2 Sensitivity Analysis

#### 5.2.1 Clinical Trial Parameters

When the chance of developing peripheral sensory neuropathy dropped to 1% the ICER decreased to $259,500 per QALYs gained (Figure 5-1), however ICER was quite robust when probability of adverse reaction fall in the range of 0.105 and 0.2. The ICER decreased by 2.1% when transition rates from transition rate from “FFTF” to “progression” state is increased by 20%. In two way sensitivity analyses we varied the probability of serious adverse event over the range of 0.01 and 0.2 and transition rate from” improve or stable” to progression by +/-20%. The ICER exceeded the 100,000 per QALYs willingness to pay threshold. One way sensitivity analysis on hazard ratio showed that ICER falls dramatically to $227,760 per QALY when hazard ratio is 0.1 and increases to $384,648 per QALY when brentuximab doesn’t yield additional survival benefit to standard of care.


$400,000
$350,000
$300,000
$250,000
$200,000
ER ($/QALY)

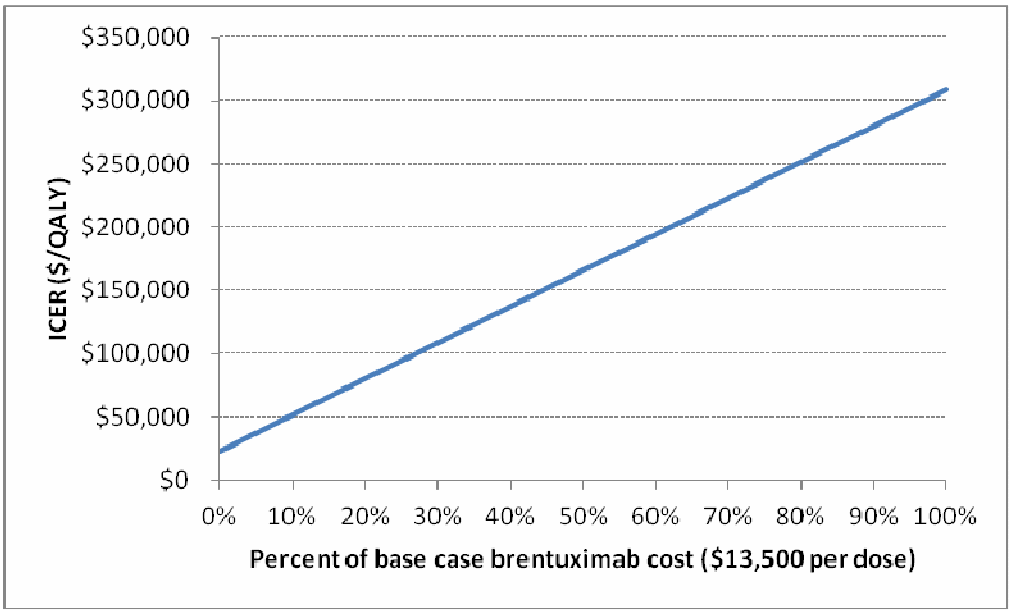



**Figure 5-2:** Threshold analysis on the cost per dose of brentuximab

The model was sensitive to most of the utility values in univariate sensitivity analyses. ICER dramatically dropped to $231,840 per QALY gained when patients on brentuximab treatment had almost perfect health. Conversely, when patients on standard of care with no evidence of progression had perfect quality of life, the baseline ICER increased to $412,404 per QALY and dropped down to $246,444 per QALY gained when patient had utility of 0.6. The change in utility of progression state did not significantly impact the ICER outcome. Twenty percent increase in utility of adverse reaction led to an ICER of $279,852 per QALYs. The model was sensitive when we varied the discounting rate of costs and utilities between 0% and 5%. The ICER dropped to $231,948 per QALY when there was no discounting. Model outcomes were quite robust to changes in other cost parameters such as cost of brentuximab administration, cost at the pre-progression

and post-progression period. In two way sensitivity analyses, ICER fell below $100,000 per QALYs when probability of adverse reaction and brentuximab cost per dose were decreased by 50% and 65% respectively. When drug cost reduces by 60% and quality of life of patients on brentuximab treatment converges to perfect health then ICER fell below the $100,000 per QALYs gained.

### 5.2.3 Probabilistic Sensitivity Analysis

In probabilistic sensitivity analyses we simultaneously sampled from distributions defined for all key parameters (costs, utilities, probabilities) shown in Table 4-5. The scatter plot shows incremental cost versus incremental effectiveness of comparing brentuximab to standard of care (Figure 5-3). Sensitivity analyses showed that 100% of samples resulted in more cost and more effectiveness, falling in quadrant I and were above the 100,000 per QALYs gained willingness to pay threshold line. Approximately 11% of the samples were below the 200,000 per QALYs willingness to pay threshold line.

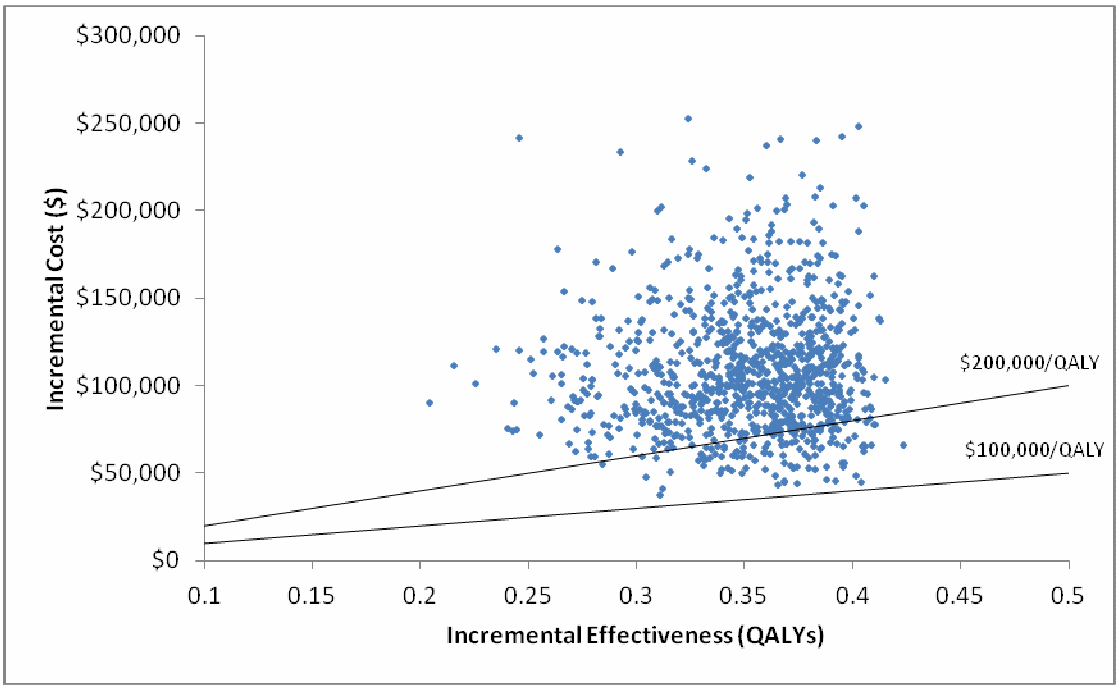



**Figure 5-3:** Incremental Cost-Effectiveness Scatter Plot

The simulations showed that brentuximab was not a preferred treatment option using willingness to pat threshold (WTP) of $100,000 per QALY gained (Figure 5-4). It was cost-effective in approximately 11% of simulations at willingness to pay of appoximately $200,000 per QALY. Finally brentximab treatment becomes equally preferred at a willingess to pay of $290,000 per QALY gained (Figure 5-4).

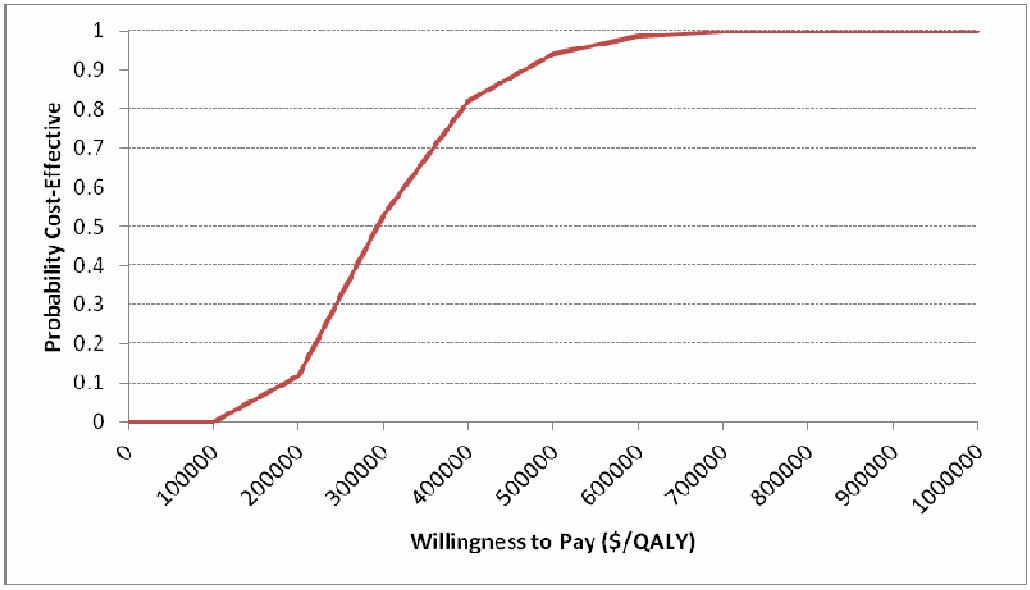



**Figure 5-4:** Cost Effectiveness Acceptability Curve

### 5.2.4 Value of Information

Model input parameters contain certain degree of uncertainity. The value of information analysis is an analytical framework that determines the monetary value a decision maker is willing to pay for conducting additional research to reduce uncertainity and hence, support the decision problem [131]. It is based on statistical theory, is the difference in expcetation of value under the perfect informaiton and value under the current information. In other words, it is the expected cost of uncertainity.

Calculation of EVPI is as follows: A probability distribution is defined for each model parameter. Using Monte Carlo simulation the model is run many times (e.g.,1000 times) which will draw a value from the distribution at each iteration. The expected payoff (i.e. net monetary benefit) is calculated across all iterations and the maximum is

selected for the baseline decision. For each simulation run, the maximum net monetary benefit is calculated for the optimal decision. The difference between the expected optimal payoff and the baseline payoff is the expected value of the perfect information. We conducted value of information analysis and found that there was no value to eliminate probabilistic uncertainity surrounding inputs at the willingness to pay threshold of $100,000 per QALY. In other words, it is not worthwhile to undertake additional effort to reduce the uncertainity (i.e., more clinical trials) at a WTP threshold of $100,000 per QALY gained.

# Chapter 6

## 6 Discussion and Limitations

### 6.1 Summary

We developed a decision analytic model to investigate cost effectiveness of brentuximab versus standard of care for the treatment of HL patients after autologous stem cell failure from Canadian healthcare payer perspective. In the base case scenario, brentuximab resulted in incremental cost of $108,500 and incremental effect of 0.352 QALYs with the ICER of $308,532 per QALYs gained. The ICER estimate is much higher than 100,000 per QALYs threshold that is graded as having "weak evidence for adoption and appropriate utilization" according to published literature in Canada [119].

In deterministic sensitivity analysis, the baseline ICER was sensitive to cost of the brentuximab, probability of adverse reaction and health utilities. Probabilistic sensitivity analysis indicated that brentuximab was not cost effective using willingness to pay of 100,000 per QALYs gained. Our analysis suggested that minimal survival benefit of brentuximab based on current clinical evidence makes it unattractive to healthcare payer in Canada. Furthermore, expected value of perfect information (EVPI) analysis showed that a healthcare payer would not be willing to pay for further research evidence to inform adoption of brentuximab at the current accepted thresholds.

The Canadian cost of the drug is not available yet. Therefore, our study plays an important role and can aid decision maker with respect to what unit cost per dose

represents good value for money. According to Canadian Patented Prices Review Board (PMPRB), drug costs in Canada must be at or below a median cost of the drug in comparator countries [132]. Using a US costing for brentuximab, we conducted preliminary pricing scenarios. We found that price reduction of at least 72% would be needed for ICER to be less than $100,000 per QALY.

## 6.2 Discussion

The survival benefit is a major driver of the ICER. The primary endpoint in the brentuximab phase II trial was objective response rate (i.e., tumor shrinkage) that is considered as a surrogate endpoint for the survival outcome. The PFS was the secondary endpoint in the trial, resulting in modest but statistically superior survival benefit in favor of brentuximab. The trial showed median PFS increment of 3.7 months.

The drug has entered the US pharmaceutical market upon US FDA approval. In Europe, the marketing authorization application (MAA) has been submitted to European Medicines Agency. The drug *brentuximab* has not been approved yet by Health Canada for use in Canada. However, like in US, in Canada it is more likely to be granted a conditional market approval, as it showed superior toxicity and effectiveness results and intends to treat the rare form of cancer where no adequate therapy exists.

Other studies have found similarly high cost-effectiveness ratios for targeted therapies. For example, economic evaluation of adding *bevacizumab* to paclitaxel and carboplatin for the treatment of ovarian cancer showed that ICER was $479,712 per life years gained

[133]. In another study, addition of *cetuximab* to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer resulted in $386,000 per QALY gained [134]. In general, cancer technologies have resulted in higher ICER values, as high as over million dollars per QALY (Table 6-1).

**Table 6-1: League Table for Cancer Treatments**

| Intervention | Country | ICER | Source |
|---|---|---|---|
| Endoscopy for Upper GI Screening in general population | US | $115,664 per QALY | [135] |
| Adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer | Canada | $386,000 per QALY | [134] |
| Denosumab versus zoledronic Acid in the management of skeletal metastases secondary to breast cancer | US | $697,499 per QALY | [136] |
| Trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastro esophageal junction cancer | China | $251,667 per QALY | [137] |
| Maintenance pemetrexed in patients with advanced nonsquamous-cell lung cancer | Switzerland | €106,202 per QALY | [138] |
| Bevacizumab in combination with paclitaxel in the first-line treatment of patients with metastatic breast cancer | US | $745,000 per QALY | [139] |
| Degarelix for advanced hormone-dependent prostate cancer | UK | £59,000 per QALY | [140] |
| Paclitaxel plus carboplatin and bevacizumab | US | $479,712 per PF-LYS | [133] |
| Paclitaxel plus carboplatin plus bevacizumab and plus bevacizumab maintenance | US | $401,088 per PF-LYS | [133] |
| KRAS-testing strategy compared with the no-cetuximab strategy for colorectal cancer | Japan | $160,000 per QALY | [141] |
| KRAS-testing strategy compared with the no-KRAS-testing strategy for colorectal cancer | Japan | $230,000 per QALY | [141] |
| Human papillomavirus DNA testing followed by Pap smear for cervical cancer screening | Taiwan | $1,247,□000 per QALY | [142] |
| Annual screening for renal cancer in recipients of kidney transplants | Australia | $320,988 per LYS | [143] |
| Addition of cetuximab to first-line chemotherapy in patients with advanced non-small-cell lung cancer | Switzerland | €376,□205 per QALY | [144] |
| Sunitinib for first-line treatment of metastatic renal cell carcinoma | Canada | $144K per QALY | [145] |
| Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck | UK | £121367 per QALY | [146] |
| Lapatinib in HER-2-positive advanced breast cancer | US | $166,113 per QALY | [147] |
| Initial HercepTest with fluorescence in situ hybridization (FISH) confirmation for metastatic breast cancer | US | $125,000 per QALY | [148] |
| Aspirin chemoprevention plus colonoscopy screening concomitantly for colorectal cancer | US | $227,607 per LYS | [149] |

In Canada, a cost effectiveness analysis is required for the drug reimbursement decisions. The oncology drugs are reviewed by a different body than non-oncology drugs. In 2007, an interim, cross-provincial Joint Oncology Drug Review (JODR) process was established for reviewing oncology drugs. As a part of JODR process, Committee to Evaluate Drugs (CED) and Cancer Care Ontario (CCO) assessed the cancer drugs and provided recommendation to provincial public funding agencies (except Quebec). Since 2010, a pan-Canadian Oncology Drug Review (pCODR) evaluates manufacturer's drug submissions for drug formulary listing and makes drug funding decisions to guide provincial healthcare payers.

There is no published implicit threshold in Canada however, in general anti-cancer drugs are approved at higher acceptable thresholds than other medications [145, 150]. The Table 6-2 summarizes funding recommendations and corresponding ICER values for the some of the recently evaluated oncology drugs which can be recommended for "list", "not list" or "listing with condition" on the formulary. Based upon past experience, the drugs with more overall clinical benefit and effective over standard treatment options might be approved at the higher ICER, conditioned on the cost-effectiveness to be improved to the WTP level of the jurisdictions.

**Table 6-2: ICER Results versus Reimbursement Recommendation**

| Drug | Recommendation | Indication | ICER | Source |
|---|---|---|---|---|
| Sunitinib (Sutent) | List with condition | First-line metastatic renal cell carcinoma | $144K/QALY | [145] |
| Sunitinib (Sutent) | Do not list | Second-line metastatic renal cell carcinoma | $56K/QALY | [145] |
| Sunitinib (Sutent) | List with condition | Gastrointestinal stromal tumor | $80K/QALY | [145] |
| Sorafenib (Nexavar) | Do not list | Second-line metastatic renal cell carcinoma | $36/LYG | [145] |
| Pazopanib hydrochloride (Votrient) | List with condition | advanced or metastatic clear cell renal carcinoma | $57,309/QALY | [151] |
| Ipilimumab (Yervoy) | List with condition | Treatment of advanced melanoma (unresectable Stage III and IV melanoma) in patients who have received prior systemic therapy | $269,299/QALY | [151] |
| Sunitinib malate (Sutent) | List with condition | Patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours, whose disease is progressive. | $204,559-$268,055/QALY | [151] |
| Vemurafenib (Zelboraf) | List with condition | Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma | $221,668-$275,707/QALY | [151] |

Because fast track approval is based on the surrogate clinical outcome, regulatory bodies require confirmatory post-marketing randomized studies to be conducted in order to confirm efficacy and safety for drugs being approved through an accelerated approval process. However, post marketing studies may take many years especially for orphan drugs, based on past experience. Waiting for the phase III survival data to conduct cost-effectiveness may not be practical from payer's perspective. Health care payers have to make a quick decision regarding funding upon market approval. Hence, we think the cost-effectiveness of the drug must be considered at earlier stages and the results must be

updated as new data become available. A confirmatory randomized control phase III trial testing survival benefit of the brentuximab is already underway.

Use of administrative databases might have missing data and misclassification challenges to some extent. The validity of the administrative databases of Ontario has been evaluated by several studies. The validity of OHIP database was assessed to ascertain the influenza vaccination status and patients with hypertension [152, 153]. OHIP had a moderate agreement (i.e., kappa statistics), higher specificity and fair sensitivity. The validity of OCR has been tested with respect to cause of death of breast cancer patients [154]. OCR had high level agreement, higher sensitivity and specificity. Similarly, the validation study of Institute for Clinical Evaluative Sciences (ICES) showed higher agreement in diagnostics, demographics and interventions data in CIHI-DAD database [155].

## 6.3 "Early Look" Model

The use of economic evaluation at early stages has been suggested by several studies [156, 157]. Despite some challenges, early economic assessment has gained popularity in the past few years [158]. It has several limitations to overcome; however, these models are worthwhile, yielding interesting results to pharmaceutical industry, the hematology community, health care payers and to society as a whole.

Early look models have several advantages. First, early economic assessment determines the potentially successful products which inform strategic research and

"go/no-go" development decisions [159]. Using preliminary data from phase II trial to build decision analytical model helps to predict the market potential and hence, economic viability of the drug before phase III trial, which is the most resource intensive stage. Second, early economic evaluation may change study design and protocols of the further clinical trials [159]. For example, early look economic models can determine the crucial sensitive variables which in turn can aid the data collection decisions. Our model showed that ICER was sensitive to quality of life of patients receiving the brentuximab treatment. Thus, quality of life assessment in phase III brentuximab trial would be very crucial. Finally, "early look" models help to conduct preliminary cost effectiveness at different pricing scenarios which identifies the optimal price at which the drug is cost-effective or below the willingness to pay (WTP) of the payer.

There are several challenges of using "early look" economic models. The available data are scarce and has considerable uncertainty due to lower sample size. Moreover, the clinical evidence data may be based on open label, single arm and non-randomized trial that may not produce definitive results. Because early data are very limited, data from literature or expert opinion are used to parameterize the model that might affect economic outcomes. Finally, using surrogate endpoints and short follow up times from early clinical trials have inherent limitations [160].

## 6.4 Limitations

We recognize some limitations of this study. First, we acknowledge that phase II results should be interpreted carefully. The PFS outcomes are based on intra-patient sub-

group analysis on 57 patients which may not reflect the treatment effect in a broad population in randomized setting. However, uncertainty around the progression rates was accounted for in probabilistic sensitivity analysis. Our definition of progression endpoint is a proxy measure and it is based on treatment switch which may not necessarily reflect the actual relapse. In practice, the progression is verified by diagnostic procedures such as CT and PET scans and biopsy before the actual treatment start. Second, our definition of progression does not capture the change in chemotherapy regimen since the same billing code may refer to more than one chemotherapy regimen. Third, OHIP service codes for chemotherapy do not specify the chemotherapy type, name or dose and hence, the cost of the chemotherapy dose is not included in analysis. Finally, there may be uncertainty around the baseline utility values which were mitigated in sensitivity analysis.

## 6.5 Strengths

To our knowledge, our analysis is the first economic analyses of brentuximab at early stage and is the first comprehensive decision analytic model developed to simulate the course of HL disease and treatment alternatives. The costs and transition probabilities of model were estimated using Canadian administrative databases. The use of population based registry and administrative databases to conduct cost analysis has gained popularity in recent years. There have been several studies from Canada using OHIP physician billing codes to define a stage of the cancer [161, 162]. However, this analysis is the first attempt to define progression using treatment records of OHIP database. In conclusion, our study may play an important role and will inform drug reimbursement decisions by

provincial funding agencies and give an idea on potential budget impact before it gets regulatory and reimbursement approval.

# Chapter 7

## 7 Conclusion

We conducted cost-effectiveness analysis of brentuximab using data from phase II clinical trial and Canadian administrative databases. In the base case scenario ICER was $308,532 per QALYs gained. The baseline ICER was significantly higher than $100,000 per QALY threshold and does not represent good value for money based upon current accepted willingness to pay thresholds. The baseline ICER was sensitive to cost of the brentuximab, probability of adverse reaction, health related quality of life estimates. EVPI analyses showed that decision maker is not willing to pay to eliminate all uncertainty at the willingness to pay of $100,000 per QALY gained. This early stage economic evaluation will guide the decision makers in the light of available information. Model inputs should be refined and updated as new data become available.

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