

# Cost-effectiveness of Brentuximab Vedotin With Chemotherapy in Treatment of CD30-Expressing PTCL

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**P**eripheral T-cell lymphomas (PTCLs) are a heterogeneous group of mostly aggressive non-Hodgkin lymphomas (NHLs) that result from the clonal proliferation of mature postthymic lymphocytes, including natural killer (NK) cell neoplasms.<sup>1</sup> The more than 25 PTCL subtypes account for approximately 10% of NHL cases in the United States and Europe and may account for up to 24% in Asia. According to the World Health Organization classification of T-cell malignancies, there were approximately 7000 new cases of mature T-/NK-cell lymphoid neoplasms in the United States in 2016.<sup>2</sup>

The frontline treatment landscape for PTCL varies by subtype. The 3 most common subtypes—PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and systemic anaplastic large cell lymphoma (sALCL)—are usually treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens.<sup>3-5</sup> However, these regimens are associated with disappointing efficacy, including low rates of complete remission, poor progression-free survival (PFS), and poor overall survival (OS).<sup>6-8</sup> The International PTCL Project reported 5-year OS for PTCL-NOS, AITL, ALK-negative ALCL, and ALK-positive ALCL to be 32%, 32%, 49%, and 70%, respectively.<sup>9</sup> Clinical studies adding active agents to the CHOP regimen have shown limited efficacy improvements,<sup>10</sup> demonstrating the high unmet need in these patients.

Brentuximab vedotin (Adcetris; Seattle Genetics, Inc; Bothell, WA) is a CD30-directed antibody-drug conjugate approved for several indications, including previously untreated sALCL or other CD30-expressing PTCLs when used in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP).<sup>11</sup>

ECHELON-2 (ClinicalTrials.gov NCT01777152) is a double-blind, double-dummy, randomized, placebo-controlled, active-comparator phase 3 trial comparing A+CHP with CHOP in patients with previously untreated CD30-expressing PTCL. The PFS hazard ratio (HR) was 0.71 (95% CI, 0.54-0.93;  $P = .0110$ ) for the A+CHP group versus the CHOP group. After a median follow-up of 36.2 months (95% CI, 35.9-41.8 months), the median PFS in the A+CHP group was longer than that in the CHOP group: 48.2 months (95% CI, 35.2 months–not evaluable) versus 20.8 months (95% CI, 12.7-47.6

## ABSTRACT

**OBJECTIVES:** To evaluate the cost-effectiveness of brentuximab vedotin (Adcetris) in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP) in the first-line setting for CD30-expressing peripheral T-cell lymphoma (PTCL).

**STUDY DESIGN:** An economic model was developed using clinical and quality-of-life (QOL) data from the ECHELON-2 trial, in which A+CHP demonstrated significant improvement in progression-free survival (PFS) and overall survival (OS) versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

**METHODS:** A partitioned survival model, consisting of 3 health states (PFS, postprogression survival, and death), was constructed from a US payer perspective over a lifetime time horizon. PFS and OS observed from ECHELON-2 were extrapolated using standard parametric distributions. The best-fitting distributions (log-normal for both arms) were selected based on statistical goodness of fit and clinical plausibility of the long-term projections. Utilities were based on the European Quality of Life 5-Dimensional data collected in ECHELON-2. Medical resource use and costs were from literature and standard sources.

**RESULTS:** The model predicted that A+CHP extended PFS and OS by 2.92 and 3.38 years, respectively, over CHOP. After incorporating QOL and discounting, A+CHP was associated with 1.79 quality-adjusted life-years gained at a total incremental cost of \$159,388, resulting in an incremental cost-effectiveness ratio (ICER) of \$89,217. Sensitivity analyses provided ICERs ranging approximately from \$57,000 to \$138,000. The estimated probability that A+CHP is cost-effective compared with CHOP was 82% at a willingness-to-pay threshold of \$150,000.

**CONCLUSIONS:** Based on the ECHELON-2 trial data, this analysis found A+CHP to be cost-effective for patients with previously untreated CD30-expressing PTCL.

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## TAKEAWAY POINTS

This cost-effectiveness evaluation, which used the data from the ECHELON-2 trial, demonstrates that the economic value for adopting brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (A+CHP) in previously untreated CD30-expressing peripheral T-cell lymphoma (PTCL) is within the widely accepted range for oncology medicines.

- ▶ The analysis of ECHELON-2 projected significant differences in long-term survival in favor of A+CHP versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP): 2.92 years in progression-free survival, and 3.38 years in overall survival.
- ▶ In a wide range of sensitivity analyses, the incremental cost-effectiveness ratio of A+CHP compared with CHOP fell below \$150,000 per quality-adjusted life-year gained.
- ▶ The sensitivity reflects that the central driver of value of brentuximab vedotin treatment in this population is extended survival.

months), respectively;  $P = .0110$ .<sup>12</sup> Treatment with A+CHP reduced the risk of death by 34% compared with CHOP (HR, 0.66; 95% CI, 0.46-0.95;  $P = .0244$ ); after a median follow-up of 42.1 months, the 75th percentile OS was not reached in the A+CHP group but was 17.5 months in the CHOP group. Adverse events (AEs) in both arms were similar and manageable.<sup>12</sup>

PTCL and other aggressive NHLs incur substantial healthcare resource utilization and high medical costs driven by hospitalizations, pharmacy services, and outpatient office visits.<sup>13,14</sup> For patients to be able to access new therapies, data are required to quantify their overall clinical benefits and incremental costs compared with current treatments. The objective of this study was to quantify the incremental benefits and costs of A+CHP compared with CHOP in patients with newly diagnosed CD30-expressing PTCL, from a US healthcare payer perspective, using a cost-effectiveness model.

## METHODS

### Patients

The model considered a patient cohort that was aligned with the eligible patients included in ECHELON-2.<sup>12</sup> The trial allowed enrollment of 7 PTCL subtypes that may express CD30: SALCL (70%), PTCL-NOS (16%), AITL (12%), and others (2%).<sup>12</sup>

### Model Overview

The model was developed in Microsoft Excel using the partitioned survival approach, which is commonly used for therapeutic interventions for cancers. The model projects the fraction of a fixed cohort in each of 3 health states—PFS, postprogression survival (PPS), and death—over time. To estimate these fractions, parametric survival functions were used to estimate the proportion of the cohort remaining free of the end points that defined the relevant health states (**eAppendix Figure** [eAppendix available at [ajmc.com](http://ajmc.com)]). Time in the PFS state was estimated directly from the area under the PFS curves, whereas time in the PPS state was estimated by the area between the PFS and OS curves based on analyses of survival data from ECHELON-2. Because the patient population is modeled as a single cohort throughout the time horizon, the efficacy of subsequent treatments is implicitly captured in the OS data. As

such, only their costs need to be captured explicitly based on the actual subsequent treatments received in ECHELON-2.

Costs and clinical outcomes were estimated at fixed time points based on the proportion of the cohort in each health state at a given time. The model utilized a 21-day cycle and was run for a lifetime time horizon over which costs and health outcomes were evaluated, with a discounting rate of 3% per annum.<sup>15</sup> The base-case analysis takes the perspective of a third-party commercial payer in the United States.

Model inputs are summarized in **Table 1**.<sup>13,16-23</sup> The main assumptions are described in the subsections that follow.

### Clinical Inputs

**Extrapolation of PFS and OS.** Clinical outcomes were based on analyses of the individual patient data from ECHELON-2 following the recommendations of the National Institute for Health and Care Excellence Decision Support Unit<sup>24</sup> on survival data extrapolation. Six parametric distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalized gamma) were fitted to ECHELON-2 PFS and OS Kaplan-Meier (KM) curves to obtain long-term survival projections by treatment arm. The best-fitting distributions were selected based on statistical goodness of fit and clinical plausibility of the long-term projections. Because median survival was not yet reached in ECHELON-2, the clinical plausibility of the extrapolations was evaluated based on input from clinical experts and a comparison with long-term survival estimates published in the literature.<sup>25,26</sup> The log-normal distribution was applied to project long-term PFS and OS for both A+CHP and CHOP. This may be a conservative approach, given the superior clinical benefits of A+CHP compared with CHOP observed in ECHELON-2 for the first 5 years following treatment initiation. Long-term OS projections were bounded such that the mortality rate was never lower than the US general mortality rate of a similar age population, truncated after 45 years.<sup>27</sup> The KM curves and fitted distributions are presented in **Figure 1**.

**Role of subsequent treatment.** Consolidative stem cell transplantation (SCT) was received by 50 (22%) patients in the A+CHP group and 39 (17%) in the CHOP group after the end of treatment, at the discretion of the investigator.<sup>12</sup> Considering that subsequent treatments were provided with varying intent (eg, consolidation, treatment of residual or progressive disease) and that the OS data from the trial had already counted the impact of downstream treatments including SCT, it was not necessary to model their efficacy explicitly, but we did incorporate their impact on costs.

**AEs.** The model considered the costs and the impact on quality of life (QOL) of treatment-related AEs. Only grade 3 and 4 AEs

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**TABLE 1.** Summary of Model Inputs<sup>13,14-23</sup>

Description	Base Value	SE	Distribution	Source	Varied in PSA
<b>General Inputs</b>					
Starting age (years)	58	5.61	Normal	ECHELON-2	Yes
<b>Model-Projected Median Survival (months)</b>					
Overall population analysis					
Progression-free survival					
A+CHP	43.47 (log-normal)	-	Cholesky	ECHELON-2	Yes
CHOP	24.15 (log-normal)	-	Cholesky	ECHELON-2	Yes
Overall survival (adjusted by US general population mortality rate)					
A+CHP	205.60 (log-normal)	-	Cholesky	ECHELON-2	Yes
CHOP	107.63 (log-normal)	-	Cholesky	ECHELON-2	Yes
<b>AEs</b>					
A+CHP					
Neutropenia	0.345	-	-	ECHELON-2	Values indirectly varied through overall cost/disutility of AEs specific to A+CHP or CHOP
Febrile neutropenia	0.184	-	-	ECHELON-2	
Anemia	0.135	-	-	ECHELON-2	
Leukopenia	0.072	-	-	ECHELON-2	
Diarrhea	0.058	-	-	ECHELON-2	
Thrombocytopenia	0.058	-	-	ECHELON-2	
Pneumonia	0.054	-	-	ECHELON-2	
Infection	0.180	-	-	ECHELON-2	
CHOP					
Neutropenia	0.336	-	-	ECHELON-2	Values indirectly varied through overall cost/disutility of AEs specific to A+CHP or CHOP
Febrile neutropenia	0.146	-	-	ECHELON-2	
Anemia	0.102	-	-	ECHELON-2	
Leukopenia	0.062	-	-	ECHELON-2	
Diarrhea	0.009	-	-	ECHELON-2	
Thrombocytopenia	0.004	-	-	ECHELON-2	
Pneumonia	0.022	-	-	ECHELON-2	
Infection	0.130	-	-	ECHELON-2	
<b>Prophylaxis Treatment</b>					
Probability of pegylated filgrastim	0.65	0.066	Beta	Morrison et al (2007) <sup>16</sup>	Yes
Probability of filgrastim	0.35	-	-	-	1 minus probability of receiving pegylated filgrastim
<b>Percent of Patients Receiving Subsequent Chemotherapy</b>					
A+CHP	0.261	0.0266	Beta	ECHELON-2	Yes
CHOP	0.416	0.0424	Beta	ECHELON-2	Yes
<b>Use of Subsequent SCT (percent of patients receiving consolidative SCT post frontline)</b>					
A+CHP					
ASCT	0.22	0.022	Beta	ECHELON-2	Yes
Allo-SCT	0	-	-	ECHELON-2	N/A
CHOP					
ASCT	0.17	0.017	Beta	ECHELON-2	Yes
Allo-SCT	0	-	-	ECHELON-2	N/A

(continued)

**TABLE 1.** (Continued) Summary of Model Inputs<sup>13,14-23</sup>

Description	Base Value	SE	Distribution	Source	Varied in PSA
<b>Utility Values</b>					
PFS	0.825	0.0842	Beta	ECHELON-2	Yes
PPS	0.795	0.0811	Beta	ECHELON-2	Yes
Disutility associated with AEs					
Anemia	-0.13	-	-	Lloyd et al (2008) <sup>17</sup>	Values indirectly varied through overall disutility of AEs specific to A+CHP or CHOP
Febrile neutropenia	-0.09	-	-	Assumed to be the same as neutropenia	
Leukopenia	-0.00	-	-	Assumption	
Neutropenia	-0.09	-	-	Nafees et al (2008) <sup>18</sup>	
Diarrhea	-0.05	-	-	Nafees et al (2008) <sup>18</sup>	
Pneumonia	-0.20	-	-	Beusterien et al (2010) <sup>19</sup>	
Infection	-0.20	-	-	Assumption	
Thrombocytopenia	-0.00	-	-	Assumption	
<b>Costs (\$)</b>					
Overall regimen cost (includes administration and treatment but not prophylactic costs)					
A+CHP	153,319	15,645	Gamma	Model calculation	Yes
CHOP	15,012	1531	Gamma	Model calculation	Yes
Total cost of prophylactic treatment by regimen					
A+CHP	6414	654	Gamma	Model calculation	Yes
CHOP	6414	654	Gamma	Model calculation	Yes
Treatment costs per 3-week cycle					
A+CHP					
Drug acquisition	24,192	-	-	RED BOOK (2019) <sup>20</sup> ; ECHELON-2	Indirectly via aggregate cost
Drug administration	1361	-	-	RED BOOK (2019) <sup>20</sup> ; ECHELON-2	
CHOP					
Drug acquisition	1227	-	-	RED BOOK (2019) <sup>20</sup> ; ECHELON-2	Indirectly via aggregate cost
Drug administration	1361	-	-	RED BOOK (2019) <sup>20</sup> ; ECHELON-2	
SCT unit costs					
ASCT	342,445	34,944	Gamma	Josephson et al (2016) <sup>21</sup>	Yes
Allo-SCT	679,083	69,296	Gamma	Josephson et al (2016) <sup>21</sup>	Yes
Medical resource use per cycle					
Preprogression	2417	247	Gamma	Burudpakdee et al (2016) <sup>13</sup> inflated to 2018 US\$	Yes
Postprogression	2417	247	Gamma	Burudpakdee et al (2016) <sup>13</sup> inflated to 2018 US\$	Yes
Terminal care, one-off	30,395	3102	Gamma	Delea et al (2018) <sup>22</sup>	Yes
AEs, per treatment					
A+CHP	13,009	1328	Gamma	HCUPnet (2014) <sup>23,a</sup> inflated to 2018 US\$; ECHELON-2	Yes
CHOP	10,473	1069	Gamma	HCUPnet (2014) <sup>23,a</sup> inflated to 2018 US\$; ECHELON-2	Yes

A+CHP indicates brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; AE, adverse event; AHRQ, Agency for Healthcare Research and Quality; allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; N/A, not applicable; PFS, progression-free survival; PPS, postprogression survival; PSA, probabilistic sensitivity analysis; SCT, stem cell transplant; SE, standard error.

<sup>a</sup>Weighted national estimates from Healthcare Cost and Utilization Project National Inpatient Sample, 2014, based on data collected by individual states and provided to AHRQ by the states. Total number of weighted discharges in the United States based on Healthcare Cost and Utilization Project National Inpatient Sample = 35,358,818.

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reported in more than 5% of patients in either the A+CHP or CHOP group from ECHELON-2 were included.

**Utilities**

The ECHELON-2 trial collected QOL data measured by the European QOL 5-Dimension (EQ-5D) instrument, which we used to assess the utilities for modeled health states. The average utility scores for the pre- and postprogression periods were estimated via a repeated-measures mixed-effects model, with random intercept to account for repeated measurements of the same subject. The analysis shows a statistically insignificant difference in utilities between A+CHP and CHOP for patients residing in the same health state (PFS or PPS); therefore, the utilities were not further stratified by treatment arm.

**Resource Use and Costs**

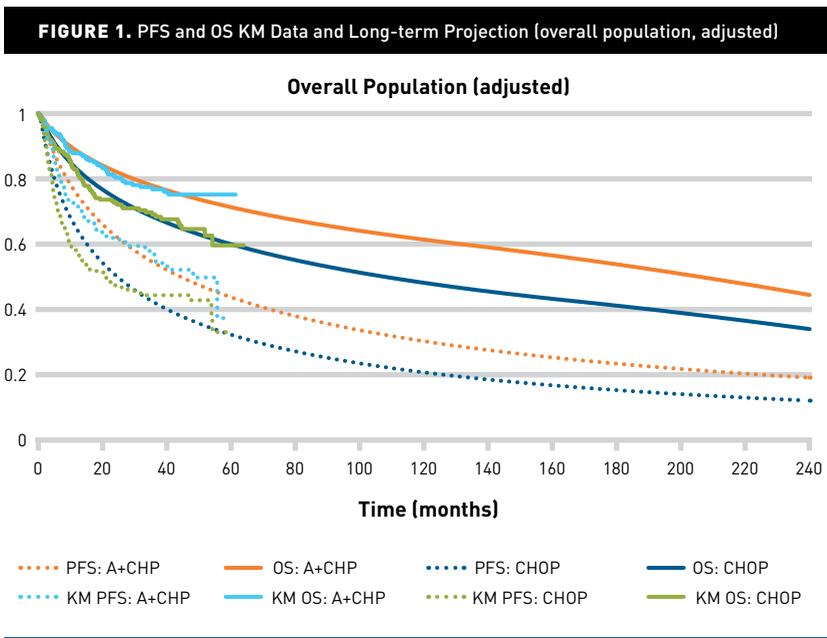
Costs in the model included drug acquisition and administration, comedications, disease management, AE management, subsequent SCT and chemotherapy, and terminal care. Costs were derived from RED BOOK 2019,<sup>20</sup> InHealth Physicians' Fee & Coding Guide 2018,<sup>28</sup> Healthcare Cost and Utilization Project (HCUPnet) 2014 data,<sup>23</sup> and the literature (Appendix Table). Costs were inflated to 2019 US dollars where applicable.

Drug cost calculations were based on the average patient profile in ECHELON-2 and accounted for drug wastage by rounding up to the next full single-use vial size available for each dose administered.<sup>29,30</sup> The treatment cost was computed based on the mean cycles of treatment received in ECHELON-2 and applied as a 1-time cost in the first cycle.

A basket cost for subsequent treatment was applied as a 1-time cost for patients whose disease progressed. The proportion of patients receiving subsequent chemotherapy for residual or progressive disease, together with the composition of subsequent treatment in each treatment arm, was derived from ECHELON-2. The SCT costs were based on findings of a real-world cost study for hematopoietic cell transplantation among a large US commercially insured population.<sup>21</sup> The costs for disease-related resource use were based on the results of an analysis of 1000 patients with PTCL from US administrative claims databases between 2007 and 2011.<sup>13</sup> Per the advice of clinical experts, it was assumed that minimal disease-related medical costs would accrue to patients in PFS after a maximum of 5 years.

**Sensitivity Analyses**

Deterministic sensitivity analyses (DSAs) and scenario analyses were conducted to evaluate the impact of various model inputs and



A+CHP indicates brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PPS, postprogression survival.

assumptions on the base-case incremental cost-effectiveness ratio (ICER). These included alternative time horizons, discount rates, or starting ages; applying other parameter distributions to extrapolate PFS and OS for A+CHP and CHOP; assuming no drug wastage; using a different mix of prophylaxis against neutropenia; and varying disease management costs, SCT costs, and utility values for health states. A probabilistic sensitivity analysis (PSA) was also conducted to address uncertainty in the parameters by randomly sampling from distributions of plausible values for each parameter over 1000 Monte Carlo simulations. Clinical efficacies in terms of survival projections were represented by multivariate normal distributions for parametric fitting parameters, whereas utilities were represented by beta distributions and costs by gamma distributions.

**RESULTS**

**Base-Case Analysis**

Results of the base-case analyses are summarized in Table 2. Over the lifetime time horizon, the model predicted that A+CHP extended undiscounted PFS by 2.92 years and OS by 3.38 years over CHOP. These survival gains, including the relative treatment benefit directly observed from the trial and the accumulated gains over extended survival beyond the trial follow-up period, drive the value in the model.

After incorporating QOL and discounting, this translated to an improvement of 1.79 quality-adjusted life-years (QALYs) (9.78 vs 7.99). A+CHP was associated with a higher healthcare cost compared with CHOP; the incremental cost for A+CHP was \$159,388 (\$678,581 vs \$519,193), which was mainly driven by the higher acquisition cost

**TABLE 2.** Base-Case Cost-effectiveness Analysis Results

Outcome	A+CHP	CHOP	Incremental
Health outcomes			
Life-years, discounted	12.04	9.86	2.18
PFS	7.11	5.20	1.91
PPS	4.93	4.66	0.27
QALYs, discounted	9.78	7.99	1.79
PFS	5.86	4.29	1.57
PPS	3.92	3.71	0.21
Cost outcomes, discounted (\$)			
Total overall costs	678,581	519,193	159,388
First-line treatment costs	191,808	52,218	139,590
Prophylactic treatments	38,489	37,206	1283
Subsequent line treatment costs	26,832	46,856	-20,024
SCT costs	99,309	92,460	6849
Disease management costs	328,126	295,720	32,406
In PFS	120,822	99,737	21,085
In PPS	207,303	195,983	11,321
Adverse event costs	13,049	10,505	2544
Terminal costs	19,456	21,434	-1978
Cost-effectiveness (\$)			
ICER per life-year gained			73,273
ICER per QALY gained			89,217

A+CHP indicates brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PPS, postprogression survival; QALY, quality-adjusted life-year; SCT, stem cell transplant.

for A+CHP versus CHOP (\$145,153 vs \$7118). The ICER for A+CHP compared with CHOP was estimated at \$89,217 per QALY gained and \$73,273 per life-year gained.

### Sensitivity Analysis

In the DSAs and scenario analyses, ICERs ranged from approximately \$57,000 to \$138,000 per QALY gained (Figure 2). Important drivers were discount rate for outcomes, time horizon, and patient’s starting age. Other drivers included disease management cost by health state and application of survival data based on alternative parametric distribution for both arms. For the latter, alternative distributions (including Weibull, log-logistic, Gompertz, and exponential) were applied to both A+CHP and CHOP. The results showed that the implementation of Weibull and Gompertz had the largest impact on the ICER: Use of Weibull decreased the ICER by 16% to \$74,590, whereas use of Gompertz increased the ICER by 22% to \$109,285.

In addition, the model was sensitive to treatment regimen costs, treatment-specific SCT rate, utility value for PFS, and maximum time period during which disease-related medical costs would accrue to patients. The ICERs remained less than \$140,000 for all the scenarios tested, however.

During the PSA, the model was run for 1000 simulations to generate a scatterplot and cost-effectiveness acceptability curve

(Figure 3). The probability that A+CHP is cost-effective compared with CHOP was 82% at a willingness-to-pay threshold of \$150,000.

## DISCUSSION

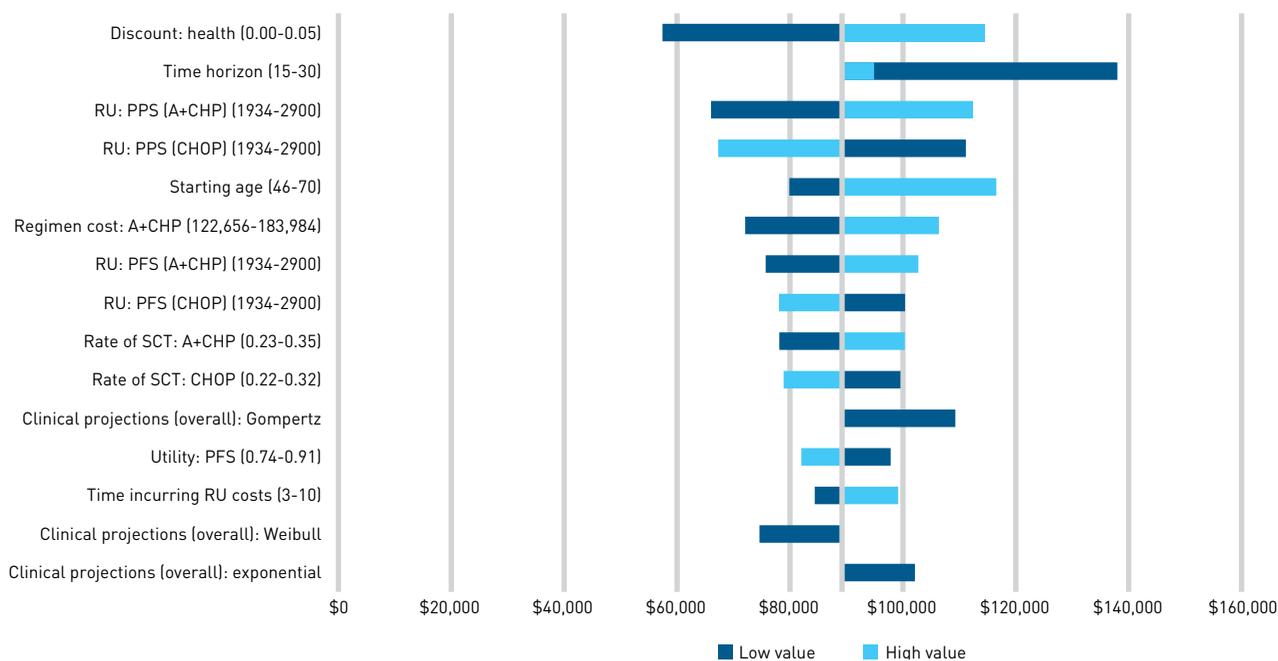
This cost-effectiveness evaluation, using data from ECHELON-2, demonstrates that the economic value for adopting A+CHP in previously untreated CD30-expressing PTCL is within accepted ranges for oncology medicines; in a wide range of sensitivity analyses, the ICER remained below \$150,000 per QALY gained. The ICER was most sensitive to parameters that affected long-term benefits: time horizon, discount rates, and starting age. This sensitivity reflects that the central driver of value of brentuximab vedotin treatment in this population is extended survival.

To our knowledge, this is the first cost-effectiveness study published for frontline treatment of PTCL. A key strength of the present analysis is the use of the ECHELON-2 trial data. ECHELON-2, by allowing enrollment of a broad range of CD30-expressing PTCL subtypes, provided a basis for more clinically meaningful analyses, although the trial was not powered to compare efficacy among individual histological subtypes given the small subgroup sizes in the non-sALCL population (30% of the cohort). Overall, the PFS and OS benefits for the study, most clearly shown with sALCL, are generally consistent across all evaluable histological subtypes with overlapping CIs.<sup>10</sup> Furthermore, the comparator investigated in the trial reflects the standard treatment available to the patient population in the United States for nearly 40 years, thus providing robust evidence for real-world clinical practice. Using patient-level data from this trial to inform the clinical and QOL inputs ensures that the modeled results are clinically meaningful.

The current analysis adopted a partitioned survival approach, which provides the most direct application of the key trial data: PFS and OS. These data can be used directly for the trial follow-up duration, and extrapolations beyond this period rely on the observed history of events and internal and external clinical judgment of face validity. For these reasons, along with their simplicity, partitioned survival models are preferred in many cost-effectiveness evaluations for oncology indications.<sup>31</sup>

As with most newly approved therapies, there is uncertainty around the extrapolation of survival data beyond the trial follow-up period. In this analysis, we applied the same distribution (log-normal) to predict the long-term survival for A+CHP and CHOP, assuming that patients in both groups would follow the same trend in terms of progression or death. In the absence of statistical or clinical evidence supporting a difference in long-term survival, applying the same distribution to both arms follows best modeling practice. The model predicted a 10-year OS of 61% for A+CHP and 48% for CHOP, which mirrors the 10-year Surveillance, Epidemiology, and End Results Program survival rate for all ages with NHL (61%) since diagnosis during 2000-2014.<sup>26</sup> Another study by Maurer et al<sup>25</sup> assessed OS in patients from the United States, Sweden, and Canada with systemic PTCL that was newly diagnosed between

**FIGURE 2.** Tornado Diagram for One-way Deterministic Sensitivity Analyses and Scenario Analyses\*



A+CHP indicates brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; PFS, progression-free survival; PPS, postprogression survival; RU, resource use; SCT, stem cell transplantation.

\*For the parameters with only 1 end of the range shown in the tornado diagram, scenario analyses were tested.

2000 and 2012 and treated with anthracycline-based chemotherapy regimens. It reported a 5-year OS of 38% for the entire cohort: 78% for patients who remained event-free and 11% for those whose disease progressed within the first 24 months.<sup>25</sup> Caution is warranted when directly comparing the outcomes from Maurer et al and ECHELON-2. Overall, patients recruited in ECHELON-2 were younger than those in the Maurer et al study, and the 2 studies had a different mix of histologies. Both age and histology were identified as key factors affecting survival by Maurer et al. In addition, other factors, such as access to supportive care or new therapies, may also lead to different survival.

No explicit benefit was implemented in the model to capture post-SCT survival. Instead, the effects of SCT were assumed to be implicit in the survival curves observed from ECHELON-2. Importantly, however, costs for all SCTs received were included in the model. Based on ECHELON-2, this includes 22% in A+CHP and 17% in CHOP who proceeded to consolidative autologous SCT as a means of improving long-term outcomes and those who received SCT post subsequent treatment. This approach avoids incorporating external data for post-SCT survival, as it can be challenging to make a direct comparison of the clinical outcomes given the difference in baseline patient characteristics and study designs between such studies.

In ECHELON-2, consolidative SCT was permitted, but it did not affect the results of PFS and OS because the benefits of A+CHP were seen both with and without censoring the patients who

received consolidative therapy: HR was 0.71 (95% CI, 0.53-0.94) for PFS, for which consolidative SCT and consolidative radiotherapy were censored.<sup>12</sup> Given that the SCT intent was prespecified by the investigator before the first cycle of chemotherapy, the exclusion of those who received SCT as a scenario analysis may lead to selection bias and confounding and therefore was not explored.

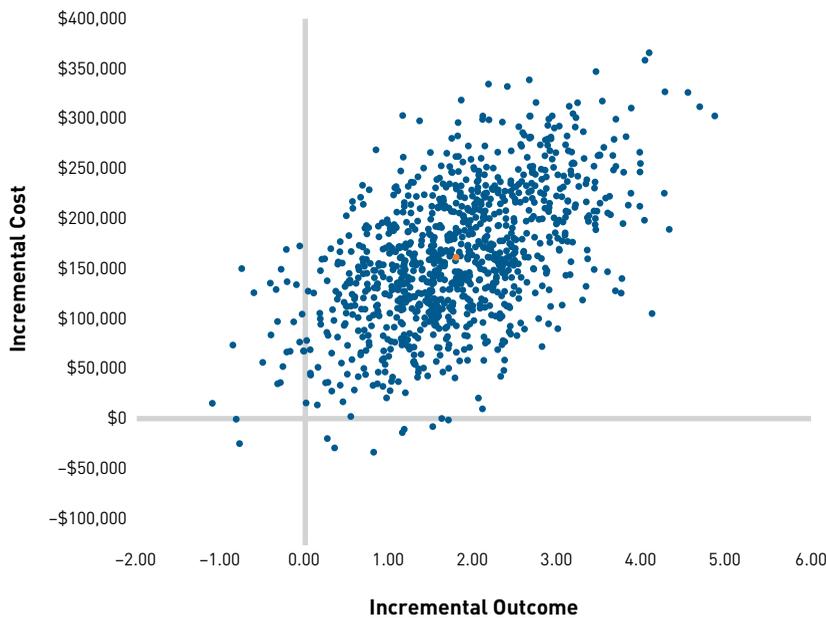
There is a lack of utility values from published literature for previously untreated PTCL. The utilities derived from ECHELON-2 address this gap. A vignette study published in 2015 by Swinburn et al estimated utility values for relapsed and refractory Hodgkin lymphoma and sALCL based on the general population in 7 countries using the time trade-off method.<sup>32</sup> Although the mean utilities reported by Swinburn et al varied by country, the combined global values overall are lower than those from ECHELON-2 for comparable health states, perhaps because different patient populations were evaluated (newly diagnosed for ECHELON-2 vs relapsed/refractory for Swinburn et al).

### Limitations

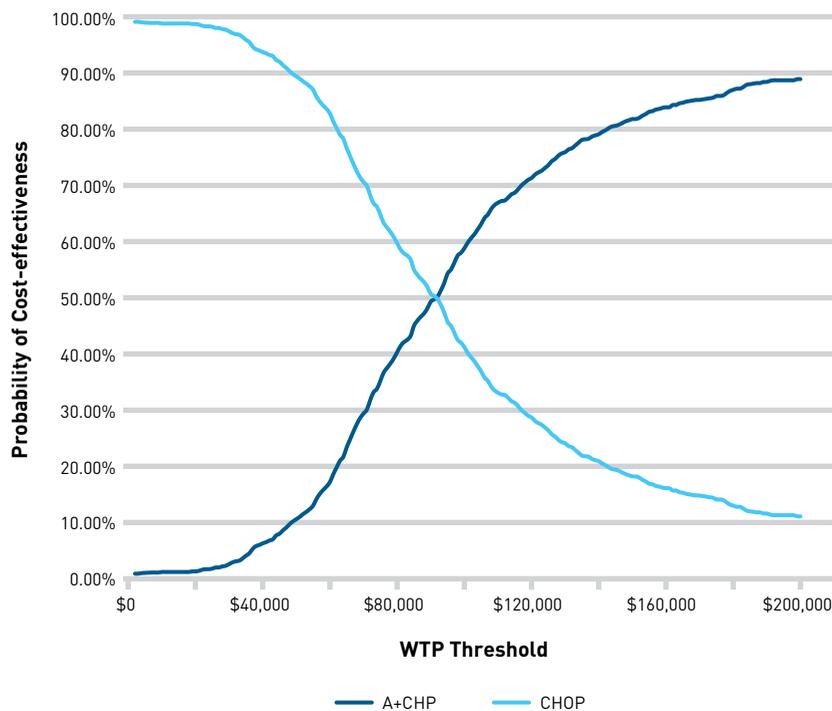
Overall, the current analysis was designed to closely reflect the clinical outcomes observed in ECHELON-2. This allows the most valid extrapolation of the trial findings but does reduce the generalizability for clinical practice that might differ substantially from the protocol followed in ECHELON-2. For example, in clinical practice, patients may follow different treatment pathways depending on

**FIGURE 3.** Probabilistic Sensitivity Analysis Cost-effectiveness Results

**A.** Cost-effectiveness Plane (incremental outcomes)



**B.** Cost-effectiveness Acceptability Curve



A+CHP indicates brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; WTP, willingness-to-pay.

factors such as PTCL subtype, response to prior treatments, disease severity, and age. Although patients could receive radiotherapy, chemotherapy, or SCT following frontline therapy for various reasons, the impact of subsequent treatment on clinical outcomes was not explicitly modeled because ECHELON-2 was not powered to detect such effects. In addition, although real-world receipt of SCT is usually determined by a patient’s response to treatment, it varies by individual and practice. The current approach assumed that the observed survival data from ECHELON-2 represented the subsequent treatments received in the trial per se. Given the limited clinical information available for this disease area, which is characterized by heterogeneous characteristics, we believe that the benefit of maximizing use of the ECHELON-2 trial data outweighs the limitations of this approach.

The current analysis considered only direct healthcare expenditures from the perspective of a US commercial payer. For a new treatment, it may be meaningful to also conduct an analysis from a societal perspective. This requires considering information not captured by the trial, such as patient out-of-pocket medication expenses and reduced productivity loss for patients and caregivers resulting from improved survival, which might have a considerable impact on the results.

**CONCLUSIONS**

Based on the ECHELON-2 trial data, this analysis found that, for patients with previously untreated CD30-expressing PTCL, treatment with brentuximab vedotin in combination with CHP was cost-effective in comparison with CHOP. ■

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**Authorship Information:** Concept and design (DZ, MR, JL, JF, AK); acquisition of data (TF, MR, MF, TM, SR); analysis and interpretation of data (TF, DZ, MR, JL, MF, TM, SR, JF, AK); drafting of the manuscript (TF, DZ, MR, JL, MF, TM, SR, JF, MH, AK); critical revision of the manuscript for important intellectual content (TF, DZ, MR, JL, MF, TM, SR, JF, MH, AK); statistical analysis (JL); model construction (MH); and supervision (DZ, AK).

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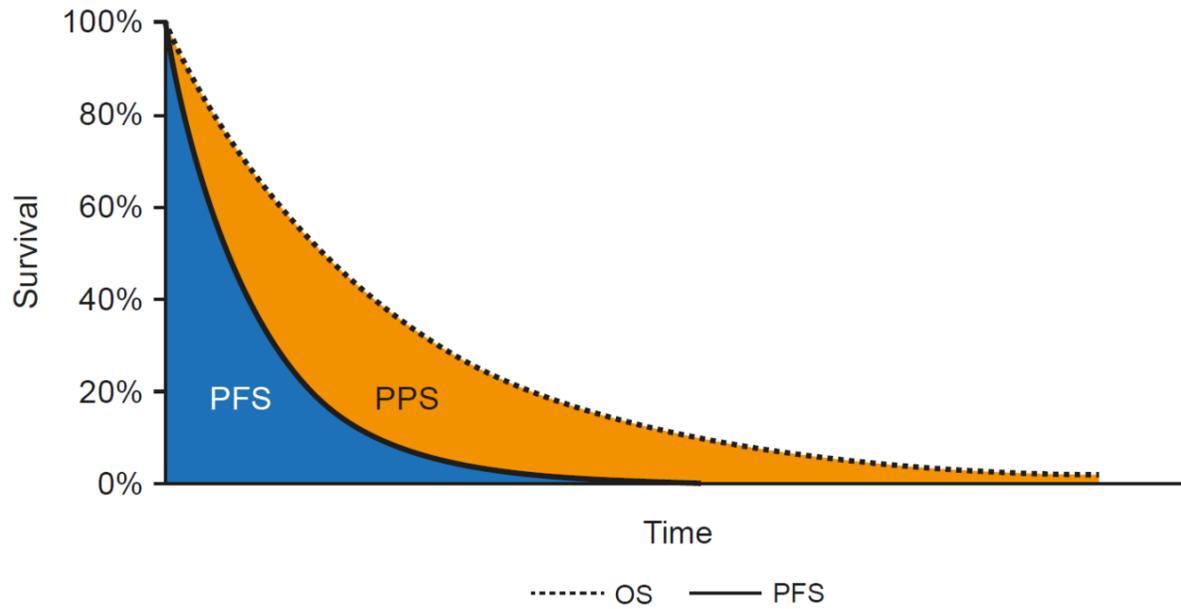
**eAppendix Table. Medication Costs**

	<b>Medication Cost per Pack or Vial (\$)</b>	<b>Dose per Pack or Vial (mg)</b>	<b>Mean Dose per Cycle (mg)</b>	<b>Medication Cost per Cycle (\$)</b>	<b>Administration Cost per Cycle (\$)</b>	<b>Cost per Cycle (\$)</b>
A+CHP						
Brentuximab vedotin 1.8 mg/kg	7662	50	150	22,986	454	23,440
Doxorubicin 50 mg/m <sup>2</sup>	64	200	200	64	454	518
Prednisone 100 mg	33	5000	500	3	0	3
Cyclophosphamide 750 mg/m <sup>2</sup>	569	1000	2000	1138	454	1592
CHOP						
Doxorubicin 50 mg/m <sup>2</sup>	64	200	200	64	454	518
Prednisone 100 mg	33	5000	500	3.26	0	3.26
Vincristine 1.4 mg/m <sup>2</sup>	11	2	4	21	454	475
Cyclophosphamide 750 mg/m <sup>2</sup>	569	1000	2000	1138	454	1592

A+CHP indicates brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone;

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

**eAppendix Figure.** Diagrammatical Representation of the AUC Methodology



AUC indicates area under the curve; OS, overall survival; PFS, progression-free survival; PPS, postprogression survival.