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Economic evaluation of brentuximab vedotin for persistent Hodgkin lymphoma

V. Babashov MSc,* M.A. Begen PhD,†‡ J. Mangel MD,§ and G.S. Zaric PhD†‡

ABSTRACT

Background We conducted a cost-effectiveness analysis of brentuximab vedotin for the treatment of relapsed and refractory Hodgkin lymphoma (HL) in the post–autologous stem-cell transplantation (ASCT) failure period, from the perspective of the Canadian health care payer.

Methods We developed a decision-analytic model to simulate lifetime costs and benefits of brentuximab vedotin compared with best supportive care for the treatment of patients with HL after failure of ASCT. Administrative data from Ontario were used to set the model parameters.

Results In the base case, treatment with brentuximab vedotin resulted in incremental quality-adjusted life-years (QALYS) of 0.544 and an incremental cost of $89,366 per patient, corresponding to an incremental cost-effectiveness ratio (ICER) of $164,248 per QALY gained. The ICER was sensitive to the cost of brentuximab vedotin, the hazard ratio used to assess the efficacy of brentuximab vedotin treatment, and health state utilities.

Conclusions In light of the available information, brentuximab vedotin has an ICER exceeding $100,000 per QALY gained, which is a level often classified as having "weak evidence for adoption and appropriate utilization" in Canada. However, it is worth noting that provincial cancer agencies take into account not only the costs and associated ICER, but also other factors such as a lack of alternative treatment options and the clinical benefits of expensive cancer drugs. Pricing arrangements should be negotiated, and risk-sharing agreements or patient access schemes should be explored.

Key Words Hodgkin lymphoma, brentuximab vedotin, cost-effectiveness analyses, Markov models

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INTRODUCTION

Hodgkin lymphoma (HL) is an uncommon type of cancer with an incidence of approximately 3 per 100,000 population in Canada[1]. In 2012, 940 new cases of HL were diagnosed in Canada[1]. Conventional treatment options for HL include chemotherapy, radiotherapy, and hematopoietic stem-cell transplantation. Although survival outcomes are favourable for most patients, a proportion do not experience a cure with standard treatment regimens[2-4].

The standard of care for young healthy patients who relapse after front-line therapy is salvage chemotherapy, followed by high-dose therapy and autologous stem-cell transplantation (ASCT). Approximately 50% of patients relapse after ASCT[5], and prognosis tends to be poor for those who relapse, with a short median progression-free survival[6,7]. Available treatment options for the latter group are limited, and of the available options, many are subject to the faults of being tested in nonrandomized settings. Furthermore, toxicity- and treatment-related mortality rates are high, making those treatments unattractive to hematologists and patients. Historically, third-line treatment options in patients who relapse after ASCT include allogeneic stem-cell transplantation, a second ASCT, radiation therapy, and single-agent or combination chemotherapy, all of which are ultimately palliative. The reported benefits of those therapies vary, with median survival ranging from 6 months to 30 months[8–11].

Brentuximab vedotin (Adcetris: Seattle Genetics, Bothell, WA, U.S.A.) is a CD30-directed antibody–drug conjugate that selectively targets and kills cancer cells expressing the CD30 antigen, such as classical HL and systemic anaplastic large-cell lymphoma. Early phase I and II clinical trials demonstrated favourable response rates

Correspondence to: Mehmet A. Begen, Ivey Business School, Western University, 1255 Western Road, London, Ontario N6G 0N1.
E-mail: mbegen@ivey.uwo.ca **DOI:** https://doi.org/10.3747/co.24.3369

and toxic effects, and promising progression-free survival rates[12,13]. The phase II trial showed that 75% of patients achieved complete or partial remission, with a median progression-free survival of 5.6 months[12]. According to recent data from the long-term follow-up of the phase II study, median overall survival was 40.5 months[14]. Reported treatment-related adverse events included peripheral sensory neuropathy, fatigue, nausea, neutropenia, diarrhea, and pyrexia. Approximately 20% of patients discontinued treatment because of a treatment-related adverse event. Peripheral sensory neuropathy and peripheral motor neuropathy were the most commonly reported reasons for stopping treatment.

In addition to being a third-line treatment option, brentuximab vedotin has been evaluated in ongoing clinical trials as monotherapy, as part of combination therapy in the first- and second-line settings[15], and as post-ASCT consolidation therapy[16].

Brentuximab vedotin received regulatory approval for the treatment of HL after failure of ASCT or after failure of 2 prior multi-agent chemotherapy regimens in transplantation-ineligible patients, and also for the treatment of patients with relapsed systemic anaplastic large-cell lymphoma[17]. In Canada, the pan-Canadian Oncology Drug Review recommended funding the drug for patients who relapse after ASCT and for patients with systemic anaplastic large-cell lymphoma, with the condition that in either case, the incremental cost-effectiveness ratio (ICER) be improved to an acceptable threshold[18]. In Ontario, Cancer Care Ontario listed brentuximab vedotin as a part of the New Drug Funding Program[19].

In light of the decision to fund brentuximab vedotin in certain clinical circumstances, we evaluated the incremental health benefits, costs, and cost-effectiveness of brentuximab vedotin treatment from the perspective of the Canadian health care payer. We developed a decision-analytic model and used the Ontario Cancer Registry, administrative databases, and published sources to set the model parameters.

METHODS

Model Overview

The decision-analytic model projects the lifetime clinical and economic consequences for HL patients who receive third-line treatment after failure of ASCT. The model starts with a clinical decision to treat with brentuximab vedotin rather than with best supportive care [Figure 1(A)]. Two distinct Markov models represent the decision alternatives: M1 models treatment with brentuximab vedotin, and M2 models the provision of best supportive care [Figure 1(B,C)]. In the base-case scenario, M2 uses single-agent gemcitabine[20] as the best supportive care agent.

In the M1 model, the simulation of lifetime costs and benefits for patients receiving brentuximab vedotin treatment includes four health states:

- Patient shows improvement or remains stable
- Patient develops a treatment-related serious adverse event that prevents continuation of treatment
- Patient's disease progresses
- Death

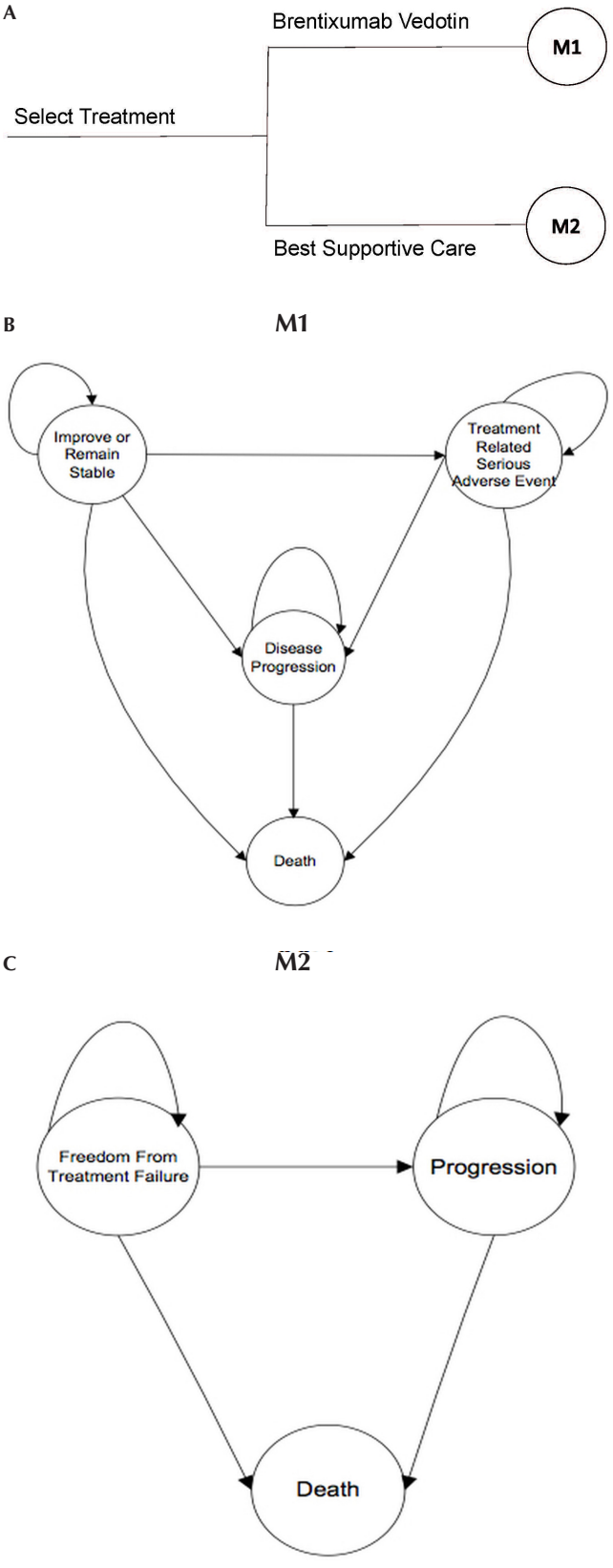

FIGURE 1 Decision-analytic model: (A) Decision tree. (B) Markov model M1 (brentuximab vedotin). (C) Markov model M2 (best supportive care).

In the M2 model, the simulation of lifetime economic and clinical outcomes for patients receiving best supportive care includes three distinct health states:

- Patient is free from treatment failure
- Patient's disease progresses
- Death

The model assumes that peripheral sensory neuropathy is the only adverse reaction that would stop a patient from continuing treatment with brentuximab vedotin, leading to a switch from brentuximab vedotin to best supportive care. A separate health state named Treatment-Related Serious Adverse Event was incorporated into the M1 model to account for changes in treatment costs, health care utilization costs, and quality of life associated with stopping brentuximab vedotin and switching to best supportive care.

The model was developed using the TreeAge Pro Suite software application (2015 release: TreeAge Software, Williamstown, MA, U.S.A.), and it was run using a lifetime horizon with half-cycle correction.

Data and Cohort

The model was populated using data from the pivotal phase II clinical trial[13] and by administrative and cancer registry data obtained from the Ontario Cancer Data Linkage Project ("cd-link," http://www.ices.on.ca/Research/Research-programs/Cancer/cd-link). Cd-link is an initiative of the Ontario Institute for Cancer Research and Cancer Care Ontario's Health Services Research Program, whereby risk-reduced coded data from the ICES Data Repository managed by the Institute for Clinical Evaluative Sciences is provided directly to researchers with the protections of a comprehensive data use agreement. Cd-link connects data from the Ontario Cancer Registry with several Ontario administrative databases, including the Discharge Abstract Databases, the Ontario Health Insurance Plan (OHIP), and the Ontario Drug Benefit.

Using the cancer registry, we identified 2475 patients diagnosed with HL in Ontario during 2000–2006. By linking the Ontario Cancer Registry data for those patients with the OHIP database, we determined that 163 patients received second-line high-dose chemotherapy followed by ASCT.

The phase II trial included only patients who experienced a failed ASCT, and we therefore restricted the study cohort to a similar group. Of the 163 patients who underwent ASCT, 77 patients who went on to receive third-line treatment—either chemotherapy, radiation therapy, a second ASCT, or allogeneic stem-cell transplantation after the ASCT—were identified. We assumed that those patients received the additional treatment because they had relapsed after the ASCT. Table I summarizes the clinical characteristics of those patients.

To conduct the survival analysis, we extracted 2-year follow-up data for the patients from the OHIP database and used treatment switch or re-treatment as a proxy for progression. We assumed that patients developed progression after third-line treatment if they satisfied at least 1 of the following criteria:

- received chemotherapy 5 months after third-line treatment,
- received chemotherapy with a difference of at least 60 days in service dates for 2 consecutive chemotherapy physician claims,
- received radiation therapy,
- underwent stem-cell transplantation, or
- received palliative care.

TABLE I Clinical characteristics of 77 patients with Hodgkin lymphoma who relapsed after autologous stem cell transplantation (ASCT)

Variable	Value
Sex [*n* (%)]	
Men	33 (43)
Women	44 (57)
Age group at initial diagnosis [*n* (%)]	
<20 Years	17 (22)
20–39 Years	37 (48)
40–59 Years	20 (26)
60–69 Years	3 (4)
Year of initial diagnosis [*n* (%)]	
2000	12 (15)
2001	10 (13)
2002	15 (20)
2003	8 (10)
2004	13 (17)
2005	10 (13)
2006	9 (12)
Time from initial diagnosis to post-ASCT relapse (years)	
Median	1.61
Mean	2.06
Range	0.59–7.67
Prior therapy	
Chemotherapy	76 (99)
Radiotherapy	15 (20)
Transplantation	77 (100)
Status at 31 March 2011	
Alive	51 (66)
Dead	26 (34)

Estimation of Transition Probabilities

We estimated transition probabilities for Freedom from Treatment Failure to Progression in the M2 model and for Progression to Death by fitting a Weibull distribution to patient follow-up data obtained through cd-link. We obtained transition probabilities for Improve or Remain Stable to Disease Progression in the M1 model by adjusting the Weibull progression-free survival curve fitted to the patient follow-up data retrieved from the cd-link for the hazard ratio of 0.41—an outcome of the subgroup analysis comparing the hazard for patients on brentuximab vedotin therapy after systemic therapy with the hazard for patients receiving prior systemic therapy as reported for the phase II clinical trial.

To compute the transition probabilities beyond the 24-month follow-up period, we extrapolated the fitted

Weibull survival curves. We used Ontario sex-specific life tables and the sex distribution in the phase II trial and in the cohort obtained from cd-link to derive all-cause mortality rates.

Finally, we assumed that patients who develop a treatment-related adverse event such as peripheral sensory neuropathy, and thus discontinue brentuximab vedotin treatment (M1 model), follow the same transition probability matrix as do patients in the best supportive care model (M2 model).

Cost and Utility Values

The list price of brentuximab vedotin in Canada is $4,840.00 per 50 mg vial[21]. The cost of gemcitabine, which is funded through the New Drug Funding Program in Ontario, is $0.0620 per milligram. The cost of administration was estimated from the internal costing database at the London Regional Cancer Program in London, Ontario.

We estimated hospitalization costs using resource intensity weights recorded in the Discharge Abstract Database and the cost per weighted case obtained from the annual report of hospital financial performance indicators released by the Canadian Institute for Health Information[22]. Physician costs were estimated from the OHIP database, and drug costs were obtained from the Ontario Drug Benefit database.

Several studies have reported health state utilities and health-related quality of life measures in connection with treatment outcomes and toxicities for patients with relapsed and refractory HL[23–27]. In the base case, we assumed that brentuximab vedotin neither improves nor worsens quality of life; thus, quality of life would be the same for the Improve or Stable and Free From Treatment Failure states. According to the published literature, long-term quality of life for persistent HL after high-dose chemotherapy plus ASCT is 0.8[28]. We also assumed that quality of life is decremented by 10% when a patient with HL relapses after third-line treatment[28]. Finally, we assumed that patients developing peripheral sensory neuropathy would have the same quality of life as an individual with breast cancer developing the same adverse reaction[29].

Costs were converted to 2012 Canadian dollars using the health and personal care consumer price index[30]. All costs and benefits were discounted at 5% according to Canadian guidelines[31].

RESULTS

Base-Case Scenario

In the base case, brentuximab vedotin treatment resulted in an average incremental utility of 0.544 quality-adjusted life-years (QALYs) per person and an average incremental cost of $89,366 per person, which resulted in an ICER of $164,248 per QALY gained.

Sensitivity Analyses

We conducted a number of sensitivity and scenario analyses. The ICER was sensitive to several model input parameters (Table II). When the probability of developing peripheral sensory neuropathy dropped to 1% compared with 5.8% in the base case, the ICER decreased to $69,540 per QALY gained. The ICER fell to $121,092 per QALY gained if patients on brentuximab vedotin treatment had perfect health (utility of 1) rather than 0.8 as was assumed in the base case.

When patients receiving best supportive care with no evidence of progression had a utility of 0.6, rather than 0.8 as was assumed in the base case, the ICER became $100,476 per QALY gained. When no discounting was in effect, the ICER dropped to $122,040 per QALY gained. The model outcomes were relatively robust to changes in other parameters such as the cost of brentuximab vedotin administration, chemotherapy cycle, pre- and post-progression health care utilization, transition probabilities, and utility of progression (Table II).

We conducted sensitivity analyses on the price of brentuximab vedotin and the relative survival advantage of brentuximab vedotin compared with best supportive care. When the cost of brentuximab vedotin was reduced by approximately 80%, the ICER was less than $50,000 per QALY gained. The ICER fell below $100,000 per QALY gained if the daily cost of the drug was lowered by approximately 45% and below $150,000 per QALY gained when the daily cost was lowered by more than 10%. The ICER fell to $129,420 per QALY gained when the hazard ratio was 0.1. In 2-way sensitivity analyses, when the drug cost was lowered by 45% and the hazard ratio was below 0.41, the ICER fell below $100,000 per QALY gained (Figure 2).

In probabilistic sensitivity analyses, we simultaneously sampled from distributions defined for all key parameters (Table III). In all observations, the ICER was greater than $50,000 per QALY gained. Approximately 17% of the ICERs were below the $100,000, 43% were below the $150,000, and 85% were below the $200,000 per QALY gained thresholds [Figure 3(A)]. Brentuximab vedotin treatment becomes equally preferred to best supportive care at a willingness to pay of $162,000 per QALY gained [Figure 3(B)].

DISCUSSION

We developed a decision-analytic model to investigate the cost-effectiveness of brentuximab vedotin compared with best supportive care for the treatment of patients with HL who relapse after ASCT, from the perspective of the Canadian health care payer. In the base case, brentuximab vedotin resulted in an incremental cost of $89,366 and an incremental effect of 0.544 QALYs, corresponding to an ICER of $164,248 per QALY gained. That ICER estimate is higher than the $100,000 per QALY gained that is often interpreted as having "weak evidence for adoption and appropriate utilization"[33]. Our estimate is also higher than the ICER of $111,752 per QALY gained submitted by the manufacturer in the original submission to the pan-Canadian Oncology Drug Review[21].

The cost-effectiveness of brentuximab vedotin has already been explored in several jurisdictions around the world[34–38]. In the United Kingdom, the National Institute for Health and Care Excellence concluded that brentuximab vedotin was not cost-effective at a given price and efficacy[39]. To the best of our knowledge, our economic analysis is the first Canadian study to use clinical practice data to establish the cost-effectiveness of brentuximab

TABLE II Summary of one-way sensitivity analyses

Variable	Change or range tested	Range of effect on ICER (CA$/QALY)	
		Lower	Upper
Cost			
Brentuximab vedotin			
Dosing	$0–$17,424	22,992	164,248
Administration[a]	±20%	163,824	164,676
Adverse effects[b]	±20%	164,208	164,292
Gemcitabine			
Dosing	±20%	164,232	164,268
Administration	±20%	164,184	164,304
Progression[c]			
Pre	±20%	165,084	163,404
Post	±20%	163,140	165,360
Health state utilities			
Improve or stable	0.6–1	255,180	121,092
Free from treatment failure	0.6–1	100,476	449,652
Progression	–30% to –5%	170,028	162,864
Adverse effects[b]	±20%	270,192	117,984
Probabilities			
Probability of adverse effects	0.01–0.2	69,540	305,916
Progression to death	±20%	161,028	166,836
Improve or stable to progression	±20%	151,008	174,912
Free from treatment failure to progression	±20%	172,524	158,652
Hazard ratio	0.1–1	129,420	261,660
Discount rate	0%–3%	122,040	146,832

[a] Administration cost includes costs of pharmacy preparation time and infusion time.
[b] One-time physician visit is assumed upon development of peripheral sensory neuropathy.
[c] Includes hospitalization and physician and drug costs.
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

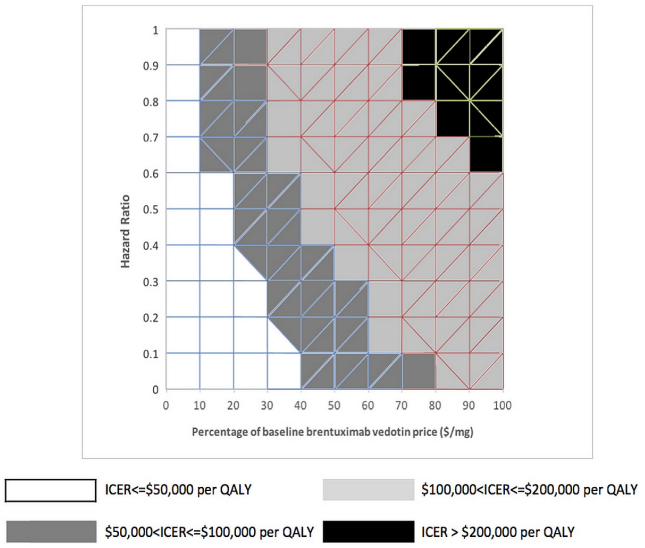

FIGURE 2 Sensitivity of the incremental cost-effectiveness ratio (ICER) to the hazard ratio and price (per milligram) of brentuximab vedotin. QALY = quality-adjusted life-year.

vedotin. In the study, we adapted brentuximab vedotin to the Canadian cancer treatment setting with the aid of both published data and Canadian administrative databases, which makes our analysis different from those in other published international studies.

Targeted therapies in general tend to have high ICERs. For example, an economic evaluation of adding bevacizumab to paclitaxel and carboplatin for the treatment of ovarian cancer resulted in an ICER of $479,712 per life-year gained[40]. The addition of cetuximab to platinum-based chemotherapy for the first-line treatment of recurrent or metastatic head-and-neck cancer resulted in an ICER of $386,000 per QALY gained[41]. Bevacizumab in combination with paclitaxel in the first-line treatment of patients with metastatic breast cancer yielded an ICER of $745,000 per QALY gained[42]. Denosumab compared with zoledronic acid in the management of skeletal metastases secondary to breast cancer resulted in an ICER of $697,499 per QALY gained[43].

We conducted pricing scenarios and found that a price reduction of at least 45% would be needed for the ICER to reach less than $100,000 per QALY gained. In sensitivity analyses, the ICER was sensitive to the hazard ratio resulting from comparing progression-free survivals for brentuximab

vedotin and for best supportive care. Considering the challenges of conducting randomized phase III clinical trials in patients with HL who relapse after ASCT, the present study provides valuable insight into the cost-effectiveness of brentuximab vedotin based on phase II data.

At the time that our study was conducted, brentuximab was the only promising treatment option for patients who relapse after ASCT. As novel drugs with activity in HL become available, one example being the PD-1 inhibitor nivolumab[44], the order of salvage treatments for patients in the relapsed and refractory setting could change, which could clearly affect our model.

Our study has several limitations. First, the hazard ratio was based on a comparison of the hazard for a subgroup of

TABLE III Model parameters and sources

Variable	Base-case value (2012 CA$)	Duration	Ranges tested in sensitivity analyses	Probability distribution (parameter)	Reference
Costs (per month)				Lognormal (μ,σ)	
Brentuximab vedotin					
Dosing[a]	17,424.00	Treatment course	$0–$17,424	9.74, 0.22	pCODR, 2016[21]
Infusion time[b]	149.53	Treatment course	±20%	4.94, 0.36	Mittmann *et al.,* 2009[32]
Pharmacy preparation time[b]	115.44	Treatment course	±20%	4.70, 0.31	Mittmann *et al.,* 2009[32]
Adverse reaction[c]	149.00	One time	±20%	4.99, 0.11	Ontario Health Insurance Plan
Gemcitabine					
Dosing[d]	355.14	Treatment course	±20%	5.86, 0.17	Cancer Care Ontario
Infusion time[b]	224.30	Treatment course	±20%	5.39, 0.19	Mittmann *et al.,* 2009[32]
Pharmacy preparation[b]	86.58	Treatment course	±20%	4.38, 0.39	Mittmann *et al.,* 2009[32]
Progression (best supportive care)					
Pre					
Hospitalization cost					Discharge Abstract Database[e]
During first 5 months	1,734.00	First 5 months	±20%	7.46, 0.07	
During subsequent months	149.00	Subsequent months	±20%	4.99, 0.12	
Physician cost					Ontario Health Insurance Plan
During first 5 months	825.00	First 5 months	±20%	6.71, 0.07	
During subsequent months	231.00	Subsequent months	±20%	5.43, 0.09	
Drug cost					Ontario Drug Benefit
During first 5 months	116.00	First 5 months	±20%	4.74, 0.13	
During subsequent months	113.00	Subsequent months	±20%	4.72, 0.13	
Post					
Hospitalization cost					Discharge Abstract Database[e]
During first 5 months	155.00	First 5 months	±20%	5.02, 0.2	
During subsequent months	1,292.00	Subsequent months	±20%	7.16, 0.05	
Physician cost					Ontario Health Insurance Plan
During first 5 months	197.00	First 5 months	±20%	5.27, 0.14	
During subsequent months	788.00	Subsequent months	±20%	6.66, 0.14	
Drug cost					Ontario Drug Benefit
During first 5 months	116.00	First 5 months	±20%	4.73, 0.23	
During subsequent months	233.00	Subsequent months	±20%	5.44, 0.16	
Health state utilities				β (*r*, *n*)[f]	
Improve or stable	0.8	Lifetime	0.6–1	80, 100	Guadagnolo *et al.,* 2006[28]
Free from treatment failure	0.8	Lifetime	0.6–1	80, 100	Guadagnolo *et al.,* 2006[28]
Progression	–10%	Lifetime	–5% to –30%	72, 100	Guadagnolo *et al.,* 2006[28]
Adverse events[g]					Brown *et al.,* 2001[29]
During first 13 weeks	0.62	13 Weeks	±20%	62, 100	
During subsequent weeks	0.8	Subsequent weeks	±20%	80, 100	
Death	0				

TABLE III Continued

Variable	Base-case value (2012 CA$)	Duration	Ranges tested in sensitivity analyses	Probability distribution (parameter)	Reference
Probabilities				β (*r*, *n*)[f]	
Probability of adverse events	0.0588	Lifetime	0.01–0.2	588, 10000	Younes *et al.*, 2012[12]
Free from treatment failure to death	Varies by month	Lifetime	±20%	Varies by month	Ontario Health Insurance Plan
Progression to death	Varies by month	Lifetime	±20%	Varies by month	Ontario Health Insurance Plan
Free from treatment failure to progression	Varies by month	Lifetime	±20%	Varies by month	Younes *et al.*, 2012[12]
Improve or stable to progression	Varies by month	Lifetime	±20%	Varies by month	ADC Review, 2015[15]
Discount rate	5%		0%–5%		Health Canada, 2016[17]

[a] Cycle length: 21 days. According to phase II clinical trials, the mean number of cycles was 10. Calculation: $96.80 (price per milligram) × 1.8 mg/kg (dose) × 70 kg (average weight) / 21 (treatment cycle length) × 30 (days in month) = $17,424.00.
[b] Hourly cost for pharmacy preparation time is $43.29 and for infusion time is $112.15.
[c] Includes cost of consultation visit.
[d] Administered on day 1 and day 8 of the 21-day treatment cycle. Calculation: $0.0620 (gemcitabine price per milligram) × 1.79 m^2 (assumed body surface area) × 800 mg/m^2 (dose) × 4 (infusions in month) = $355.14.
[e] Maintained by the Canadian Institute for Health Information.
[f] Parameters of β distributions are integers.
[g] Peripheral sensory neuropathy is an adverse event that stops treatment continuation. Median time to resolution is 13.2 weeks.
pCODR = pan-Canadian Oncology Drug Review.

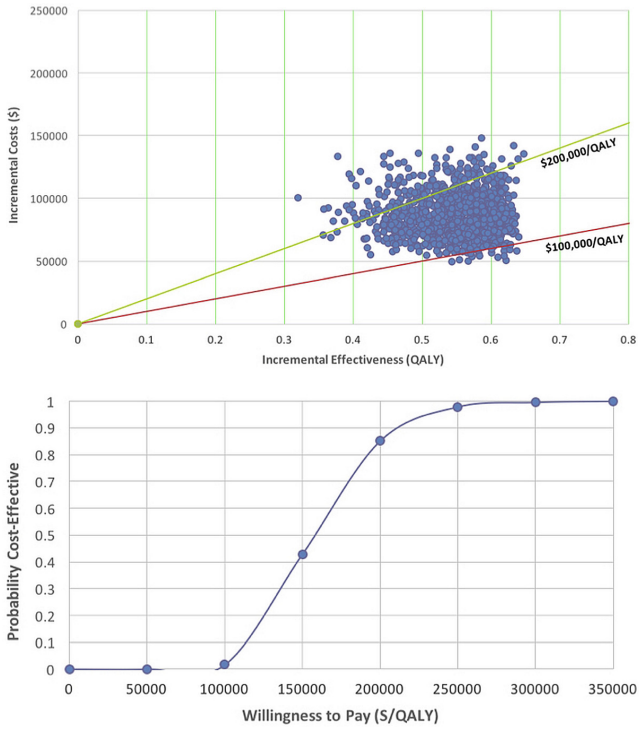

FIGURE 3 Probabilistic sensitivity analysis: (A) Incremental cost-effectiveness scatter plot. (B) Cost-effectiveness acceptability curve. QALY = quality-adjusted life-year.

patients who received brentuximab vedotin after systemic therapy and the hazard for the same group of patients on the preceding systemic therapy in a nonrandomized phase II trial; our estimate might therefore have considerable uncertainty, given that the latter setting differs from the setting used in our economic analysis. Second, our definition of progression in the data analysis is a proxy, given that it is based on treatment switch, which might not necessarily reflect a true relapse. In practice, progression is verified by diagnostic procedures such as imaging by computed tomography or positron-emission tomography, and a biopsy. Also, considering that Guadagnolo *et al.*[28] served as the primary source for the utilities, there could be uncertainty in the baseline utility values, which were extensively tested in sensitivity analyses. Finally, like the administrative data used in any study, our data might contain coding errors that could affect the results. One specific example is the lack of chemotherapy treatment reported before ASCT for 1 of the 77 patients in the OHIP database (most likely a fee-for-service code entry error).

CONCLUSIONS

In the base-case scenario, the ICER for brentuximab vedotin was $164,248 per QALY gained. That ICER might not represent "good value for money" based on commonly accepted cost-effectiveness standards. However, reimbursement decisions must take into account not only the cost, effectiveness, and associated ICER of a new treatment, but also other factors such as burden of disease and lack of effective alternative treatment options. A risk-sharing agreement or patient access scheme could help to reduce the cost-per-patient burden to the health care payer and ensure appropriate medical care utilization[45].

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing of conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Telfer School of Management, University of Ottawa, Ottawa, ON; †Ivey Business School, Western University, London, ON; ‡Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, and §Department of Medicine, Division of Hematology, Schulich School of Medicine and Dentistry, Western University, London, ON.

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