CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Brentuximab (Adcetris) for Hodgkin Lymphoma - Resubmission

February 21, 2018

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding brentuximab vedotin (Adcetris) for Hodgkin Lymphoma (HL) (post-ASCT consolidation). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding brentuximab vedotin (Adcetris) for HL (post-ASCT consolidation) conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from a patient advocacy group; input from the Provincial Advisory Group; and input from registered clinicians.

The systematic review is fully reported in Sections 6. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on brentuximab vedotin (Adcetris) for HL (post-ASCT consolidation), a summary of submitted Provincial Advisory Group Input on brentuximab vedotin (Adcetris) for HL (post-ASCT consolidation), and a summary of submitted Registered Clinician Input on brentuximab vedotin (Adcetris) for HL (post-ASCT consolidation) are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of brentuximab vedotin (BV) (Adcetris) for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with HL at increased risk* of relapse or progression.

*The definition of increased risk of post-ASCT relapse or progression is based on the AETHERA trial: refractory to frontline therapy, relapsed less than 12 months following frontline therapy, or relapse at greater or equal to 12 months with extranodal involvement.

BV (Adcetris®) is a CD30-directed antibody-drug conjugate. BV is comprised of: (1) brentuximab, an antibody specific for CD30, (2) monomethyl auristatin E (MMAE), an agent that induces target cell death, and (3) a synthetic protease-cleavable linker that attaches MMAE to brentuximab and releases the agent in the target cells. BV has a Health Canada indication that reflects the requested patient population for reimbursement. BV has been issued marketing authorization for the post-autologous stem cell transplant (ASCT) consolidation treatment of patients with HL at increased risk of relapse or progression. The recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks. As per the Health Canada indication, BV treatment should be initiated within 4-6 weeks post-ASCT or upon recovery from ASCT and continued until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Trial

One randomized controlled trial was identified that met the selection criteria of this review.[1] AETHERA is an ongoing, double-blind, randomized phase 3 trial comparing brentuximab vedotin and best supportive care (BSC) to placebo plus BSC as early consolidation treatment after ASCT in patients with HL at high-risk for disease progression.

High-risk was defined in the trial as the presence of at least one of three possible risk factors for disease progression post-ASCT, including:

a) primary refractory HL defined as failure to achieve complete remission (as determined by investigator),
b) relapsed HL with an initial remission duration of <12 months, or
c) presence of extranodal involvement at the start of pre-ASCT salvage chemotherapy.

Only patients with complete or partial remission, or stable disease following pre-ASCT salvage chemotherapy were randomized. Patients and treating investigators were blinded to treatment assignment, while data-analysts performing efficacy analyses were not. Upon disease progression, patients in the placebo group had the option to receive brentuximab vedotin as part of a separate clinical study. The median number of treatment cycles received by patients was 15 (range, 1 to 16) in both trial arms. Dose reductions were required in 32% and 3% of patients receiving brentuximab vedotin and placebo, respectively. A total of 85 patients (52%) in the placebo group discontinued on study and received subsequent anti-cancer therapy. Seattle Genetics and Takeda Pharmaceuticals International funded the trial and reported involvement in all aspects of trial conduct.

The primary outcome was progression-free survival by independent review (PFS-IR). PFS-IR was performed by an independent review facility. Progression-free survival by investigator assessment (PFS-IA) was also assessed and analysed as an a priori sensitivity analysis. For both PFS endpoints, disease progression was determined with CT imaging. PET imaging was performed at the discretion of investigators but not used in the determination of disease status. Investigator assessment of disease progression (PFS-IA) guided all treatment decisions and administration of any new anti-cancer therapy. After 24 months, patients were followed for survival and disease status by clinical assessment only every 6 months until trial closure (PFS-IA). The secondary outcomes of the trial included overall survival (OS), safety, and quality of life (QOL).

A total of 329 patients were randomized in AETHERA; 165 were assigned to the brentuximab vedotin group and 164 to the placebo group. The treatment groups were generally well balanced with respect to baseline patient characteristics. Trial patients were generally young (median age 32-33 years) with an ECOG performance status of 0 or 1. The majority of patients had refractory HL or had relapsed within 12 months of receiving first-line treatment. Approximately one third of patients presented with extranodal disease at the time of salvage therapy. Patients' best response to salvage chemotherapy was as follows: 37% of patients had complete remission, 34% had partial remission, and 28% had stable disease, with 45% of patients receiving at least two salvage therapies.

At the time of the primary efficacy analysis all patients had discontinued study treatment. Fifty-one patients (31%) in the brentuximab vedotin group and 85 patients (52%) in the placebo group went on to receive some form of anti-cancer therapy post-progression.

Limitations

Overall, the AETHERA trial was well conducted owing to its design features (double-blind, placebo-controlled) and a robust assessment of the primary outcome (independent central review). The trial did have some limitations, however, which include:

- Appropriately, the sample size of the trial was determined prospectively and based on a power calculation that included a PFS event rate of 202, which provided 80% power to detect an HR=0.677 with a one-sided alpha=0.025. The statistical analysis plan was changed after a planned analysis showed a low event rate at 24 months in both treatment groups. The low event rate may have been related to the inclusion of a proportion of patients with lower risk disease (15% of patients had one risk

factor upon trial entry and patients with PD were excluded). The final analysis occurred after all scheduled CT scans had been performed, at which time the PFS event rate was 135. This change reduced the power of the trial and cannot eliminate the possibility that the observed treatment effect may be inflated, as lower power has been shown to exaggerate true treatment effects that are moderate to large in magnitude.[2-4]

- The updated efficacy analyses performed after three and four years of patient follow-up have limitations; therefore, these results should be interpreted within this context, specifically:
    - Three-year PFS-IR data reflect event rates based on unscheduled CT scans performed as clinically indicated after 24 months and submitted to the independent review facility at the discretion of the investigator, and therefore, do not include the scans of all patients remaining on trial.
    - Three- and four-year PFS-IA data reflect event rates based on clinical assessment only.
- The use of subsequent anti-cancer therapies after disease progression, including brentuximab vedotin, differed between the treatment groups and thus confounds the assessment of OS (OS is likely underestimated in the trial) and also precludes making any inferences about the optimal timing of consolidation treatment (early versus after PD).
- The higher incidence of peripheral neuropathy and the larger proportion of dose reductions that occurred in the brentuximab vedotin treatment group may have introduced bias into the PFS assessment by investigator (favouring brentuximab vedotin treatment) since these occurrences had the potential to unblind treatment assignment.
- Subgroup analyses performed of the primary outcome were considered exploratory and therefore were not controlled for type 1 error arising from multiple testing, and some patient subgroups included a small number of patients (patients with stable disease, relapse ≥12 months, aged ≥45, and presence of B symptoms after first-line therapy). The treatment estimates obtained for subgroups therefore may be unreliable and should be interpreted with caution.
- QOL data are confounded by the crossover nature of the trial since assessments were performed regardless of disease progression and receipt of subsequent anti-cancer therapy. These confounders make quantifying the effect of brentuximab vedotin on QOL difficult.

A brief summary, highlighting the key outcomes of the trial, is provided in Table 1. All efficacy analyses were performed by intent-to-treat and the safety analysis included all patients who received at least one dose of study medication. The EQ-5D (EuroQoL 5-Dimensions) was used to measure health-related QOL during treatment and follow-up phases of the trial.

Efficacy

After a median follow-up time of 30 months, PFS-IR was significantly longer in patients treated with brentuximab vedotin compared to placebo, with an improvement in PFS of approximately 19 months with brentuximab vedotin compared with placebo (42.9 months versus 24.1 months, Table 1). The PFS benefit was evident among all patient subgroups

examined; however, it was not statistically significant in all subgroups. PFS-IA was also improved in the brentuximab vedotin group (HR=0.50, 95% CI, 0.36 to 0.70; p-value not reported). Updated analyses of PFS-IA showed the treatment benefit was maintained after three and four years of follow-up.[5,6]

The interim analysis of OS demonstrated no difference between treatment groups. The data are currently immature, with the final analysis of OS data expected in 2020, which is approximately ten years after the first patient was treated.

In both treatment groups EQ-5D utility index scores worsened over time,[7] with worse scores observed in the brentuximab vedotin group compared to placebo. At most assessment periods, however, the mean differences in index scores between treatment groups were small (<-0.07), except at months 15 and 18, where they met the minimal clinically important difference (MCID) of 0.08. During the treatment phase, mean differences in index scores did not exceed the MCID at any treatment cycle, but were worse in the brentuximab vedotin group compared to placebo. Patients experiencing disease progression in both the brentuximab vedotin and placebo groups showed worse mean EQ-5D index scores compared to patients who did not have disease progression; the MCID was exceeded from months 15 to 24 in the brentuximab vedotin group and months 9 to 24 in the placebo arm. In patients with and without peripheral neuropathy in the brentuximab vedotin group, mean differences in EQ-5D index scores did not exceed the MCID at any time point.

Harms

The most common treatment-emergent adverse events, of any grade, observed in patients treated with brentuximab vedotin were neutropenia (78%),[8] peripheral sensory neuropathy (56%), thrombocytopenia (41%),[8] and peripheral motor neuropathy (23%); the percentage of patients with these events at grade 3 or higher, were 39%, 10%, 6%, and 6%, respectively. Serious adverse events occurred in 25% of patients treated with brentuximab vedotin and 13% of patients treated with placebo.[9]

The incidence of peripheral neuropathy in the trial, including sensory and motor, was analyzed more extensively using a standardized MedDRA query (SMQ)-based analysis.[i 1] Treatment-emergent peripheral neuropathy occurred in 67% (n=112) and 19% (n=31) of patients in the brentuximab vedotin and placebo groups, respectively. The median time-to-onset of peripheral neuropathy events was 13.7 weeks in the brentuximab vedotin group. The majority of these events were sensory and low severity in nature. Peripheral neuropathy led to treatment discontinuation in 23% of patients (n=38) and dose reductions or delays in 31% (n=51). Considering all patients with peripheral neuropathy (n=112), 85% (n=95) experienced resolution of symptoms, with a median time-to-resolution of 23.4 weeks.

Deaths

During the treatment phase of the trial there was one patient death in the brentuximab vedotin group. The patient died within 30 days of receiving the last dose of study drug from treatment-related acute respiratory distress syndrome (ARDS) associated with pneumonitis.

At the time of primary analysis, 17% (n=28) of patients in the brentuximab vedotin group and 16% (n=25) of patients in the placebo group had died on study. The majority of deaths

[i] MedDRA SMQ analysis includes: peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, muscular weakness, hypoesthesia, gait disturbance, neuralgia, amyotrophy, decreased vibratory sense, hyporeflexia, peroneal nerve palsy, and sensory disturbance.

were deemed disease-related (i.e., unrelated to study treatment) in both treatment groups (11% in both groups). There were nine (5%) and seven (4%) treatment-related deaths in the brentuximab vedotin and placebo groups, respectively. Of note, during the follow-up period there were 85 patients (52%) in the placebo group who received subsequent therapy after disease progression.

Table 1: Highlights of key outcomes in the AETHERA trial.[1,5-7,10,11]

Key Outcomes	AETHERA Treatment Groups	
	Brentuximab Vedotin (n=165)	Placebo (n=164)
Efficacy[I]		
Primary Outcome - PFS by Independent Review[A]		
Median in months (95% CI)	42.9 (30.4-42.9)	24.1 (11.5-NE)
HR (95% CI)*	0.57 (0.40-0.81)	
p-value	p=0.0013	
Key Secondary Outcome - OS		
Median in months (95% CI)	Not reached	Not reached
HR (95% CI)*	1.15 (0.67-1.97)	
p-value	p=0.6204	
Sensitivity analysis - PFS by investigator assessment[A]		
Median (95% CI)	Not reached	16 (NR)
HR (95% CI)*	0.50 (0.36-0.70)	
3-year median in months (95% CI)[5,10]	Not reached	15.8 (8.5-44)
HR (95% CI)*[5,10]	0.52 (0.37-0.71)	
4 year median in months (95% CI)[6,11]	Not reached	15.8 (9-49)[11]
HR (95% CI)*	0.52 (0.37-0.71)[11]	
QOL - EQ-5D[J]**, n**	n=154	n=157
EQ-5D mean at 12 months	0.76	0.83
Mean difference (95% CI)[B]	-0.07 (-0.13 to -0.02)	
EQ-5D mean at 24 months	0.73	0.77
Mean difference (95% CI)[B]	-0.04 (-0.12 to 0.04)	
Harms, n (%)	(n=167)	(n=160)
Grade ≥3	93 (56)	2 (1)
TRAE (any grade)	163 (98)	142 (89)
WDAE	54 (33)	10 (6)

Abbreviations: AE - adverse event; CI - confidence interval; EQ-5D - EuroQoL 5-Dimensions; HR - hazard ratio; QOL - health-related quality of life; NR - not reported; PFS = progression-free survival; OS - overall survival; TRAE - treatment-related adverse event; WDAE - withdrawal due to adverse event.

Notes:
*HR < 1 favours brentuximab vedotin group.
[A] PFS by independent review reflects regular scheduled CT scans up to 24 months, with CT scans performed at the discretion of investigators beyond 24 months. PFS by investigator assessment reflects CT scans/clinical assessment up to 24 months, with scheduled clinical assessments only beyond 24 months.
[B] The minimal clinically important difference (MCID) for the EQ-5D is 0.08 (based on analyses using UK-based weights).

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Lymphoma Canada (LC), provided input on brentuximab vedotin (BV) for the consolidation treatment of patients with post-ASCT high-risk Hodgkin Lymphoma (HL).

From a patient's perspective, there are a number of symptoms associated with HL that impact quality of life, which include fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough and mental/emotional problems such as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by HL, including ability to work, personal image, family obligations, intimate relations friendships and ability to attend school. Most respondents indicated that current treatment options (e.g. ABVD, GDP, BEACOPP and MOPP/COPP, radiation, stem cell transplant, BV and surgery) work well in managing their HL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many respondents; specifically, fatigue, hair loss, nausea/vomiting, "chemo-brain", peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility and lung damage were the most commonly reported. LC also indicated that respondents experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). In the current sample LC noted that 93% of respondents had been treated with at least one line of conventional chemotherapy and 16% of respondents had received ≥ 3 lines of therapy. Patients expressed that they seek individualized treatment options that will offer disease control and remission, ideally with fewer side effects than current treatments. Respondents' expectations about the new drug under review were most importantly "effectiveness" followed by "minimal side effects" or "less side effects than current treatments". Respondents who have experience with BV reported several side effects with peripheral neuropathy being one of the more significant concern of patients. Some of the most common side effects reported with BV included fatigue, peripheral neuropathy, nausea/vomited, diarrhea, muscle or joint pain, itching, and constipation. The majority responded that BV had overall positively impacted their health and well-being and that they would take BV again, if their doctor thought it was the best choice. Notably, as reported by patients, BV had a positive impact on the ability to work and attend school, spend time with family and participate in activities or travel.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- There is no maintenance option for this subgroup of patients
- Treatment intent is not curative
- Benefits of treatment with brentuximab vedotin in earlier stages of disease compared to later stage
- Re-treatment with brentuximab vedotin
  Sixteen cycles of brentuximab vedotin may be difficult to tolerate due to the neuropathy adverse effect

Economic factors:

- Large incremental cost per patient

Registered Clinician Input

Two clinician inputs were provided: One from an individual oncologist and one joint submission from four oncologists.

Overall the clinicians providing input agreed that this indication and funding will only affect a very small number of patients and that observation only is the current approach in this setting. One key benefit identified by the clinicians providing input was the encouraging progression free survival

gain. An increase in adverse events was identified as key harm with the most typical side effects being peripheral neuropathy and hematologic toxicity. However, clinician input suggested that these toxicities can be mitigated with careful dose modification and/ or dose delay and that the trial demonstrate that BV consolidation therapy can be given safely in patients after autologous stem cell transplantation (ASCT). An unmet need was identified by the clinicians providing input as observation only is the current approach in this setting. The clinicians providing input agreed that availability of brentuximab vedotin (BV) as consolidation therapy in the post-ASCT setting may reduce the number of recurrences and hence the need for BV therapy for relapsed disease post-ASCT. The clinicians also noted that the testing for CD30 is typically assessed in the immunohistochemistry panel used for HL diagnostics and is typically positive.

Summary of Supplemental Questions

The pCODR Clinical Guidance Panel and the pCODR Methods Team identified the following supplemental issue:

- **Review of post-hoc analyses of the AETHERA trial data related to time-to-treatment failure, time-to-next treatment, and PFS analyzed by number of risk factors.**

Post-hoc analyses of the AETHERA trial data were performed to gain insight into whether the PFS improvement with brentuximab vedotin was clinically meaningful in the absence of an OS and QOL benefit; and further, to assess if subgroups of the trial population, based on number of risk factors present, benefited more or less from consolidation treatment. The post-hoc analyses performed included assessment of time-to-treatment failure (TTF), time-to-next treatment (TTNT), and PFS analyzed by number of risk factors. These analyses were exploratory and should be interpreted with caution since the trial was not powered to detect relative differences between the treatment groups for these additional endpoints and subgroups. Refer to Section 7 for an explanation of outcome definitions and the biases associated with each analysis.

Time-to-treatment failure was similar between the treatment groups (median TTF of 11 months in both groups; HR=0.86, 95% CI, 0.65-1.13 by IR assessment).[11] The Kaplan Meier curves demonstrated TTF favoured brentuximab vedotin during the first 12 months following randomization (treatment phase) with no difference between groups during the follow-up phase of the trial.

There were 52% (n=85) and 31% (n=51) of patients in the placebo and brentuximab vedotin treatment groups, respectively, who received subsequent treatment.[11] The median TTNT was 20.9 months in the placebo group and not reached in the brentuximab vedotin group, demonstrating a reduced risk of receiving subsequent treatment with brentuximab vedotin (HR=0.45 (95% CI, 0.32-0.64).

Eligibility criteria for the AETHERA trial required patients have at least one of the following risk factors: refractory HL, relapsed HL within <12 months of frontline treatment, and extranodal involvement at the time of pre-ASCT relapse. In the post-hoc risk factor analysis,[1,6,12-14] additional risk factors for which data were available for all patients were also examined and included best response to most recent salvage therapy, B symptoms at relapse, and two or more prior salvage therapies. The results showed a trend for improved PFS (by independent review) by increasing number of risk factors [for patients with ≥1, ≥2, and ≥3 risk factors, HRs were 0.57 (95% CI, 0.40-0.81), 0.49 (95% CI, 0.34-0.71), and 0.43 (0.27-0.68), respectively] but not for patients with only one risk factor (HR=1.65, 95% CI, 0.60-4.55).[11,14] The small number of patients in the one risk factor subgroup (n=49) should be considered when interpreting the result for this subgroup, as small sample size can produce an unreliable and inprecise treatment estimate.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for brentuximab vedotin HL (post-ASCT consolidation).

Domain	Factor	Evidence AETHERA trial[1]	Generalizability Question	CGP Assessment of Generalizability
Population	Performance status	The AETHERA trial limited eligibility to patients with an ECOG performance status of 0 or 1. ECOG 0: n=184 (56%) ECOG 1: n=144 (44%) ECOG 2: n=1 (1%) Exploratory subgroup analyses were conducted by performance status, and showed a PFS-IR benefit in both groups of patients (ECOG 0 and 1), that was statistically significant in patients with an ECOG of 1 (HR not reported).	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Performance status of Canadian patients receiving BV post-ASCT would be expected to be the same as the patients enrolled in the AETHERA trial (i.e. ECOG PS 0-1).
	Age	The AETHERA trial limited to patients ≥18 years. Median age was approximately 33 years. Age <45: n=272 (83%) Age ≥45: n=57 (17%) There were eight patients in the trial who were 60 years and older (five in brentuximab vedotin group and three in the placebo group). Exploratory subgroup analyses were conducted for patients <45 and ≥45 years old, and showed a PFS-IR benefit in both groups that was statistically significant in patients <45 years (HR not reported). The result in the ≥45 age group may reflect small sample	Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?	Appropriate to extend these results to the adolescent population undergoing ASCT there was no upper age limit to enrolment and most Canadian Centres would offer ASCT to patients up to age 70.

Domain	Factor	Evidence AETHERA trial[1]	Generalizability Question	CGP Assessment of Generalizability
		size.		
	Organ dysfunction	The AETHERA trial limited eligibility to patients with adequate liver, kidney, and bone marrow function.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Treatment is suitable for patients with less than complete blood count/bone marrow recovery after ASCT; safety in patients with significant liver and renal dysfunction has not yet been established; most patients who proceed to ASCT would not have significant organ dysfunction
	Earlier stages of disease (pre-ASCT)	Trial eligibility criteria required that patients have received high-dose chemotherapy followed by ASCT prior to randomization, among other requirements. Therefore, the trial did not include patients pre-ASCT.	Did the exclusion of patients with e*arlier stages of disease (p*re-ASCT) limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The intent of the AETHERA trial is for the use of brentuximab vedotin as post-ASCT consolidation, and not pre-ASCT use. Results are not generalizable to the pre-transplant setting.
	Ethnicity or Demographics	The AETHERA trial was conducted in 13 countries (Europe and US) and did not include Canadian patients. Included patients were primarily white (94%).	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	No reason to believe that the results would be different in the Canadian population of patients undergoing ASCT for relapsed or refractory HL.

Domain	Factor	Evidence AETHERA trial[1]	Generalizability Question	CGP Assessment of Generalizability
	BV re-treatment	a) Eligibility criteria used in the AETHERA trial required that patients had <u>not</u> previously received BV. b) The AETHERA trial assessed BV consolidation treatment post ASCT.	a) Are the results of the trial generalizable to patients who have received and responded to BV pre-ASCT? b) If BV was available in the maintenance post-ASCT setting, would re-treatment (i.e., for relapse) be possible in patients that have received BV maintenance post-ASCT?	a) Patients who respond to BV as part of their induction regimen pre-ASCT, who are therefore BV sensitive, are also likely to benefit from post-ASCT BV. b) There is some evidence that patients who have responded to BV may respond to re-treatment with acceptable neurotoxicity; these data could be applied to patients who have received BV maintenance therapy post-ASCT, and such treatment would be reasonable if checkpoint inhibitor therapy is not available.[15]
	High risk of relapse post-ASCT	High risk of relapse post-ASCT is defined by the Submitter according to status following front-line therapy: refractory, relapse within 12 months, or relapse at greater or equal to 12 months with extranodal disease.	Is the Submitter's definition of highrisk of relapse post-ASCT generalizable to the Canadian practice?	It is reasonable to assume that patients with other high-risk features than those defined in the AETHERA trial would derive similar PFS benefit from BV consolidation therapy. Additional high-risk features include: B symptoms or stage IV at relapse, less than a complete response to salvage therapy as assessed by CT or PET scan, or relapse in a prior radiation field.
	Low risk of relapse post-ASCT	Patients were excluded from the trial if they did not meet at least one of three possible risk factors for disease progression post-ASCT, including: primary refractory HL, relapse within 12 months, or relapse at greater or equal to 12 months with extranodal disease.	Are the results of the trial generalizable to other patient populations such as patients who do not have primary refractory HL, or who have relapsed after 12 months without extranodal disease?	As BV has activity in HL that has relapsed after ASCT and often multiple other regimens, it is safe to assume that similar magnitude of benefit may be seen in patients without the high-risk features that defined study eligibility; that is, patients who relapse >12 months postASCT, and without extranodal disease would benefit to a

Domain	Factor	Evidence AETHERA trial[1]	Generalizability Question	CGP Assessment of Generalizability
				similar degree.
Intervention	Treatment Intent	Adjuvant treatment intent.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	Use of ASCT in relapsed or refractory HL is with curative intent, and the addition of BV post-ASCT would therefore be adjuvant. BV is already approved for use in the palliative treatment of relapse AFTER ASCT.
	Dose and Schedule	1.8 mg/kg intravenous infusion over 30 minutes every 3 weeks up to 16 cycles.	If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	BV as given in the trial reflects standard dose and schedule as used in Canada.
	Number of treatment cycles	Median number of treatment cycles 15 (up to 16 cycles allowed in the consolidation phase).	Are the number of treatment cycles allowed in the trial applicable in the Canadian setting?	Number of cycles given in the AETHERA trial is acceptable in Canadian practice.
Comparator	Standard of Care	Placebo intravenous infusion over 30 minutes every 3 weeks up to 16 cycles.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Standard of care in Canada is no further systemic chemotherapy after ASCT; some patients may benefit from involved field radiation, but this would not be replaced by BV.
Outcomes	Appropriateness of primary and secondary outcomes	Primary: PFS by PFS-IR Secondary: OS, safety, and QOL)	Were the primary and secondary outcomes appropriate for the trial design?	Primary and secondary outcomes are appropriate; PFS is an accepted surrogate endpoint for OS in the setting of salvage therapy and ASCT and the most appropriate primary endpoint for such a trial (due to long post-progression survival and availability of other therapies).
Setting	Countries participating in the trial	The AETHERA trial was conducted in the following countries: Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Russia, Spain, Serbia,	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada?	No reason to believe that the results achieved in this trial in patients in other countries would be different from those attainable with the same therapy in Canada.

Domain	Factor	Evidence AETHERA trial[1]	Generalizability Question	CGP Assessment of Generalizability
		Spain, UK, and US. No Canadian sites participated in the trial.		
	Location of the participating centres	The AETHERA trial was conducted primarily in academic centres.[11]	If the trial was conducted only in academic centres are the results applicable in the community setting?	Results would be generalizable to community practice settings, as BV is currently given there to patients who relapse after ASCT.
	Supportive medications, procedures, or care	All patients in the AETHERA trial received BSC that comprised of infection prophylaxis for herpes simplex virus, varicella-zoster virus, and pneumocystis jiroveci post-ASCT, as well as growth factor and blood product support.	Are the supportive medications, procedures, or care used with the intervention in the trial the same as those used in Canadian clinical practice?	Supportive therapies used in this trial are the same as those used in Canadian clinical practice.
Abbreviations: ASCT - autologous stem cell transplant; BSC - best supportive care; BV - brentuximab vedotin; CT scan - Computerized Tomography scan; ECOG - Eastern Cooperative Oncology Group; HL - Hodgkin Lymphoma; OS - overall survival; PET scan - Positron Emission Tomography; PFS - progression free survival; PFS-IR - PFS by independent review; QOL - quality of life.				

1.2.4 Interpretation

Burden of Illness and Need

Hodgkin lymphoma is an uncommon, distinctive lymphoma subtype, affecting approximately 900 Canadians a year. The median age at diagnosis is between 35-40 years; approximately 10% of cases affect adolescents and 15% of cases are diagnosed in those age >65. There are approximately 160 deaths per year from HL in Canada.[16] While the majority of patients with HL are cured with initial therapy, up to 30% of patients with advanced stage disease (Ann Arbor stage 3 and 4) and 10-15% with limited disease will experience disease progression during or relapse after primary therapy.[17] For the majority of patients up to age 65, second-line therapy including high-dose chemotherapy and autologous stem cell transplantation (ASCT) represents a standard treatment approach with the potential for cure. Approximately 50% of those undergoing ASCT will be alive and relapse-free five years after treatment and are generally considered cured.[18] It is estimated that 75-100 autologous transplants are performed in Canada each year for this indication (Dr. K Paulson, Health Sciences Centre and CancerCare Manitoba, Winnipeg, Manitoba: personal communication, 2016 Feb 16).

Despite the possibility of cure for patients with progression or relapse following frontline therapy, there are a number of risk factors that reduce the likelihood of progression-free survival (PFS) after ASCT. These include primary refractory HL or relapse early (within 1 year of completion of therapy); advanced stage or involvement of extranodal sites of disease, relapse in a previous radiation field and less than a complete response to second-line (salvage therapy) as assessed by CT scan or FDG-PET scanning.[19,20] Patients who experience relapse after ASCT have very limited

treatment alternatives—especially those who relapse early, within the first year of transplant—and are generally treated with palliative intent. After failure of ASCT at least 85% of patients will receive some form of chemotherapy; prior to the availability of brentuximab vedotin (BV) this would have been platinum-based in many centres or single agent treatments.[17]

Most relapses following ASCT occur within the first year, and prognosis is particularly poor for those with recurrence within 6 months of transplant (median survival 15 months vs 36 months for those relapsing after 6 months).[21] Median survival of 122 patients who experienced relapse following ASCT at Princess Margaret Hospital prior to 2008 (40% within 6 months of transplant) was 27 months.[22]

There are no treatments following ASCT that have been shown to improve progression-free or overall survival for those at high risk of disease recurrence. Some centres employ involved field irradiation post-transplant to nodal areas of bulky disease at the time of initiation of second-line chemotherapy, but for most patients, no additional treatment is offered to maintain remission, and observation with best supportive care is an appropriate comparator for interventions after ASCT.

Effectiveness

Brentuximab vedotin (BV) is a CD30 chemoimmunoconjugate which is active and well tolerated in the treatment of relapsed HL, among patients who have experienced disease progression following ASCT. In a large phase 2 trial, the response rate to BV at a dose of 1.8 mg/kg every 3 weeks was 75% and complete response rate 34%; median progression-free survival was 6 months and median duration of complete response 20.5 months], with a low incidence of grade 3-4 toxicities (grade 3 neutropenia 14%, grade 4 6%; other grade 3-4 events $\leq$ 2%). The most common ($\geq$ 10%) treatment-related adverse events were peripheral sensory neuropathy (42%; grade 3 in 8%), nausea (35%), fatigue (34%), neutropenia (19%) and diarrhea (18%). The only other toxicity grade 3 or greater was neutropenia (Gr 3: 14%, Gr 4: 6%). With longer follow-up, resolution of neuropathy was reported in 76% of affected patients and at least some improvement in 14%.[23]

The AETHERA phase 3 trial[1] randomized 329 patients with HL at high risk of relapse following ASCT (treatment 165, control 164), and demonstrated that maintenance therapy with BV every 3 weeks for up to 16 treatments resulted in an improvement in progression-free survival compared to placebo infusions (hazard ratio [HR] 0.57, 95% CI 0.40–0.81; p=0.0013). Median progression-free survival (by independent review of events) was improved among patients treated with BV: 42.9 months (95% CI 30.4–42.9) compared with 24.1 months (11.5–not estimable) for those in the placebo group. Progression free survival at 2 years was improved in patients receiving BV according to independent review (63% vs 51%) and according to investigator assessment (65% vs 45%). In pre-planned subset analyses, consistent benefit was seen in PFS across a number of patient subgroups including those with initial remission <12 months, more than two prior lines of chemotherapy, and those with B symptoms at relapse.

After a median follow-up of 30 months, there was no difference in overall survival between the two study arms.[1] Similar numbers of patients received subsequent single or multi-agent chemotherapy for treatment of relapse after ASCT; however 44% of patients in the placebo arm received BV as subsequent therapy vs 5% of patients on the BV arm.

The CGP acknowledge that while it is too early to evaluate the true survival benefit, the PFS results compare favourably to currently available observation and best supportive care options. The CGP agreed with the Clinician groups providing input to this submission, that the PFS improvement of the magnitude observed in the AETHERA trial is highly clinically relevant. As most relapses in patients post-ASCT occur within 2 years, one would expect that patients continuing in remission beyond 2 years are likely to be cured. Current application of salvage therapy and ASCT

for relapsed and refractory HL is based on two randomized trials[24,25] with significant improvement in PFS compared to salvage therapy alone; because relapsed HL is an uncommon malignancy, trials to date are not large enough to be powered for overall survival.

Assessment of patient reported outcomes using the EQ-5D instrument showed a modest decrease in quality of life in both arms. Patients experiencing disease progression in both the BV and placebo arms showed lower mean EQ-5D index scores compared to patients who did not have disease progression. Although time trade off scores did not exceed the minimally important difference between treatment arms, scores were lower in the BV arm from month 9 through 18 post-randomization. The decrease in quality of life as compared to baseline could not be associated with treatment-emergent peripheral neuropathy at any time point.[7] Overall, the AETHERA data did not show a negative effect of BV on quality of life compared to placebo. The CGP considered that the quality of life observed in the trial was in line with patient group inputs for this submission. Patients indicated that "effectiveness" was the most import expectation regarding brentuximab vedotin consolidation therapy, which might be reflective of the lower mean EQ-5D scores in patients experience progression compared to remission. Of all patients who were treated with BV consolidation therapy, about one third felt that BV had a minimally negative impact on their quality of life and day-to-day activities while the other two thirds of patients felt that it either had a minimally positive or positive impact. Less than one third of patients indicated that peripheral neuropathy was a significant concern.

Safety

Grade 3 adverse events occurred in 56% of patients receiving BV and 32% of patients receiving placebo. Maintenance therapy with BV after ASCT results in more treatment-emergent peripheral neuropathy (BV 79% vs placebo 18%), although most events were grade 1 or 2. Both peripheral sensory neuropathy (all grades 56% vs 16%, grade 3 10% vs 1%) and motor neuropathy (all grades 23% vs 2%, grade 3 6% vs 1%) were more frequent in patients treated with BV. Peripheral neuropathy led to dose reductions or delays in 31% of patients and of those 23% discontinued treatment. This highlights the fact that while development of grade 3 neuropathy mandated discontinuing treatment according to the study protocol, grade 1 or 2 neuropathy frequently results in dose reduction or stopping treatment in this patient population. Of 112 patients in the BV group, 95 (85%) had resolution or improvement of neuropathy symptoms, with a median time to resolution of 23.4 weeks (range 0.1–138). Neutropenia grade $\geq$3 was reported more frequently in the BV arm (39% vs 10%) but did not result in treatment discontinuation, and there was only one episode of febrile neutropenia.[1] Growth factor support with G-CSF was given to 25% of patients in the BV arm and 11% of those receiving placebo. Pulmonary toxicity was uncommon and observed in 8 patients (5%) and 5 patients (3%) in the BV and placebo groups, respectively; 2 patients in the BV arm died of pulmonary complications. Overall The CGP concluded that these results indicate the BV can be given safely as consolidation therapy and toxicities can be mitigated with careful dose modification and/or dose delay. The CGP agreed with the clinicians providing input for this submission that the improvement in PFS outweighs the safety concerns. This was echoed by patient input suggesting that the majority of patients which have been treated with BV consolidation therapy considered that side effects were tolerable and would take this drug again if their doctor thought it was their best choice.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to BV consolidation treatment following ASCT for relapsed and refractory Hodgkin lymphoma at high risk for disease progression. This is based on a single high quality randomized placebo controlled trial, which showed a significant improvement in progression-free survival, with an acceptable degree of

treatment-related toxicity and no significant decrement overall in quality of life, compared to patients receiving placebo infusion. Benefit was seen among patients with increasing numbers of risk factors for treatment failure. Hematologic toxicities were manageable. Peripheral neuropathy was the main reason for treatment delay or discontinuation, and generally recovered within 12-16 weeks of stopping BV.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The follow-up of the AETHERA trial was short and no difference in overall survival has yet been observed; this may be in part attributed to the use of brentuximab vedotin in the control arm following disease progression, in addition to multiple other therapies that may be received by patients who experience relapse after ASCT, including allogeneic stem cell transplantation.
- Progression-free survival improvement of the magnitude observed in the AETHERA trial is highly clinically relevant and sufficient to warrant a change in practice. While long-term remission has been reported among patients who obtain a complete response with BV following *relapse after* ASCT, this likely occurs in less than 5% of all patients who receive BV in the relapse setting. PFS is the most important initial endpoint in the evaluation of therapies for the palliation of advanced, multiply relapsed HL. Current application of salvage therapy and ASCT for relapsed and refractory HL is based on two randomized trials with significant improvement in PFS compared to salvage therapy alone; because relapsed HL is an uncommon malignancy, trials to date have not large enough to be powered for overall survival.
- In addition to patients who met the eligibility for the AETHERA trial, the CGP felt that patients who had other high risk features at the initiation of salvage therapy (B symptoms or stage IV at relapse, less than a complete response to salvage therapy as assessed by CT or PET scan, or relapse in a prior radiation field), would also derive similar PFS benefit from BV consolidation treatment. Based on a post-hoc risk factor analysis conducted on the AETHERA trial data, patients who had durations of first remission longer than 1 year or who otherwise relapse without risk factors may be less likely to benefit from BV consolidation treatment. [6,14] However, the small number of patients in the risk factor subgroup (n=49) should be considered when interpreting the results, as small sample size can produce an unreliable and inprecise treatment estimate. There might have been simply too few patients and events to detect a PFS benefit in the patient group with only 1 risk factor.
- Patients who have received BV as a component of salvage therapy prior to ASCT and who had a response to this therapy, would also likely derive benefit from post-ASCT consolidation therapy with BV.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma Clinical Guidance Panel (CGP). It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Hodgkin lymphoma (HL) is an uncommon but distinct lymphoma subtype that typically presents in young adults, but is seen in both children and adolescents, and those over the age of 60 years. HL accounts for approximately 8-10% of all diagnoses of lymphoma. The median age at diagnosis in most reported series is 35-40 years and approximately 15% are older than 60 years. There are approximately 900 new cases of Hodgkin lymphoma in Canada each year and approximately 160 Canadians will die annually from this disease.[16]

2.2 Accepted Clinical Practice

Approximately two thirds of patients with HL will present with localized disease (stage I and II according to the Ann Arbor classification), and are generally treated with combination chemotherapy and involved field radiation (IFRT). Those who present with advanced stage disease (stage III and IV) and some with stage I and II who present with constitutional ("B") symptoms are usually managed with combination chemotherapy alone. In Canada, the standard regimen is ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for 6 or 8 cycles; patients with large tumour masses at presentation (areas of bulky disease >10 cm), may also receive IFRT. Despite the excellent complete remission rates with current ABVD chemotherapy (>95% for localized and >80% for advanced stage disease), relapse is experienced by up to 10-15% of patients with early and 30% of those with advanced disease.[26,27]

Management of refractory and relapsed HL

Patients who experience treatment failure (disease progression on or relapse after primary therapy) are usually candidates for second-line (sometimes called salvage) chemotherapy followed by high-dose chemotherapy supported by autologous stem cell transplantation (ASCT).[17,28] The outcomes of this second treatment are most favourable in those with first remission duration longer than one year, lower disease burden at relapse (lower stage, absence of B symptoms) and a complete response to second line chemotherapy assessed by either CT scan or FDG-PET scanning. Approximately 50% of those undergoing ASCT will be alive and relapse-free five years after treatment and are generally considered cured. ASCT is not considered appropriate treatment for older patients (those older than 70 years), especially those with significant medical co-morbidities. The results of ASCT are poor in patients with HL that is refractory to initial therapy (progression during or within 3 months of completion of treatment), those with less than a complete response to salvage therapy or those who require more than one second-line regimen prior to progressive disease following salvage chemotherapy.[29] Other risk factors that portend a greater likelihood of disease progression following ASCT that have been reported are the presence of extranodal lymphoma, relapse in a prior radiation field, and the presence of advanced stage and B symptoms at relapse.[17,19] For those who experience disease progression following ASCT, the prospects of long term remission with additional therapy are very limited, and the duration of disease control (as measured by progression free survival) is very short with currently available therapies. The median survival following relapse after ASCT is approximately 2 years, and is shorter for patients who relapse within 6 months of transplant and for those transplanted with disease that was refractory to primary therapy.[21]

There are few reports of prospective evaluation of strategies aimed at improving the outcome of patients with HL at high risk of relapse following ASCT. Josting et al conducted a study of high-

dose sequential therapy that included patients with early relapse and stage IV HL following primary therapy. Patients responding to DHAP salvage treatment were randomized to receive sequential high dose cyclophosphamide, methotrexate and etoposide before intensive therapy and ASCT, or to proceed directly to transplant. The addition of sequential high dose treatment prior to ASCT did not improve progression free or overall survival compared to ASCT alone.[30] Morschhauser et al performed a prospective single arm trial of tandem (double) ASCT for patients with HL that was refractory to primary therapy, or relapsed with at least two high risk features (relapse within 12 months, within a prior radiation field or with stage III/IV disease). Seventy percent of primary refractory or high risk patients (105/150) were able to complete tandem ASCT: five year freedom from treatment failure (FFTF) (intention to treat) was 46% and overall survival 57%. Patients with a single risk factor (n=95) underwent standard single ASCT: in this group, five year FFTF was 73% and overall survival 85%.[19] These results, appear favourable compared to other reports in high risk HL, refractory patients; randomized data from use of tandem ASCT are not available.

Treatment of patients with relapse after ASCT has generally been for relief of symptoms and employs single agent chemotherapy. The most common drugs used are vinblastine, gemcitabine or vinorelbine, which are given every other week (vinblastine) or weekly intravenously for 3 weeks out of 4 each month, unless hematologic toxicity mandates a shorter cycle of 2 doses every 3 weeks (vinorelbine, gemcitabine).[31-33] Reported response rates range from 20-40% and progression-free survival from 6-8 months. Combination regimens, such as, gemcitabine, vinorelbine and liposomal doxorubicin (GVD) may achieve response rates that appear higher than with the single agents above, but progression-free survival is similar and hematologic toxicity of this combination therapy is significant.[34] Due to restrictions on reimbursement in many provinces, this regimen is not generally available in Canada, and other combination regimens such as COPP (cyclophosphamide, vincristine, procarbazine, prednisone) are used if patients have good performance status and bone marrow reserve. Involved field radiation is beneficial for those with localized relapse outside of a previous radiation field, but there are few long-term survivors.[35]

In some centres, for young patients who have relapsed after ASCT with a long disease-free interval (more than one year), and a good response to additional salvage therapy, reduced intensity allogeneic stem cell transplantation from an HLA-matched sibling donor or unrelated matched donor is sometimes used. While some centres have reported good short-term outcomes with this strategy, these results have not always been reproducible, and many centres consider that allogeneic transplantation post-ASCT is still investigational. Overall, allogeneic transplantation considered appropriate therapy for approximately 10-15% of patients who relapse after ASCT.[36-39] Otherwise, treatment following relapse after ASCT is generally symptomatic and considered palliative.

Brentuximab Vedotin (BV) is now approved for the treatment of patients with HL after failure of ASCT or at least two prior multi-agent chemotherapy regimens.[40] In a large phase II trial in heavily pretreated patients (median number of prior regimens 3.5, range 1-11), the response rate to BV at a dose of 1.8 mg/kg every 3 weeks was 75% and complete response rate 34%; median progression-free survival was 6 months and median duration of complete response 20.5 months.[23] In most provinces, BV has become the treatment of choice as initial therapy for relapse after ASCT because of its favourable toxicity profile (grade 3 neutropenia 14%, grade 4 6%; other grade 3-4 events $\leq$ 2%). Direct comparison to other agents has not been carried out, but in a correlated survival analysis of a subgroup of patients who had received systemic therapy for relapse following ASCT and before treatment with BV, PFS was significantly longer with brentuximab vedotin compared to the prior systemic treatment (7.8 vs 4.1 months, $p<.001$).[23] The favourable toxicity profile of this single agent and the durability of remissions in heavily pre-treated patients[41] suggests that it is an attractive agent to consider for testing in a consolidation strategy post-ASCT to reduce disease recurrence for patients who are at high risk of relapse.

2.3 Evidence-Based Considerations for a Funding Population

It is estimated that 75-100 ASCTs are performed in Canada each year for this indication (Dr. K Paulson, Health Sciences Centre and CancerCare Manitoba, Winnipeg, Manitoba: personal communication, 2016 Feb 16).

In the trial reported by Moskowitz et al, patients with HL refractory to primary therapy, relapse within one year of completion of therapy or extranodal involvement at time of treatment failure were randomized following completion of ASCT to brentuximab vedotin consolidation (1.8mg/kg IV every 3 weeks for 16 doses) or placebo infusion. These risk factors for treatment failure are present in approximately 50% of patients who undergo ASCT in Canada, although the exact proportion may vary according to the referral practice of the transplant centre. Variables associated with risk of early treatment failure post-ASCT are easily identifiable clinical factors, and to date do not require testing for specific pathologic or molecular abnormalities.

BV targets CD30, a surface membrane protein expressed on the majority of HL Reid-Sternberg cells at diagnosis and at relapse. It would be expected that patients who are considered candidates for BV would have pathological confirmation of the presence of CD30 on initial biopsy or one taken at any time after disease recurrence.[42]

2.4 Other Patient Populations in Whom the Drug May Be Used

It is anticipated that BV consolidation therapy could be considered an appropriate treatment following ASCT for patients with primary refractory and early relapsed HL, and patients with stage IV disease at recurrence after one year of complete remission. It is possible that clinicians may generalize these results to patients with lower risk of recurrence post-ASCT, since the consequence of relapse in this patient population is significant, with the probability of curative therapy (allogeneic stem cell transplant; involved field radiation for local recurrence) in most patients being very small.

Based on a post-hoc risk factor analysis conducted on the AETHERA trial data, it may be that patients who had durations of first remission longer than 1 year or who otherwise relapse without risk factors may be less likely to benefit from BV consolidation treatment.[6,14]However, the small number of patients in the risk factor subgroup (n=49) should be considered when interpreting the results, as small sample size can produce an unreliable and inprecise treatment estimate. There might have been simply too few patients and events to detect a PFS benefit in the patient group with only 1 risk factor.

In addition to patients who met the eligibility for the AETHERA trial, it is reasonable to assume that patients with other high risk features (B symptoms or stage IV at relapse, less than a complete response to salvage therapy as assessed by CT or PET scan, or relapse in a prior radiation field), would derive similar PFS benefit from BV consolidation therapy.

Current trials are evaluating the impact of the addition of brentuximab vedotin to primary therapy in patients with advanced stage HL, and as a component of induction therapy prior to transplant, either in combination or in the setting of poor response to standard platinum-based salvage treatment. Patients enrolled in the trial reported by Moskowitz, et al, had not been previously exposed to BV.[1]

The CGP addressed PAG input seeking clarity on BV-retreatment options after BV consolidation treatment and subsequent relapse. The CGP noted that in most provinces, BV has become the treatment of choice as initial therapy for relapse after ASCT. If BV consolidation therapy would be

considered an appropriate treatment following ASCT, fewer patients would be likely to recur post ASCT and this would reduce the need for BV therapy of relapse post ASCT. For patients experiencing relapse after BV consolidation therapy, there is some evidence to suggest patients who have responded to BV may respond to re-treatment with acceptable neurotoxicity; these data could be applied to patients who have received BV maintenance therapy post-ASCT, and such treatment would be reasonable if checkpoint inhibitor therapy is not available.[15]

The CGP discussed that the OS analysis in the AETHERA trial was immature and confounded by the high cross over rate of patients in the placebo group to brentuximab vedotin. Importantly this precluded a conclusion on the optimal timing of brentuximab (that is as consolidation therapy versus treatment after progression).

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Lymphoma Canada, provided input on brentuximab vedotin (BV) for the consolidation treatment of patients with post-ASCT high-risk Hodgkin Lymphoma (HL).

Lymphoma Canada (LC) conducted two anonymous online surveys, which were directed via e-mail to patients and caregivers registered on the LC database. Responses were collected from June 5th to 30th, 2017. An additional survey of patients who have direct experience with BV was conducted from July 26th - August 10th, 2017. Links were also made available via LC Twitter and Facebook accounts, as well as through HL patient forums, other HL-dedicated social media pages and groups, and international lymphoma organizations own contacts.

Overall, LC received input from a total of 97 patients and 15 caregivers. Please see the table below listing participants by country and those with/without BV experience who participated in the surveys. Of those patients who provided their demographic information, 51% (n = 40/78) live in Canada, 70% (n = 52/74) are female, and 84% (n = 62/74) are between 20-59 years-old, see Tables 1 and 2.

Table 1: Respondents by Country

Respondents	CAN	USA	UK	EU	Other	Skipped	Total
Patients WITH BV experience	3	6	2	2	0	2	15
Patients WITHOUT BV experience	37	5	10	6	7	17	82
Caregivers	5	2	4	1	0	3	15

Table 2: Gender and age of survey and interview respondents

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	Did not answer	Female	Male	Did not answer
Patients WITH BV experience	1	9	3	0	2	9	4	2
Patients WITHOUT BV experience	2	32	18	9	21	43	18	21
Caregivers	0	2	7	3	3	9	3	3
Total	**3**	**43**	**28**	**12**	**26**	**61**	**25**	**26**

The surveys designed by LC had a combination of multiple choice, rating and open-ended questions. There was also skipping logic that was built into the surveys allowing respondents to be asked questions that were only relevant to them. The open-ended responses to surveys and quotes obtained from interviews that reflected the sentiment of a majority were included verbatim to provide a deeper understanding of patient and caregiver perspectives.

From a patient's perspective, there are a number of symptoms associated with HL that impact quality of life, which include fatigue or lack of energy, enlarged lymph nodes, drenching night sweats, itching, persistent cough and mental/emotional problems such as anxiety and difficulties with concentrating. Respondents also reported on aspects of their life negatively impacted by HL, including ability to work, personal image, family obligations, intimate relations friendships and ability to attend school. Most respondents indicated that current treatment options (e.g. ABVD, GDP, BEACOPP and MOPP/COPP, radiation, stem cell transplant, BV and surgery) work well in managing their HL symptoms. LC noted that toxicity associated with their previous treatments were of great concern to many respondents; specifically, fatigue, hair loss, nausea/vomiting, "chemo-brain", peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility

and lung damage were the most commonly reported. LC also indicated that respondents experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). In the current sample LC noted that 93% of respondents had been treated with at least one line of conventional chemotherapy and 16% of respondents had received ≥ 3 lines of therapy. Patients expressed that they seek individualized treatment options that will offer disease control and remission, ideally with fewer side effects than current treatments. Respondents' expectations about the new drug under review were most importantly "effectiveness" followed by "minimal side effects" or "less side effects than current treatments". Respondents who have experience with BV reported several side effects with peripheral neuropathy being one of the more significant concern of patients. Some of the most common side effects reported with BV included fatigue, peripheral neuropathy, nausea/vomited, diarrhea, muscle or joint pain, itching, and constipation. The majority responded that BV had overall positively impacted their health and well-being and that they would take BV again, if their doctor thought it was the best choice. Notably, as reported by patients, BV had a positive impact on the ability to work and attend school, spend time with family and participate in activities or travel.

Please see below for a summary of specific input received from LC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Hodgkin Lymphoma

According to LC, 74% (n = 71/96) of patient respondents who completed a survey were a teenager or young adults (13-39 years-old) when they were diagnosed with HL.

LC indicated that respondents with HL reported that the symptoms associated with their disease could significantly impact their quality of life. Of particular note, the most commonly reported symptoms include: fatigue or lack of energy (72%), enlarged lymph nodes (67%), drenching night sweats (43%), itching (42%), and persistent cough (40%). Other symptoms affecting quality of life for > 10% of respondents included unexplained weight loss, loss of appetite, trouble breathing, fever and chills and chest pain. Ongoing fatigue (constant, lasting fatigue or waves of fatigue) was also reported by 63% of survey respondents.

LC also examined which aspects of patients' lives had been negatively impacted by HL. Notably, the majority of patient respondents (61%) indicated that HL had a negative impact on their ability to work. Additional responses are summarized in Table 3.

Table 3: Effect of HL on day-to-day life of patients (Total responses = 83)

Aspect of life NEGATIVELY impacted by HL	# of respondents	% of respondents
Ability to work	51	61%
Personal Image	39	47%
Family obligations	38	46%
Intimate relations	31	37%
Friendships	30	36%
Ability to attend school	13	16%
None of these	11	13%

Many respondents also reported that their quality of life was negatively affected by mental and emotional problems associated with their disease. The most common symptom/ problem effecting quality of life was anxiety/worry (48%). Other symptoms are listed in Table 4.

Table 4: Effect of HL on current quality of life of patients (Total responses = 88)		
Symptom or problem related to HL	# of respondents	% of respondents
Anxiety/worry	42	48%
Problems concentrating	32	37%
Loss of sexual desire	29	33%
Stress of diagnosis	25	29%
Difficulty sleeping	25	29%
Memory loss	25	29%
Depression	20	23%
None of these	10	11%

Below are some of the key comments gathered from three (n = 3) patient respondents to help illustrate the impact of HL on patients' quality of life:

"I experience more fatigue than I used to and although I'm able to work, I'm exhausted at the end of the day. Exercise is difficult to do on a weekday." Female, 21-39, USA

"I immediately lost my job, as I worked in an environment not safe for someone with a compromised immune system. I had to give up my study at university, and both devastated me. I was very fit, but now if I try to exercise at the same level I become exhausted very easily. It's very hard." Female, 21-39, Australia

"I almost feel like I suffer from Post-traumatic stress disorder (PTSD) from this experience. I went into remission for about a year and then had a recurrence. I'm always worried it might come back. If I smell alcohol swabs - like they use before taking blood or administering chemo - my mind goes right back to treatment days - and that's more than 25 years ago." Female, 50-59, Canada

3.1.2 Patients' Experiences with Current Therapy for Hodgkin Lymphoma

LC reported that all patient respondents had previously received treatment or were currently undergoing treatment. Of the 73 patients who provided responses regarding their treatments, 93% had been treated with at least one line of conventional chemotherapy and 16% of respondents had received ≥3 lines of therapy. The most common conventional chemotherapy regimen received was ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) (81%), followed by GDP (gemcitabine, dexamethasone, cisplatin) (10%), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) (8%), and MOPP/COPP (mechlorethamine/cyclophosphamide, vincristine, procarbazine, prednisone) (5%). Other types of treatment individuals had received included radiation therapy (50%), autologous stem cell transplant (26%), surgery (10%), allogeneic stem cell transplant (4%), nivolumab (1%), and CAR-T therapy (1%).

In terms of treatment phases, LC indicated that of respondents, indicating their treatment phase, 66% are in remission following their most recent line of therapy, 30% have been in remission for longer than 5 years and 15% of respondents had previously relapsed after one or more lines of therapy.

When LC asked respondents to rate their level of agreement with the statement "*My most recent therapy could manage my HL symptoms*", on a 10-point scale; 10=strongly agree, 72% of respondents gave a rating of ≥7, indicating that their most recent treatment was able to manage most or all of their HL symptoms.

Side effects of current treatments

Regarding side effects of current treatments, LC noted that toxicity associated with their previous treatments was of great concern to many respondents. The most common side effects patient respondents experienced during their HL treatments are listed in Table 5. In particular, respondents noted that fatigue (95%; n = 70/74), hair loss (91%; n = 67/74) and nausea/vomiting (88%; n = 65/74), were the most difficult side effects to tolerate. Many respondents (n = 66) also experienced one or more late or long-term treatment-related side effect (lasting longer than 2 years or appearing later than 2 years after the end of treatment). Fatigue (65%), "chemo-brain" (59%), peripheral neuropathy (32%), loss of menstrual periods (23%), thyroid dysfunction (18%), sterility (15%) and lung damage (14%) were the most commonly reported.

Table 5: Side effects of current HL therapies

Side effect	# of respondents (total = 74)	% of respondents
Fatigue	70	95%
Hair loss	67	91%
Nausea/vomiting	65	88%
Mouth sores	51	69%
Peripheral neuropathy	39	53%
Low platelets	36	49%
Anemia and/or neutropenia	34	46%
Diarrhea	33	45%
Skin rashes/severe itching	29	39%
Loss of menstrual periods	26	35%
Breathing difficulties	23	31%
Infections	23	31%
Back pain	22	30%
Cough	20	27%
Irregular heartbeat	15	20%
Bowel obstruction	12	16%
Viral reactivation (e.g. shingles)	9	12%

LC asked respondents to rate the NEGATIVE impact of previous treatments on specific aspects of their quality of life. The aspect of treatment that most significantly impacted patients was treatment related fatigues, see Table 6.

Table 6: Negative impact of specific aspects of treatment on quality of life

Aspect of treatment	Weighted average	% who rated 7-10 (significant impact)	% who rated Not applicable	Total number of responses
Treatment-related fatigue	7.5	80%	0%	74

Table 6: Negative impact of specific aspects of treatment on quality of life				
Aspect of treatment	Weighted average	% who rated 7-10 (significant impact)	% who rated Not applicable	Total number of responses
Ability to tolerate treatment	6.6	59%	0%	74
Infusion reaction	6.3	55%	8.5%	71
Infusion time	6.3	54%	6.8%	74
Number of clinic visits	6.2	59%	0%	73
Number of infections	4.3	22%	10%	73
Frequency of infections	4.0	15%	11%	74

LC also asked respondents to rate the NEGATIVE impact of previous treatments on specific aspects of day-to-day life, see Table 7. The aspects of day-to-day life most significantly impacted by treatment were activities (76%), travel (75%) and ability to work (69%), see Table 7.

Table 7: Negative impact of previous treatments on day-to-day live				
Aspect of life	Weighted average	% who rated 7-10 (significant impact)	% who rated Not applicable	Total number of responses
Ability to attend	8.86	24%	66%	74
Ability to work	7.89	69%	14%	74
Travel	7.47	75%	7%	73
Activities	7.35	76%	1%	74
Intimate relations	7.08	68%	5%	71
Family obligations	6.14	55%	3%	74
Friendships	5.76	54%	0	74

Below are some of the key comments by four (n = 4) respondents regarding experience with current treatments for HL:

"The chemotherapy I received before and with my bone marrow transplant put me into premature menopause (I'm in my 20s) and that has negatively affected my intimate relations." Female, 21-39, USA

"My short term memory from chemo is very bad on some days, which affects me at work and home. I'm constantly tired, I work full time and have 4 children. One of whom I was pregnant with when diagnosed." Female, 21-39, UK

"I was unable to finish the first semester of nursing school at the time. I was unable to help coach basketball because of low self-esteem from hair loss and fatigue. Did not really want to go places and visit friends because of hair loss." Female, under 20, USA

"Unable to work due to long-term side effects of chemotherapy. Pain and muscle weakness. I'm constantly exhausted, dialed from my stem cell transplant, have issue taking care of my toddler without help." Female, 21-39, USA

LC also examined how difficult it was for patients to access treatment in their own community. The majority, 79% (n = 59/74) of individuals were able to access treatment in their own community. For those who could not access treatment in their own community (n = 15), 73% lived in a community without a cancer centre, or the treatment was not available in their province (20%) or country (7%). The most commonly reported financial impact of treatment was absence from work or school 69% (n = 48/70). Other financial burdens included parking (40%), cost of medications (30%), and travel to and from appointments (29%).

Below are key comments by two (n = 2) patients about the financial impact of treatment.

"Medications cost me over $80,000 over the last 7 years to help deal with side-effects of chemo. I am now on long-term disability, because I cannot work." Female, 20-39, Canada

"Absence from work caused me to get into debt, first and second time." Female, 50-59, UK

Furthermore, LC enquired about patients' choice of treatment. Respondents were asked how important it is for them and their physician to have a choice of deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 signifying not important as long as there is at least one treatment choice, to 10 signifying extremely important to have choice of treatment. LC reported that 82% (n = 70/85) of respondents rated the importance as 7, 8, 9 or 10, with a weighted average of 8.5. Of 76 respondents, 55% reported that they would take a drug with known side effects, potentially serious, if their doctor recommended it was the best choice for them (No = 3%; I don't know = 43%). LC noted that these results could indicate that many patients would be willing to tolerate significant side effects if the treatment is effective.

3.1.3 Impact of Hodgkin Lymphoma and Current Therapy on Caregivers

There were fifteen (n = 15) caregiver respondents who completed the survey to address the impact on day-to-day life and challenges caregivers face with this type of cancer. Respondents were asked to rate on a scale of 1 (no impact) to 10 (very significant impact) how caring for the person with HL has impacted their day-to-day life. Please see Table 8 below for significant impacts on caregivers' daily activities.

Table 8: Effects of caregiving on quality of life

Daily activity (Total responses = 15)	7-10 (significant impact)
Ability to concentrate	10 (67%)
Contribute financially to household	9 (60%)
Travel	9 (60%)
Attend to household chores	8 (53%)
Volunteer	8 (53%)
Spend time with family and friends	7 (47%)
Exercise	5 (33%)
Fulfill family obligations	4 (27%)

Below are some key comments as described by three (n = 3) caregiver respondents:

- *"My 20 year old son was diagnosed with hl. This last year has been a nightmare. Family, friends don't call or even know what to say. We are left alone, while everyone's life continues."* Female, 40-59, USA

- *"I was pregnant with twins while caring for my man and we did what we had to do and we stuck together. It was hard to be away from our older kids when he was receiving treatments but nurses in oncology dept. are angels."* Female, 20-39

- *"I've become a caregiver. Scheduling my daughters' appointments, managing her medicine. Taken over her care. She was in between jobs at diagnosis and her prospects for a new job has significantly decreased. We support her financially now."* Female, over 60, Canada

3.2 Information about the Drug Being Reviewed

Patient Expectations for Brentuximab Vedotin

Based on no experience using the drug:

Patients expressed that they seek individualized treatment options that will offer disease control and remission, ideally with fewer side effects than current treatments. Regarding respondents' expectations about the new drug under review "effectiveness" was most important to 70% (n = 31/44) of individuals. A large number of patients (57%) also reported that "minimal side effects" or "less side effects than current treatments" was very important to them.

What Experiences Have Patients Had To Date with Brentuximab Vedotin

Based on no experience using the drug:

LC reported that 15 patient respondents had experience with BV. Of the 13 respondents who provided their demographic information, 77% were younger than 40 years-old and 69% were female. Six (n = 6) respondents had received BV as consolidation therapy following an auto-SCT; seven (n = 7) as salvage therapy, alone or in combination with other drugs; one (n = 1) as consolidation therapy prior to an auto-SCT and one (n = 1) as first-line therapy.

Table 9 below shows the characteristics of patients who have experience with BV including demographics.

Table 9: HL patients with BV/Adcetris experience

Patient	Gender	Age	Location	Year of dx	Year started BV
1	Female	< 20	UK	2016	2017
2	Female	20-39	Canada	2014	2015
3	Female	20-39	USA	2011	2011
4	Female	20-39	Greece	-	2015
5	Female	20-39	USA	2016	2017
6	Female	20-39	Belgium	2015	2017
7	Female	20-39	Canada	2013	2016
8	Female	20-39	USA	2013	2014
9	Female	40-49	USA	2011	2013
10	Male	20-39	USA	2017	2017

Table 9: HL patients with BV/Adcetris experience					
Patient	Gender	Age	Location	Year of dx	Year started BV
11	Male	20-39	USA	2016	2017
12	Male	50-59	Canada	1985	2016
13	Male	50-59	UK	2008	2011
14	-	-	-	2015	-
15	-	-	-	2016	2017

In terms of previous treatments all fifteen (n = 15) patients had received at least 2 prior lines of conventional chemotherapy and 53% (n = 8/15) of patients had received 4 or more lines of therapy. Previous chemotherapy regimens included ABVD (n = 11), GDP (n = 5), BEACOPP (n = 2), GVD (n = 2), ESHAP (n = 2), Bendamustine (n = 2), COPP (n = 1), DHAP (n = 1), and Stanford V (n = 1). Eleven (n = 11) patients had undergone an autologous stem cell transplant, three (n = 3) had undergone an allogeneic stem cell transplant and four (n = 4) had received nivolumab. Three (n = 3) patients were still undergoing treatment with BV, three (n = 3) had completed the full course of treatment, one (n = 1) stopped treatment early due to intolerable side effects, and seven (n = 7) did not complete the full course of treatment because their HL did not respond to BV. One (n = 1) respondent skipped this question.

Side effects of BV

When LC asked about side effects experienced with BV all fifteen (n = 15) patient respondents reported experiencing side effects during treatment with BV. Peripheral neuropathy was reported as a significant concern by four (n = 4) out of fifteen (n = 15) respondents. Table 10 summarizes the most commonly experienced side effects.

Table 10: Side effects experienced with BV/Adcetris	
Side effect	Number of responses; n=14
Fatigue	10 (71.43%)
Peripheral neuropathy	8 (57.14%)
Nausea/vomiting	5 (35.71%)
Diarrhea	4 (28.57%)
Muscle or joint pain	4 (28.57%)
Itching	3 (21.43%)
Constipation	3 (21.43%)
Low blood counts	2 (14.29%)
Rash	2 (14.29%)
Cough	2 (14.29%)
Headache	2 (14.29%)
Fever	1 (7.14%)
Upper respiratory infection	1 (7.14%)
Infusion reactions	1 (7.14%)
Other	2 (14.29%)

Below are two quotes from 2 (n = 2) patient respondents that summarize significant concerns regarding peripheral neuropathy experienced from BV:

"…the neuropathy came on quite sudden and to the point where I didn't have any strength in my lower legs. I couldn't stand on my toes, I still to this day can't wiggle my toes like I used to and still battle numbness in my feet. They also get cold very quickly." Female, 20-39, Canada

"Felt cold all the time and wore sweatshirts and hats in summer. Tingling in fingers was beginning to get scary. Constant fear of permanent neuropathy." Male, 20-39, USA

LC also asked respondents if they would take BV again, if their doctor thought it was the best choice, knowing the potential side effects. The majority 79% (n = 11/14) responded "yes". When asked, on a scale of 1-10 (1= will not tolerate side effects; 10= will tolerate significant side effects), to what extent they are willing to tolerate the side effects of BV, 86% (n = 12/14) of respondents rated this question 7, 8, 9 or 10.

Impact on day-to-day life and quality of life

LC also asked respondents about patients' day-to-day life and quality of life with BV. Fourteen (n = 14) patients provided responses to this question. When asked how BV had changed their overall health and well-being, 57% (n = 8/14) patient respondents reported that the drug had a positive impact. For those who reported that BV did not have a positive impact on their health and well-being, treatment failure was the most common reason (n= 4/14) followed by significant side effects (n = 1/14) and no reason given (n = 1/14). Furthermore, LC asked respondents to rate on a scale of 1 (significant negative impact) to 10 (significant positive impact) how BV had impacted different areas of their life. The majority of patients reported that BV had a minimal positive or positive impact on their ability to work and attend school (n = 7/14 and n = 2/14, respectively), spend time with family and friends (n = 12/14 and n = 11/14, respectively), and participate in activities or travel (n = 10/14 and n = 9/14, respectively), see Table 11.

Table 11: Impact of BV/Adcetris on aspects of life

Aspect of life	Negative impact (rating = 1-4)	Positive impact (rating = 7-10)	Minimal impact (rating = 5-6)	Not applicable	Total responses	Weighted average
Work	4 (29%)	3 (21%)	4 (29%)	3 (21%)	14	6.29
School	1 (7%)	2 (14%)	0 (0%)	10 (79%)	13	9.15
Family	1 (7%)	4 (29%)	8 (57%)	1 (7%)	14	6.21
Friendships	1 (7%)	5 (36%)	6 (43%)	2 (14%)	14	6.57
Intimate relations	4 (29%)	5 (36%)	4 (29%)	1 (7%)	14	6.07
Activities	3 (21%)	5 (36%)	5 (36%)	1 (7%)	14	5.79
Travel	3 (21%)	6 (43%)	3 (21%)	2 (14%)	14	6.29

Below are some key comments described by four (n = 4) respondents when asked how BV changed their health and well-being:

"Changed it for the better. I am now in remission and have never been so that has overall helped me mentally and has bettered my wellbeing." Respondent - no demographic info reported.

"I am very happy with the outcome of the treatment I received. Obviously I would like to be able to feel my toes right now but I'm hopeful those nerves will come back. I had no problem living my life the way I wanted to." Female, 20-39, Canada

"…it has helped me to stay cancer free for 3 years and counting!" Female, 20-39, USA

"I am a healthy person now, I feel good and that part I am most thankful for. I'm thankful for the drug..." Female, 20-39, Canada

3.3 Additional Information

None provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- There is no maintenance option for this subgroup of patients
- Treatment intent is not curative
- Benefits of treatment with brentuximab vedotin in earlier stages of disease compared to later stage
- Re-treatment with brentuximab vedotin
- Sixteen cycles of brentuximab vedotin may be difficult to tolerate due to the neuropathy adverse effect

Economic factors:

- Large incremental cost per patient

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that there is currently no treatment available for consolidation post stem cell transplant and best supportive care is the appropriate comparator.

4.2 Factors Related to Patient Population

This subgroup of patients have no treatment options and are currently being observed and monitor for relapse or progression.

PAG noted that the trial had no overall survival advantage. PAG indicated the additional months of survival would be of value as the patients are generally younger. However, PAG noted that consolidation treatment with brentuximab vedotin is not curative, whereas allogeneic stem cell transplant is curative.

PAG indicated that the current treatment pathway is treatment with (1) combination chemotherapy (ABVD); (2) if relapsed or progression, ASCT; (3) if relapsed or progression, brentuximab vedotin. In some cases when a patient relapses or progresses after ASCT, allogeneic stem cell transplant may be an option. PAG is seeking information and clarity on the benefits of treatment with brentuximab vedotin in earlier stages of disease, as consolidation treatment post ASCT, compared to later stage when patient has relapsed or progressed after ASCT.

PAG is seeking information and guidance for patients who:

- have relapsed after 12 months, without extranodal disease

- received and responded to brentuximab vedotin prior to ASCT, would they be eligible to receive and respond to brentuximab vedotin as consolidation treatment post-ASCT
- received brentuximab vedotin for consolidation treatment and relapsed, would they be eligible to receive and respond to brentuximab vedotin again

PAG is recognizes that tumour groups may need to re-evaluate current treatment algorithms and eligibility criteria of other therapies for Hodgkin Lymphoma and post-ASCT consolidation treatment.

4.3 Factors Related to Dosing

The administration schedule of every three weeks only slightly increases the frequency of clinic visits as these patients already regularly seen in clinic for follow-up and observation.

4.4 Factors Related to Implementation Costs

PAG noted that drug wastage may become a significant barrier as only 50mg vials are available and patients may require up to four vials (180mg = 1.8mg/kg IV for 100kg patient) per treatment cycle. In addition, PAG noted that the drug has 24hr stability after reconstitution and vial sharing may be unlikely.

The infusion time for brentuximab vedotin is 30 minutes and frequency of administration is every three weeks. PAG noted that additional chemotherapy chair time is not required for monitoring post-infusion reactions and the infusion does not require intense nursing resources.

The incremental costs per patient is large, given that it is a new treatment for patients who previously received best supportive care and if all 16 cycles are administered.

4.5 Factors Related to Health System

As an intravenous drug, brentuximab vedotin would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of infusion related reactions. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients which is an enabler. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients.

Brentuximab vedotin is already used for other indications and health care professionals are familiar with its preparation, administration and monitoring for adverse events.

4.6 Factors Related to Manufacturer

The cost of brentuximab vedotin will be a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided: One from an individual oncologist and one joint submission from four oncologists.

Overall the clinicians providing input agreed that this indication and funding will only affect a very small number of patients and that observation only is the current approach in this setting. One key benefit identified by the clinicians providing input was the encouraging progression free survival gain. An increase in adverse events was identified as key harm with the most typical side effects being peripheral neuropathy and hematologic toxicity. However, clinician input suggested that these toxicities can be mitigated with careful dose modification and/ or dose delay and that the trial demonstrate that BV consolidation therapy can be given safely in patients after autologous stem cell transplantation (ASCT). An unmet need was identified by the clinicians providing input as observation only is the current approach in this setting. The clinicians providing input agreed that availability of Brentuximab vedotin (BV) as consolidation therapy in the post-ASCT setting may reduce the number of recurrences and hence the need for BV therapy for relapsed disease post-ASCT. The clinicians also noted that the testing for CD30 is typically assessed in the immunohistochemistry panel used for HL diagnostics and is typically positive.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for this Type of Cancer

The clinicians in both inputs agreed that there is currently no standard of care in the consolidation setting in relapsed or refractory Hodgkin Lymphoma (HL) post-ASCT. They noted that consolidation therapy with currently available and reimbursed therapies is not indicated in patients after ASCT. Observation would be the typical approach.

5.2 Eligible Patient Population

The clinicians in both inputs agreed that this indication and funding will only affect a very small number of patients. In general HL is an uncommon malignancy and relapses are not typical given the favourable cure rates with primary treatment. One group of clinicians estimated that less than 50% of HL patients are eligible for ASCT.

5.3 Identify Key Benefits and Harms with New Drug Under Review

The key benefit identified by all clinicians providing input was the encouraging progression free survival gain.

One clinician providing input noted that the majority of relapses in patients post ASCT occur within 2 years. Consequently one would expect that PFS curves with more than 2 years of follow-up should be stable and that patients continuing in remission at this point are at high likelihood of cure. While PFS was significantly improve in HL patients treated with BV, this PFS benefit was not associated with an OS advantage, as the trial was not powered to study this endpoint. Crossover with the experimental agent would be expected as BV is an approved therapy for relapses of HL post ASCT.

The clinicians in both inputs agreed that BV consolidation therapy is associated with an increase in adverse events with the most typical worrisome side effects including peripheral neuropathy and hematologic toxicity.

One clinician providing input suggested that these toxicities can be mitigated with careful dose

modification and/ or dose delay. The results of the trial demonstrate that this therapy can be given safely in the post-ASCT setting, if maintenance BV is used. The potential improvement in cure rate (based on improved PFS in this study) likely overweighs this concern.

One clinician providing input noted that availability of BV in the maintenance setting should reflect the patient population enrolled in the clinical trial.

5.4 Advantages of New Drug Under Review Over Current Treatments

The clinicians in both inputs identified an unmet need for a consolidation therapy after ASCT in patients with relapsed or refractory HL, as there is currently no standard of treatment for these patient beyond observation. They noted that BV consolidation therapy after ASCT would be able to fulfill that need for patients in this setting.

One clinician providing input noted that with long-term follow-up, approximately 50% of the typical post-ASCT HL population would be expected to relapse. Given the available RCT data, the clinician noted that BV consolidation therapy represented an obvious advantage. The clinician added that while patients at high risk of relapse post-ASCT have a particular high unmet need, the goal should be to improve the outcome of all patients proceeding through ASCT, given that ASCT is the last standard approach that is considered curative.

One group of clinicians noted that BV, as early consolidation therapy after ASCT in HL patients who were at risk of relapse or progression after ASCT, demonstrated substantial PFS benefit. The median PFS by independent review was 42.9 months (95% CI 30.4-42.9) in the BV-treated group, compared with 24.1 months (11.5-not estimable) in the placebo group. The median number of treatment cycles received in the study was 15 (up to 16 cycles allowed in the consolidation phase).

5.5 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians in both groups agreed that availability of BV as consolidation therapy in the post-ASCT setting would likely reduce the need for BV therapy for relapsed disease post-ASCT.

One clinician providing input noted that access to BV in Ontario is specifically limited to patients who have relapsed post-ASCT, based on the single arm registrational trial of BV in this patient population. It was noted that if BV was available in the maintenance post-ASCT setting, fewer patients would be likely to recur and this would reduce the need for BV therapy of relapse. The clinician providing input noted that a key clinical question would be the role of BV re-treatment (i.e., for relapse), in patients who have received BV maintenance post-ASCT. It was noted that this an unknown area and that there are few reports examining the role of BV re-treatment which demonstrate that the drug has reasonable efficacy.

5.6 Companion Diagnostic Testing

The clinicians in both inputs identified testing for CD30. One clinician noted that this test is typically assessed in the immunohistochemistry panel used for HL diagnostics and is typically positive.

5.7 Additional Information

The group of clinicians providing input noted that the subgroup analysis has no clear distinction between refractory and early relapsed disease states.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of brentuximab vedotin (Adcetris) as consolidation treatment after autologous stem cell transplant (ASCT) compared to standard therapy (observation with best supportive care) in adult patients with Hodgkin lymphoma (HL) at high-risk of relapse or progression post-ASCT. High-risk is defined by disease status after first-line therapy and includes primary refractory HL, relapse within 12 months, or relapse after 12 months with extranodal disease.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are indicated in bold.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

RCT	• Adult patients (≥18 years at time of ASCT)
	• Histologically confirmed classic HL
	• Received ASCT in previous 90 days
	• Considered high-risk for relapse/progression post-ASCT if ≥1 criteria** present:
	  ○ Refractory HL
	  ○ Relapsed within 12 months or progressive HL after first-line treatment
	  ○ Extranodal involvement at start of pre-ASCT salvage chemotherapy
		brentuximab vedotin	• Observation with best supportive care
			• Placebo
				• PFS
				• **OS**
				• Adverse Events
				  ○ Neuropathy
				• **QOL**

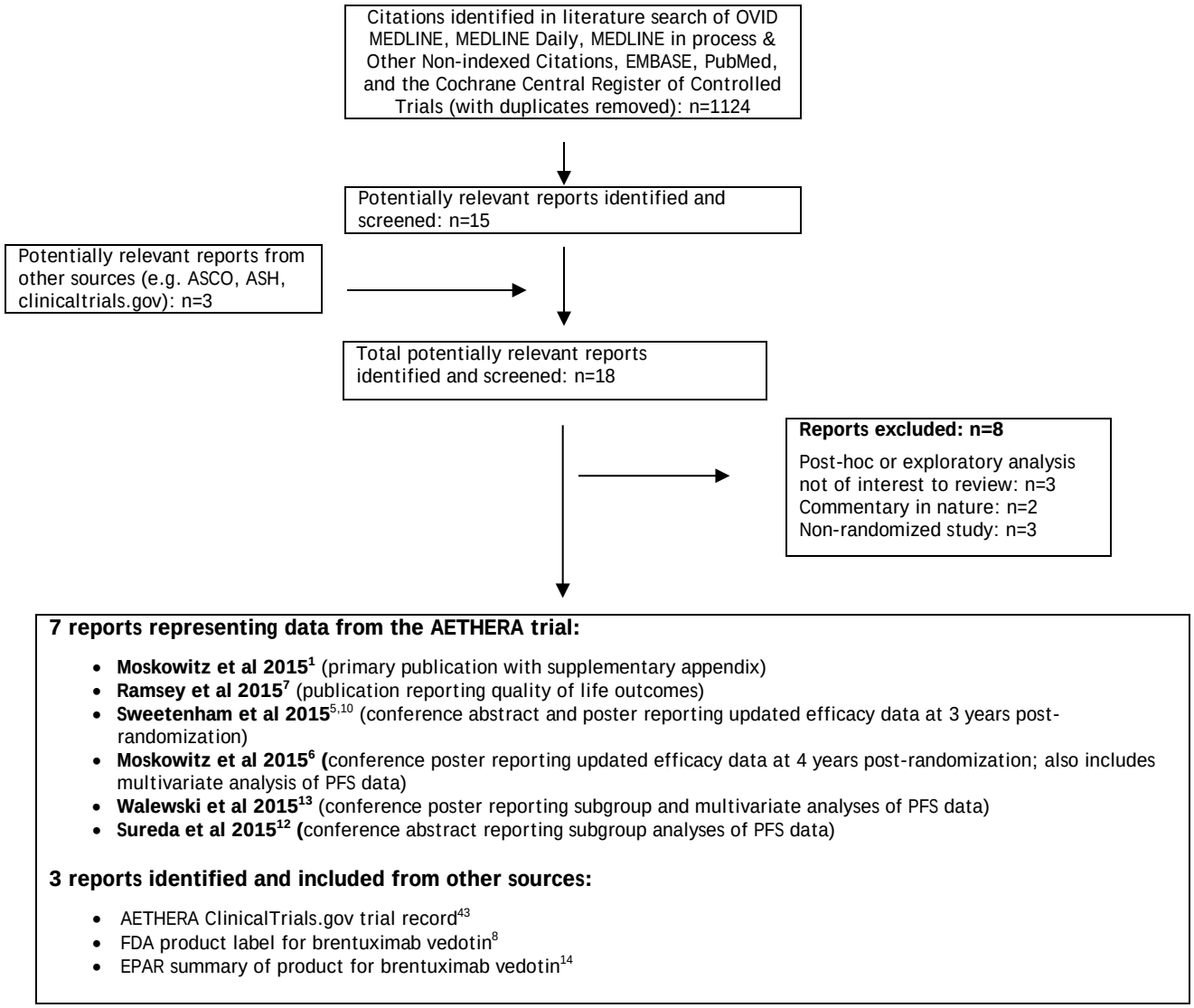
Abbreviations: ASCT - autologous stem cell transplant; HL - Hodgkin lymphoma; OS - overall survival; PFS - progression-free survival; QOL - quality of life; RCT - randomized controlled trial				
Notes: *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). ** Assessment performed by CT scan.				

6.3 Results

6.3.1 Literature Search Results

Of the 18 potentially relevant reports identified for full text review, ten reports[1,5-8,10,12-14,43] were included in the pCODR systematic review and eight reports[44-51] were excluded. Reports were excluded for the following reasons: they were either post-hoc or exploratory analyses of trial data not of interest to this review,[45,46,50] they were commentary or editorial in nature,[44,51] or they reported results of a non-randomized study.[47-49]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



**Note: Additional data related to the AETHERA trial were also obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One randomized controlled trial was identified that met the selection criteria of this review.[1] AETHERA is a double-blind, randomized phase 3 trial comparing brentuximab vedotin and best supportive care (BSC) to placebo plus BSC as early consolidation treatment after ASCT in patients with HL at high-risk for disease progression. Key characteristics of the AETHERA trial are summarized in Table 4 and specific aspects of trial quality are detailed in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of the Included AETHERA trial.[1]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

AETHERA[1]
 	
Phase 3, double-blind, placebo-controlled RCT (1:1 ratio)
 	
N randomized=329
N treated=327
 	
78 centres in 13 countries (U.S. and Europe)
 	
Patient enrolment: April 6, 2010 - September 21, 2012
 	
Data cut-off date: August 18, 2014
 	
Updated efficacy analysis at 3 years data cut-off date: October 14, 2015[11]
 	
Updated efficacy analysis at 4 years data cut-off date: August 26, 2016[11]
 	
Final analysis of OS in 2020[6]
 	
Funded by Seattle Genetics and Takeda Pharmaceuticals International
	Key Inclusion Criteria:
	• Aged ≥ 18 years
	• Histologically confirmed classic HL
	• Received high-dose therapy and ASCT
	• At least 1 of the following risk factors for progression post-ASCT:
	  ○ Primary refractory HL[A]
	  ○ Relapsed HL with initial remission duration of <12 months
	  ○ Extranodal involvement at the start of pre-ASCT salvage chemotherapy
	• CR, PR or SD after pre-ASCT salvage chemotherapy
	• ECOG performance status of 0 or 1
	• Adequate organ function
	
	Key Exclusion Criteria:
	• Previously treated with brentuximab vedotin
	• Previously received allogeneic transplant[11]
		Brentuximab vedotin 1.8 mg/kg iv over 30 minutes on day 1 of 21 day cycle every 3 weeks up to 16 cycles
		
		vs.
		
		Placebo iv over 30 minutes on day 1 of 21 day cycle every 3 weeks up to 16 cycles
		
		All patients in each arm received BSC comprised of infection prophylaxis[B] post-ASCT; growth factor and blood product support were permitted.
			Primary:
			PFS by independent review[C]
			
			Secondary:
			OS
			Safety
			
			Sensitivity analysis:
			PFS by investigator assessment[C]

Abbreviations: ASCT - autologous stem-cell transplant; **BSC** - best supportive care; **CR** - complete remission; **ECOG** - Eastern Cooperative Oncology Group; **HL** - Hodgkin Lymphoma; **iv**- intravenous; **OS** - overall survival; **PFS** - progression-free survival; **PR** - partial remission; **SD** - stable disease; **vs.** - versus.			

Notes:
[A] Defined as failure to achieve complete remission, as determined by investigator.
[B] For herpes simplex virus, varicella-zoster virus, and pneumocystis jiroveci.
[C] PFS defined as time from randomization to the first documentation of tumour progression or death.

Table 5: Select quality characteristics of the included AETHERA trial.[1].

Study	Treatment vs. comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Ethics approval
AETHERA[1]	Brentuximab vedotin vs. placebo	PFS by IR[A]	*Original:* 202 PFS events required to provide 80% power to detect an HR=0.667 using a one-sided alpha=0.025 *Revised:*[B] PFS analysis performed upon completion of all scheduled radiographical assessments, with one planned interim analysis for futility when 50% of original PFS events accrued (101 events) using HR=0.667 and a boundary for futility of p=0.2879	329	Stratified,[C] fixed-block central randomization with computer generated random numbers	NR	DB	Yes	Yes	No	Yes

Abbreviations: DB - double blind; IR - independent review; ITT - intent to treat; HR - hazard ratio; NR - not reported; PFS - progression-free survival.

Notes:
[A] Treatment decisions and administration of new therapy were based on investigator assessment of PFS. For data analysis, patients without progression by independent review but with disease progression by investigator assessment were censored at the time of last radiographical assessment before receipt of subsequent therapy.
[B] After all patients were enrolled, a planned analysis of masked, pooled PFS data was performed as part of event tracking prior to database lock. It showed 202 events were unlikely to be observed in the trial. The protocol was subsequently amended to conduct the primary analysis of PFS upon completion of all scheduled radiographical assessments.
[C] Randomization was stratified by best clinical response after completion of salvage chemotherapy (complete response vs. partial response vs. stable disease, according to international consensus criteria), primary refractory HL vs. relapsed disease <12 months after completion of first-line therapy vs. relapse ≥12 months after treatment completion.

a) Trial

AETHERA[1] is an ongoing, double-blind, placebo-controlled phase 3 trial conducted in 78 sites in 13 countries across Europe and the United States; no Canadian sites were included.[43] The majority of participating sites were academic centres.[11] Patient enrolment occurred from April 2010 through to September 2012.

Trial eligibility criteria required that patients have the following:

i. histologically confirmed classical HL,
ii. received high-dose chemotherapy followed by ASCT prior to randomization,
iii. at least one of three possible risk factors for disease progression post-ASCT, that included:
    - primary refractory HL defined as failure to achieve complete remission (as determined by investigator),
    - relapsed HL with an initial remission duration of <12 months, or
    - presence of extranodal involvement at the start of pre-ASCT salvage chemotherapy.

Only patients with complete or partial remission, or stable disease following pre-ASCT salvage chemotherapy were randomized. Adequate organ function and ECOG performance status of 0 or 1 were also eligibility requirements. Patients who had more than one previous ASCT were permitted in the trial. Excluded from the trial were patients who had a best clinical response of progressive disease (PD)[11] to salvage chemotherapy, previous exposure to brentuximab vedotin, and a history of allogeneic transplant.[11]

Eligible patients were randomized in a 1:1 ratio to treatment groups using fixed-block randomization methods. The randomization procedure was stratified by best response to pre-ASCT salvage chemotherapy (complete, partial, or stable disease), primary refractory HL (yes/no), and relapsed HL after completion of first-line therapy (<12 months versus ≥12 months). Both patients and treating investigators were blinded to treatment assignment.

Seattle Genetics and Takeda Pharmaceuticals International funded the trial. The Sponsor reported a role in all aspects of its conduct including design, data analysis and interpretation, and writing of the final trial publication. The Submitter indicated data analysts were not blinded during the course of the trial.[11] The primary author had full access to the trial data; however, it should be noted that many of the authors, including the primary author, disclosed potential conflicts of interest related to consultancy relationships, receiving honoraria, serving on sponsor advisory boards, or having equity interest in the trial Sponsor.

The primary outcome was progression-free survival by independent review (PFS-IR), which was defined as the time from randomization to the first documentation of tumour progression or death. PFS-IR was performed by an independent review facility. Progression-free survival by investigator assessment (PFS-IA) was also assessed in the trial and analysed as an a priori sensitivity analysis.

For both PFS endpoints, disease progression was determined with CT imaging and biopsy results (when available) conducted at baseline and every three months up to month 24. It is unknown how often biopsy results were used in the determination of progression. PET imaging could be used at the discretion of the investigator, but PET scans were not used in the determination of disease status. Investigator assessment of disease progression guided all treatment decisions and administration of any new anti-

cancer therapy. After 24 months, patients were followed for survival and disease status by clinical assessment only (PFS-IA), conducted every 6 months until trial closure. CT scans were not mandated by the trial protocol after 24 months but instead were performed at the discretion of the treating investigator, and therefore, not systematically performed for all patients remaining on trial.

For the PFS-IR analysis, patients without disease progression by independent review but with disease progression by investigator assessment were censored at the time of the last scan before receiving subsequent therapy. For the PFS-IA analysis, patients without disease progression were censored at the time of last scan or physical exam without known progression before receiving subsequent therapy.

The secondary outcomes of the trial included overall survival (OS), safety, and health-related quality of life (QOL). Quality of life was considered a pre-specified but exploratory endpoint of the trial, and these data were published separately from the primary trial publication.[7]

b) Populations

A total of 329 patients were randomized in AETHERA; 165 were assigned to the brentuximab vedotin group and 164 to the placebo group. The treatment groups were generally well balanced with respect to baseline patient characteristics (refer to Table 6) with the exception of a higher proportion of female patients (54% versus 41%) and black patients (6% versus 1%) in the brentuximab vedotin group. Trial patients were generally young (median age 32-33 years) with a performance status of 0 or 1. There were a total of eight patients in the trial who were aged 60 years and older (five in the brentuximab vedotin group and three in the placebo group).[11] The majority of patients in the trial had refractory HL or had relapsed within 12 months of receiving first-line treatment. At the time of salvage therapy, approximately a third of patients presented with extranodal disease. Patients' best response to salvage chemotherapy was as follows: 37% of patients had complete remission, 34% had partial remission, and 28% had stable disease, with 45% of patients receiving at least two salvage therapies.

c) Interventions

Patients allocated to the active treatment group received brentuximab vedotin at a dose of 1.8 mg/kg. Brentuximab vedotin and placebo were both administered over 30 minutes on day one of each 21-day cycle, starting on day 30 up to day 45 post-ASCT, for a maximum of 16 cycles. All patients received BSC that comprised of infection prophylaxis for herpes simplex virus, varicella-zoster virus, and pneumocystis jiroveci post-ASCT, as well as growth factor and blood product support. Dose reductions were permitted according to pre-specified criteria for hematologic and non-hematologic toxicities.[11] There was limited information reported in the primary trial publication on the treatment exposure of patients; therefore, additional data were requested from the Submitter. The median number of treatment cycles was 15 (range, 1 to 16) in both trial arms, however, median duration of treatment was longer in the brentuximab vedotin group at approximately 38 weeks (mean number of doses=12) compared to 34 weeks in the placebo group (mean number of doses=11).[11] Dose reductions were required in 32% and 3% of patients receiving brentuximab vedotin and placebo, respectively; the dose of brentuximab vedotin was reduced from 1.8mg to 1.2mg in these patients. A delay in dosing occurred in 9% (n=186) of 2004 doses of brentuximab vedotin and 3% (n=56) of 1756 doses of placebo.

Upon radiologic evidence of disease progression, as determined by the treating investigator, patients in the placebo group had the option to receive brentuximab vedotin as part of a separate clinical study. A total of 73 patients (45%) received brentuximab vedotin as subsequent anti-cancer therapy.

d) Patient Disposition

The disposition of patients through the AETHERA trial is summarized in Table 7. At the time of the primary efficacy analysis, all patients had discontinued study treatment, with the primary reason for discontinuation attributed to patients completing the maximum number of treatment cycles. Almost all patients entered long-term follow-up with the exception of 11 patients (3%) who could not be followed due to withdrawal of consent (9 patients) or death (2 patients); 76% of those patients remained in long-term follow-up. The primary trial publication did not report on protocol deviations that took place during the trial. It is evident, however, that deviations did occur as two patients received unallocated treatment. A request was made to the Submitter for more complete data. A total of 69 (21%) of the 329 patients randomized had an important protocol deviation, including 39 (24%) in the brentuximab vedotin group and 30 (18%) in the placebo group.[11] The distributions of deviations appeared similar among the two treatment groups; considering both groups, the majority of deviations related to study conduct (9%), drug administration (7%) and informed consent (5%).[11]

Subsequent anti-cancer therapies received by patients after disease progression are summarized in Table 8. Fifty-one patients (31%) in the brentuximab vedotin group and 85 patients (52%) in the placebo group went on to receive some form of anti-cancer therapy post-progression. There were 73 patients (45%) in the placebo arm who received brentuximab vedotin. Considering all other subsequent therapies, a higher percentage of patients in the placebo group received allogeneic stem cell transplant compared to the brentuximab vedotin group (14% versus 7%).

Table 6: Baseline characteristics of patients included in the AETHERA trial.[1]

Patient Characteristics, n (%) unless otherwise specified	Brentuximab vedotin (n=165)	Placebo (n=164)
Age, median (range)	33 (18-71)	32 (18-76)
Sex		
Male	76 (46)	97 (59)
Female	89 (54)	67 (41)
Race		
Asian	2 (1)	3 (2)
Black or African American	10 (6)	2 (1)
White	153 (93)	156 (95)
Other	0	3 (2)
ECOG PS		
0	87 (53)	97 (59)
1	77 (47)	67 (41)
2	1 (1)	0
Centrally confirmed Hodgkin's lymphoma	159 (96)	156 (95)
Number of previous systemic salvage therapies:		
1	94 (57)	86 (52)
≥2	71 (43)	78 (48)
>1 previous ASCT	5 (3)	10 (6)
First-line therapy:		
ABVD	119 (72)	129 (79)
BEACOPP	26 (16)	20 (12)
Other	20 (12)	15 (9)
Time from ASCT to first dose, days (range)	41 (28-49)	41 (30-51)
Stem-cell transplantation conditioning regimen:		
BEAM	106 (64)	96 (59)
CBV	13 (8)	22 (13)
Other	46 (28)	46 (28)
Any radiation	11 (7)	10 (6)
Disease status after first-line therapy:		
Refractory	99 (60)	97 (59)
Relapse <12 months	53 (32)	54 (33)
Relapse ≥12 months	13 (8)	13 (8)
Best response to salvage therapy after ASCT:		
Complete remission	61 (37)	62 (38)
Partial remission	57 (35)	56 (34)
Stable disease	47 (28)	46 (28)
Pre-ASCT PET status:		
FDG positive	64 (39)	51 (31)
FDG negative	56 (34)	57 (35)
Unknown	45 (27)	56 (34)
Extranodal involvement at pre-ASCT relapse	54 (33)	53 (32)
B symptoms after first-line therapy	47 (28)	40 (24)

Abbreviations: ASCT - autologous stem cell transplant; **ABVD** - doxorubicin, bleomycin, vinblastine, and dacarbazine; **BEACOPP** - bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; **BEAM** - carmustine, etoposide, cytarabine, and melphalan; **CBV** - cyclophosphamide, carmustine, and etoposide; **ECOG** - Easter Cooperative Oncology Group; **FDG** - fluorodeoxyglucose; **HL** - Hodgkin's lymphoma; **PET** - positron emission tomography; **PS** - performance status.

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Table 7: Patient disposition in the AETHERA trial.[1]

Patient Disposition, n (%)	Brentuximab vedotin	Placebo
Randomized	**165**	**164**
Received allocated treatment	165 (100)	160 (98)
Did not receive allocated treatment	0	2 (1)
Received unallocated treatment	0	2 (1)[A]
Withdrew consent	4 (2)	5 (3)
Discontinued randomized treatment	165 (100)[B]	164 (100)[B]
Excluded from long-term follow-up	6 (4)[C]	5 (3)[D]
Entered long-term follow-up	159 (96)	159 (97)
Remained in long-term follow-up	122 (74)	129 (79)
Included in intent-to-treat efficacy analyses	165 (100)	164 (100)
Included in safety analyses	167 (101)[E]	160 (98)
Primary reasons for treatment discontinuation:		
Completion of 16 cycles of treatment	78 (47)	81 (49)
Disease progression	24 (15)	69 (42)
Adverse events	54 (33)[F]	10 (6)
Patient decision	9 (5)	4 (2)

Notes:
[A] Two patients received a dose of brentuximab vedotin.
[B] All patients had discontinued treatment at the time of data cut-off for the primary efficacy analysis, which was August 18, 2014.
[C] Four patients withdrew consent and two patients died.
[D] Five patients withdrew consent.
[E] Includes the two patients allocated to placebo who received a dose of brentuximab vedotin.
[F] The most common adverse events leading to treatment discontinuation of brentuximab vedotin were peripheral sensory and motor neuropathies.

Table 8: Subsequent anti-cancer therapy received by patients in the AETHERA trial.[9]

Subsequent Anti-Cancer Therapy	Brentuximab vedotin (n=165)	Placebo (n=164)
Subsequent treatment ever received, n (%):	**51 (31)**	**85 (52)**
Stem cell transplant*	13 (8)	24 (15)
Single-agent brentuximab vedotin	8 (5)	72 (44)
Multi-agent therapy including brentuximab vedotin	1 (1)	1 (1)
Multi-agent therapy	35 (21)	34 (21)
Single-agent therapy	22 (13)	22 (13)
Radiation	22 (13)	23 (14)
Donor lymphocyte infusion	2 (1)	1 (1)
Other treatment	1 (1)	2 (1)
First subsequent treatment, n (%)		
Allogeneic stem cell transplant	3 (2)	0
Single-agent brentuximab vedotin	3 (2)	63 (38)
Multi-agent therapy including brentuximab vedotin	1 (1)	0
Multi-agent therapy	27 (16)	12 (7)
Single-agent therapy	7 (4)	5 (3)
Radiation	10 (6)	4 (2)
Other treatment	0	1 (1)

Notes:
*In the brentuximab vedotin group, 12 of 13 patients received allogeneic stem cell transplant; in the placebo group, 23 of 24 patients received allogeneic stem cell transplant.

Reprinted from The Lancet, Vol. 385, Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al, Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's

lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial [supplementary appendix]. pp. 1853-62, Copyright 2015, with permission from Elsevier. http://www.thelancet.com/

e) Limitations/Sources of Bias

Overall, the AETHERA trial was well conducted owing to its design features (double-blind, placebo-controlled), the use of appropriate methods to randomize patients, clear explanation of the disposition of patients through the trial, a robust assessment of the primary outcome (independent central review), and conducting all efficacy analyses by assigned treatment. The trial did have some limitations, however, which are summarized below:

- The sample size of the trial was determined prospectively and based on a power calculation that included a PFS event rate of 202, which provided 80% power to detect an HR=0.677 with a one-sided alpha=0.025. The statistical analysis plan (SAP) was amended, however, after a planned analysis showed a low event rate after 24 months among the two treatment groups. The final analysis was changed to occur after all scheduled CT scans had been performed, at which time the PFS event rate was 135. The low event rate may have been related to the inclusion of a proportion of patients with lower risk disease (15% of trial patients had one risk factor for trial entry), as the trial excluded patients with PD; however, the trial sample size was estimated using historical data that included such patients.[11] The SAP of trial reported that an event rate between 130 and 140 would have provided the trial between 64% and 67% power.[11] With reduced power there is the possibility that the observed treatment effect may be inflated, as low power has been shown to exaggerate true treatment effects (as function of chance and the use of flexible statistical approaches) when significance testing is based on statistical thresholds.[2-4]
- The updated efficacy analyses performed after three and four years of patient follow-up have limitations; therefore, these results should be interpreted within this context, specifically:
    - Three-year PFS-IR data reflect event rates based on unscheduled CT scans performed as clinically indicated after 24 months and submitted to the independent review facility at the discretion of the investigator, and therefore, do not include the scans of all patients remaining on trial.
    - Three- and four-year PFS-IA data reflect event rates based on clinical assessment only.
- Subgroup analyses performed of the primary outcome were considered exploratory in nature and therefore were not controlled for type 1 error arising from multiple testing, and some patient subgroups included a small number of patients (patients with stable disease, relapse ≥12 months, aged ≥45, and presence of B symptoms after first-line therapy). The treatment estimates obtained for subgroups therefore may be unreliable and should be interpreted with caution.
- Upon disease progression, patients were permitted to receive subsequent anti-cancer therapy including brentuximab vedotin. The use of these therapies differed between the treatment groups. This aspect of the trial confounds the assessment of OS (OS is likely underestimated in the trial), and also precludes making any inferences about the optimal timing of brentuximab vedotin consolidation treatment (early versus after disease progression).
- The higher incidence of peripheral neuropathy and the larger proportion of dose reductions that occurred in the brentuximab vedotin treatment group may have introduced bias (performance bias, detection bias) into the PFS assessment by

investigator, since these occurrences had the potential to unblind treatment assignment. The larger number of discordant assessments in the placebo arm (PD determined by investigator assessment but not by IR assessment) supports this notion.

- Data analysts, who were not independent of the Sponsor, were unblinded after data-base lock, and thus were aware of treatment assignment while performing primary efficacy analyses. The extent to which this knowledge influenced the interpretation and reporting of outcomes is unknown.
- The QOL data are confounded by the crossover nature of the trial since assessments were performed regardless of disease progression and the receipt of subsequent anti-cancer therapy. These confounders make quantifying the effect of brentuximab vedotin on QOL difficult.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

In the AETHERA trial,[1] all efficacy analyses were based on the intent-to-treat (ITT) principle. For time-to-event outcomes, including PFS and OS, Kaplan-Meier methods were used to generate survival curves and differences between treatment groups were analyzed using the log-rank test stratified by randomization factors. Stratified Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs), and subgroup analyses were pre-specified and performed according to baseline prognostic risk factors.[ii] Although patient subgroups were identified in advance of the trial, all subgroup analyses were considered exploratory in nature.[11] Refer to Table 5 for a summary of statistical and sample size considerations in the trial.

The data cut-off date for the primary efficacy analysis of PFS was August 18, 2014. At that time an interim analysis of OS data was also planned, with the final analysis of OS data expected in 2020, approximately ten years after the first patient was treated. Updated efficacy data at three and four years of follow-up have been published in abstract and poster form for some outcomes.[5,6,10] The data cut-off dates for the three[5,10] and four year[6] updated efficacy analyses were October 14, 2015 and August 26, 2016, respectively.[11]

The EQ-5D (EuroQoL 5-Dimensions), a validated self-report questionnaire, was used to measure health-related QOL during treatment and follow-up phases of the trial.[7] The EQ-5D Health State Index assesses health across five dimensions that include mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three possible outcomes: no problems, some problems, and extreme problems. EQ-5D index scores were calculated using the time trade-off method, incorporated UK utility weights,[7] and were analyzed based on ITT. Possible scores range from -0.50 to 1, with higher scores indicative of better QOL. A change in score of ≥ 0.08 has been established as the minimal clinically important difference (MCID) in UK cancer patients. Additional analyses were performed that examined EQ-5D index scores for specific subgroups of patients: those who did/did not experience disease progression post-ASCT (both treatment groups), and those who did/did not experience treatment-emergent peripheral neuropathy (brentuximab vedotin group). The EQ-5D visual analogue scale (VAS), which records patient self-rated health on a vertical scale ranging from best imaginable health (rated as 100) to worst imaginable health (rated as 0), has a MCID of 7.

The analysis of safety included all patients who received at least one dose of study drug. Incidence data on adverse events (AEs) were captured and classified by organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and graded using NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.

Efficacy Outcomes

Progression-free survival by independent review (PFS-IR)

After a median follow-up time of 30 months, PFS-IR was significantly longer in patients treated with brentuximab vedotin compared to placebo (HR=0.57, 95% CI, 0.40 to 0.81; p=0.0013). Median PFS was 42.9 months in the brentuximab vedotin group and 24.1 months in the placebo group, which is an improvement in PFS of approximately 19 months with brentuximab vedotin. The PFS benefit was evident among all patient subgroups examined; however, a statistically significant benefit was detected in the following subgroups: those with a partial response to pre-ASCT salvage therapy, relapse <12 months, <45 years old, female gender, ECOG PS of 1, >2 systemic

[ii] Patient subgroups examined included: response to salvage therapy pre-ASCT (complete or partial, or stable disease), status after first-line therapy (refractory, relapse <12 months, ≥12 months, age (<45 years or ≥45 years), sex, ECOG status (0 or 1), number of systemic treatments pre-ASCT (≤2 or >2) FDG positive or negative pre-ASCT, presence or absence of B symptoms after first-line treatment, and presence or absence of extranodal involvement pre-ASCT.

treatments pre-ASCT, and presence of B symptoms after first-line therapy. PFS benefit was observed irrespective of extranodal involvement pre-ASCT; however, the magnitude of benefit was greater in patients with involvement at baseline. It should be noted that some patient subgroup results might have been affected by small sample size (patients with stable disease, relapse ≥12 months, age ≥45, and presence of B symptoms after first-line therapy).

Updated data were reported for PFS-IR. At three years the PFS benefit associated with brentuximab vedotin was still maintained (HR=0.58, 95% CI, 0.41-0.82).[10] However, unlike the primary analysis, the updated analysis reflects an assessment of unscheduled CT scans performed as clinically indicated after 24 months and submitted to the independent review facility at the discretion of the investigator. Therefore, it does not include the scans of all patients remaining on trial, and should be interpreted within this context.

Progression-free survival by investigator assessment (sensitivity analysis)

Progression-free survival by investigator assessment was also improved in the brentuximab vedotin group (HR=0.50, 95% CI, 0.36 to 0.70; p-value not reported). Median PFS was not reported for each treatment group.[1]

Overall, more progression events were observed in the analysis of PFS-IA compared to independent review (Table 9). The concordance between the two methods was 87%. Of note, a small proportion of patients (13% in the placebo group and 4% in the brentuximab vedotin group) were censored from the PFS-IR analysis due to investigator determination of progressive disease and initiation of subsequent therapy without independently reviewed documented progression.[1] These occurrences were treated as events in the PFS-IR analysis.

After three years of follow-up, the treatment benefit associated with brentuximab vedotin was maintained (HR=0.52; 95% CI 0.37-0.71; p-value not reported).[10] Median PFS-IA was not reached in the brentuximab vedotin group and was 15.8 months in the placebo group. Similar findings were reported after four years of follow-up (HR=0.52; 95% CI not reported; median PFS-IA not reached in the brentuximab vedotin group and 15.8 months in the placebo group).[6]

For the results of a post-hoc analysis of PFS (IA and IR) by number of risk factors, refer to Section 7.

Overall survival

The interim analysis of OS demonstrated no difference between the treatment groups (HR=1.15, 95% CI, 0.67-1.97; p=0.62). The data are currently deemed immature and are confounded by the subsequent anti-cancer therapies received by patients post-progression (Table 9).

Table 9: Efficacy outcomes in the AETHERA trial.[1,5,6,10,11]

Efficacy outcomes[1]	Brentuximab vedotin (n=165)	Placebo (n=164)
Median follow-up, months (range)	30 (0-50)	
Primary outcome **- PFS by independent review**		
No. PFS events	60	75
Median PFS in months (95% CI)	42.9 (30.4-42.9)	24.1 (11.5-NE)
HR (95% CI)*; log-rank p-value	0.57 (0.40-0.81); p=0.0013	
PFS rate (%) at 2 years, (95% CI)	63 (55-70)	51 (43-59)
Sensitivity analysis (pre-specified) **- PFS by investigator assessment**		
No. PFS events	60	89
Median PFS in months (95% CI)	NR	NR
HR (95% CI)*	0.50 (0.36-0.70)**	
PFS rate (%) at 2 years, (95% CI)	65 (57-72)	45 (37-52)
Updated data at 3 years[5,10]		
No. PFS events	63	91
Median PFS in months (95% CI)	Not reached	15.8 (8.5-44)
HR (95% CI)*	0.52 (0.37-0.71)	
PFS rate (%) at 3 years, (95% CI)	61 (52-68)	43 (36-51)
Updated data at 4 years[6,11]		
No. PFS events	65	93
Median PFS in months (95% CI)	Not reached	15.8 (9-49)[11]
HR (95% CI)	0.52 (0.37-0.71)[11]	
PFS rate (%) at 4 years, (95% CI)	59 (50-66)[11]	43 (35-50)[11]
Secondary outcome **- OS**		
No. deaths	28	25
Median OS in months (95% CI)	Not reached	Not reached
HR (95% CI);* p-value	1.15 (0.67-1.97); p=0.6204	

Abbreviations: CI - confidence interval; HR - hazard ratio; NE - not estimable; NR - not reported; OS - overall survival; PFS - progression-free survival.

Notes:
*Stratified hazard ratio, where hazard ratio <1 favours treatment with brentuximab vedotin.
**PFS by independent review reflects regular scheduled CT scans up to 24 months, with CT scans performed at the discretion of investigators beyond 24 months. PFS by investigator assessment reflects CT scans/clinical assessment up to 24 months, with scheduled clinical assessments only beyond 24 months.

Quality of Life[7]

EQ-5D questionnaires were administered to patients every three weeks over 16 cycles during the treatment phase of the trial, at the end of treatment, and every three months up to 24 months during the follow-up phase of the trial regardless of PD or receipt of further therapies. Adherence in completion of EQ-5D questionnaires was reported as high (87.5%) and comparable between treatment groups during both the treatment phase and follow-up. In both treatment groups EQ-5D index scores declined over time, with worse scores observed in the brentuximab vedotin group compared to placebo following month six through to month 18 (Table 10). At most assessment periods the mean differences in index scores between treatment groups were small (<-0.07), except at months 15 and 18, where they met the MCID of 0.08. During the treatment phase, mean differences in index scores did not exceed the MCID at any treatment cycle, but were worse in the brentuximab vedotin group compared to placebo. Patients experiencing disease progression in both the brentuximab vedotin (n range, 47 to 105) and placebo (n range, 63 to 86) groups showed worse mean EQ-5D index scores compared to patients who did not have disease progression; the MCID was exceeded from months 15 to 24 in the brentuximab vedotin group and months 9 to 24 in the placebo arm. In patients with and without peripheral neuropathy in the brentuximab vedotin group, mean differences in EQ-5D index scores did not exceed the MCID at any time point or within any of the five subscales. No differences in mean VAS scores were observed at any time point between the treatment groups.

Table 10: EuroQOL 5 Dimensions (EQ-5D) data from the AETHERA trial.[7]

Time since randomization	Brentuximb vedotin (n=165)		Placebo (n=164)		Mean Difference[B] (95% CI)
	N	Mean	N	Mean	
Baseline	139[A]	0.87	129	0.89	-0.02 (-0.05 to 0.01)
Month 3	153	0.84	150	0.85	-0.02 (-0.6 to 0.03)
Month 6	160	0.84	154	0.84	-0.00 (-0.05 to 0.04)
Month 9	158	0.77	156	0.83	-0.06 (-0.11 to 0.01)
Month 12	158	0.76	157	0.83	-0.07 (-0.13 to -0.02)
Month 15	157	0.74	158	0.83	-0.08 (-0.14 to 0.03)
Month 18	157	0.74	157	0.82	-0.08 (-0.14 to 0.01)
Month 21	156	0.76	156	0.79	-0.04 (-0.11 to 0.03)
Month 24	154	0.73	155	0.77	-0.04 (-0.12 to 0.04)
Abbreviations: CI - confidence interval; MCID - minimal clinically important difference.					
Notes: [A] Seventeen patients were enrolled in the trial prior to a protocol amendment directing collection of baseline EQ-5D data. [B] The MCID for the EQ-5D is 0.08 (based on analyses using UK-based weights).					

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Harms Outcomes

Adverse Events

The analysis of AEs was based on a safety population of 167 patients in the brentuximab vedotin group and 160 patients in the placebo group. The treatment-emergent AEs observed in the AETHERA trial,[1,8,9] occurring in ≥10% of patients in the brentuximab vedotin group, are summarized in Tables 11 to 13.

In both groups, patients received a median of 15 cycles of study drug. Dose reductions and delays due to AEs occurred in 32% and 9% of patients in the brentuximab vedotin group, respectively; and 3% and 3% of patients in the placebo group, respectively. The most commonly reported events (refer to Tables 11 and 12), of any grade, were neutropenia (78%),[8] peripheral sensory neuropathy

(56%), thrombocytopenia (41%),[8] and peripheral motor neuropathy (23%); the percentage of patients with these events at grade 3 or higher, were 39%, 10%, 6% and 6%, respectively. Neutropenia resulted in dose delays in 22% of patients but these did not require treatment discontinuation. Serious infections (≥ grade 3) were reported in 7% and 6% of patients in the brentuximab vedotin and placebo groups, respectively. There were 25% of patients receiving brentuximab vedotin and 11% of patients receiving placebo that required growth factor support.

Serious AEs (Table 13) occurred in 25% of patients treated with brentuximab vedotin and 13% of patients treated with placebo.[9] The trial also reported treatment-emergent pulmonary toxic effects in 5% of patients receiving brentuximab vedotin and in 3% of patients receiving placebo.

Peripheral Neuropathy

The incidence of peripheral neuropathy in the trial, including sensory and motor, was analyzed using a standardized MedDRA query (SMQ)-based analysis.[iii1]Treatment-emergent peripheral neuropathy occurred in 67% (n=112) and 19% (n=31) of patients in the brentuximab vedotin and placebo groups, respectively. The median time-to-onset of peripheral neuropathy events was 13.7 weeks in the brentuximab vedotin group. The majority of these events were sensory and low severity in nature (i.e., grade 1-2: 56%; grade ≥3: 10%, refer to Table 11). When only unique patients are considered (versus preferred MedDRA term), the incidence of grade 3 events was 13% (22 patients) with no grade 4 events observed. Peripheral neuropathy led to treatment discontinuation in 23% of patients (n=38) and dose reductions or delays in 31% (n=51). Of the patients requiring dose reductions or delays, 25% (n=13) eventually discontinued treatment due to peripheral neuropathy and 57% (n=29) completed all 16 cycles of brentuximab vedotin. Patients completing fewer than 16 cycles received a median of 10.5 cycles. Considering all patients with peripheral neuropathy (n=112), 85% (n=95) experienced resolution of symptoms, with a median time-to-resolution of 23.4 weeks. After three years of follow-up, the percentage of these patients with resolution or improvement of symptoms was 88% (n=99), of whom 66% (n=74) experienced complete resolution; the median-time to resolution of symptoms was not reported.[5] At four years,[5] resolution or improvement of symptoms was observed in 89% of patients (n=100), and complete resolution was experienced in 71% (n=80).[6]

Deaths

During the treatment phase of the trial, one patient in the brentuximab vedotin group died within 30 days of receiving the last dose of study treatment. This patient died of treatment-related acute respiratory distress syndrome (ARDS) associated with pneumonitis. Another patient in the brentuximab vedotin group died on day 40 of the trial, however, the cause of death was deemed unrelated to treatment (ARDS following an episode of treatment-related acute pancreatitis and ARDS).

All deaths that occurred in the AETHERA trial, during treatment and follow-up, are summarized in Table 12. At the time of primary analysis, 17% (n=28) of patients in the brentuximab vedotin group and 16% (n=25) of patients in the placebo group had died on study. In both treatment groups, the majority of deaths were deemed disease-related (i.e., unrelated to study treatment) with death rates similar between treatment groups. There were nine (5%) treatment-related deaths in the brentuximab vedotin group and seven (4%) in the placebo group. Of note, during the follow-up period there were 85 patients (52%) in the placebo group who received subsequent treatment after disease progression.

[iii] SMQ analysis includes: peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, muscular weakness, hypoesthesia, gait disturbance, neuralgia, amyotrophy, decreased vibratory sense, hyporeflexia, peroneal nerve palsy, and sensory disturbance.

Table 11: Treatment-emergent adverse events in the AETHERA trial.[1]

Adverse events, n (%)	Brentuximab vedotin (n=167)		Placebo (n=160)	
	Any grade*	≥ Grade 3**	Any grade	≥ Grade 3
Any event	163 (98)	93 (56)	142 (89)	51 (32)
Peripheral sensory neuropathy	94 (56)	17 (10)	25 (16)	2 (1)
Neutropenia	58 (35)	49 (29)	19 (12)	16 (10)
Upper respiratory tract infection	44 (26)	0	37 (23)	2 (1)
Fatigue	40 (24)	3 (2)	29 (18)	4 (3)
Peripheral motor neuropathy	38 (23)	10 (6)	3 (2)	1 (1)
Nausea	36 (22)	5 (3)	12 (18)	0
Cough	35 (21)	0	26 (16)	0
Diarrhea	33 (20)	3 (2)	16 (10)	1 (1)
Pyrexia	31 (19)	3 (2)	25 (16)	0
Weight decrease	32 (19)	1 (1)	9 (6)	0
Arthralgia	30 (18)	1 (1)	15 (9)	0
Vomiting	27 (16)	4 (2)	11 (7)	0
Abdominal pain	23 (14)	3 (2)	5 (3)	0
Constipation	21 (13)	4 (2)	5 (3)	0
Dyspnea	21 (13)	0	10 (6)	1 (1)
Decreased appetite	20 (12)	1 (1)	9 (6)	0
Pruritus	20 (12)	1 (1)	12 (8)	0
Headache	19 (11)	3 (2)	13 (8)	1 (1)
Muscle spasms	18 (11)	0	9 (6)	0
Myalgia	18 (11)	1 (1)	6 (4)	0
Chills	17 (10)	0	8 (5)	0
Paraesthesia	16 (10)	3 (2)	2 (1)	0

Notes:
*Treatment-emergent adverse events with an incidence of ≥10% in the brentuximab vedotin group among the safety population of patients.
**Includes all treatment-emergent adverse events with an incidence of 5% or higher in the brentuximab vedotin group.

Reprinted from The Lancet, Vol. 385, Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al, Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. pp. 1853-62, Copyright 2015, with permission from Elsevier. http://www.thelancet.com/

Table 12. Treatment-emergent adverse events in the AETHERA trial derived from other source.[8]

Adverse events, n (%)	Brentuximab vedotin (n=167)		Placebo (n=160)	
	Any grade*	≥ Grade 3*	Any grade	≥ Grade 3
Neutropenia	78	39	34	10
Thrombocytopenia	41	6	20	5
Anemia	27	4	19	2

Notes:
*Treatment-emergent adverse events with an incidence of ≥10% in the brentuximab vedotin group among the safety population of patients.

Table 13. Treatment-emergent serious adverse events in the AETHERA trial. [9]

Serious adverse events, n (%)*	Brentuximab vedotin (n=167)	Placebo (n=160)
Any event	41 (25)	20 (13)
Pneumonia	7 (4)	4 (3)
Pyrexia	6 (4)	2 (1)
Vomiting	5 (3)	1 (1)
Nausea	4 (2)	1 (1)

Serious adverse events, n (%)*	Brentuximab vedotin (n=167)	Placebo (n=160)
Hepatotoxicity	3 (2)	1 (1)
Peripheral sensory neuropathy	3 (2)	0
Acute respiratory distress syndrome	2 (1)	1 (1)
Constipation	2 (1)	0
Headache	2 (1)	0
Herpes zoster	2 (1)	1 (1)
Pneumonitis	2 (1)	0
Notes: *Serious adverse events occurring in ≥2 patients in the brentuximab vedotin group.		

Reprinted from The Lancet, Vol. 385, Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al, Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial [supplementary appendix]. pp. 1853-62, Copyright 2015, with permission from Elsevier. http://www.thelancet.com/

Table 14: Summary of deaths in the AETHERA trial.[9]

Deaths,[A] n (%)	Brentuximab vedotin (n=167)	Placebo (n=164)
All Deaths	**28 (17)**	**25 (16)**
Disease-related	**18 (11)**	**17 (11)**
Acute respiratory distress syndrome	0	1 (1)
Disease progression	5 (3)	9 (6)
Hodgkin lymphoma	13 (8)	7 (4)
Not Disease-related	**9 (5)**	**7 (4)**
Acute respiratory distress syndrome	2 (1)[B]	0
Aplastic anemia	0	1 (1)
Bladder cancer	1 (1)	0
Cardiac arrest	1 (1)	0
Graft versus host disease	0	3 (2)
Influenza	0	1 (1)
Lung infection	1 (1)	0
Myelodysplastic syndrome	1 (1)	1 (1)
Myocardial infarction	1 (1)	0
Pancreatic carcinoma	1 (1)	0
Pneumonia	0	1 (1)
Sepsis	1 (1)	0
Disease Relationship Unknown	1 (1)	1 (1)
Fungal pneumonia	0	1 (1)
Other	1 (1)	0
Deaths prior to progression per independent review	4 (2)	3 (2)
Deaths prior to progression by investigator	5 (3)	3 (2)
Notes: [A] - Includes deaths occurring during the treatment and follow-up phases of the trial. During the follow-up period there were 72 patients (44%) in the placebo group who received brentuximab vedotin after disease progression. [B] - One death occurred within 30 days of last dose of study treatment, which was associated with pneumonitis; the other patient died at day 40 after an episode of treatment-related acute pancreatitis.		

Reprinted from The Lancet, Vol. 385, Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al, Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial [supplementary appendix]. pp. 1853-62, Copyright 2015, with permission from Elsevier. http://www.thelancet.com/

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of brentuximab vedotin as early consolidation treatment after ASCT in patients with HL at high-risk for disease progression:

- Review of post-hoc analyses of the AETHERA trial data related to time-to-treatment failure, time-to-next treatment, and PFS analyzed by number of risk factors.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Post-hoc Analyses of the AETHERA Trial Data

7.1.1 Objective

Post-hoc analyses of the AETHERA trial data were performed at the request of Health Canada, as their review of the trial raised the question of whether the observed PFS improvement with brentuximab vedotin was clinically meaningful in the absence of an OS and QOL benefit; and further, whether subgroups of the trial population based on number of risk factors present benefited from consolidation treatment.[11] Post-hoc analyses were performed and included (but not limited to) assessment of time-to-treatment failure (TTF),[11] time-to-next treatment,[11] and PFS analyzed by number of risk factors.[1,12,14] A brief summary of the results of these analyses is provided below.

7.1.2 Findings

The post-hoc analyses conducted on the trial data were exploratory and therefore should be interpreted with caution since the trial was not powered to detect relative differences between the treatment groups for the additional endpoints and subgroups examined, and the results were not adjusted for multiple testing to control for type 1 error, which increases the likelihood of obtaining positive findings.

Time-to-Treatment Failure

- Time-to-treatment failure, in the context of the blinded AETHERA trial, is potentially helpful in that it can capture differences in treatment discontinuation for toxicity and/or patient preferences, in addition to disease progression. There is, however, potential for bias in the TTF endpoint, if criteria for initiation of therapy at progression are not stipulated in the trial protocol. For example, if, at unblinding for progression, it is determined that a patient was on placebo, both the patient and their physician may be more likely to initiate chemotherapy while the patient is asymptomatic (that is earlier, when disease burden and symptoms might not otherwise warrant therapy).

Time-to-treatment failure was calculated as the time from randomization to the first occurrence of any one of the following: early discontinuation of treatment (received fewer than 16 cycles of treatment due to disease progression, toxicity, or patient or investigator decision), start of subsequent therapy, disease progression, or death). Time-to-treatment failure per IR and IA were similar, with HRs of 0.86 (95% CI, 0.65-1.13) and 0.91 (95% CI, 0.69-1.21), respectively, and a median TTF of 11 months in both groups.[11] The Kaplan Meier curves for both analyses showed a positive trend in TTF favouring brentuximab vedotin during the first 12 months post-randomization (treatment phase); however, no difference between groups was observed during the follow-up phase of the trial.

Time-to-Next Treatment

- Time-to-next treatment is an unblinded assessment of first subsequent treatment received by patients in the AETHERA trial, and therefore, is subject to bias. For example, knowledge of assigned treatment may influence first subsequent treatment choice; placebo patients or their physicians may immediately start treatment with brentuximab vedotin knowing that placebo was previous treatment.

Time-to-next treatment was calculated as the time from randomization to investigator-reported receipt of treatment for HL subsequent to placebo (in the placebo treatment group) or brentuximab vedotin (in the brentuximab vedotin treatment group), where receipt of subsequent treatment was the TTNT event.[11] There were 52% (n=85) and 31% (n=51) of patients in the placebo and brentuximab vedotin treatment groups, respectively, who received subsequent treatment; median TTNT was 20.9 months in the placebo group and not reached in the brentuximab vedotin group, showing a significant reduced risk of receiving subsequent treatment with brentuximab vedotin (HR=0.45 (95% CI, 0.32-0.64). At 36 months, the TTNT event-free rate was 46% in the placebo treatment group and 66% in the brentuximab vedotin treatment group.

Progression-free Survival by Number of Risk Factors

- For the analysis of PFS by number of risk factors, randomization was not stratified by number of risk factors and therefore, this factor, as well as other baseline characteristics affecting outcome may be unevenly distributed in the treatment groups. Further, the results obtained are specific to the risk factors used in the analysis and may not necessarily generalize to a different set of risk factors.

Eligibility criteria for the AETHERA trial required patients have at least one of the following risk factors: refractory HL, relapsed HL within <12 months of frontline treatment, and extranodal involvement at the time of pre-ASCT relapse.[1] In the post-hoc risk factor analysis,[1,6,12-14] additional risk factors known to be associated with increased risk of progression and for which data were available for all patients were also examined, including best response (partial response or stable disease to most recent salvage therapy), B symptoms at relapse, and two or more prior salvage therapies. The results of the post-hoc subgroup analyses of PFS by risk factor groups showed a trend for improved PFS by increasing number of risk factors but not for patients with only one risk factor (Table 15).[14] The small number of patients in the one risk factor subgroup (n=49) should be considered when interpreting the result for this subgroup, as small sample size can produce an unreliable and inprecise treatment estimate. It is the opinion of the CPG that therapy with brentuximab vedotin in the one risk factor group is unlikely to make PFS worse, as the positive hazard ratio for progression might suggest.

The impact of risk factors on PFS outcome was further analyzed using multivariate analysis;[6] interaction terms comprising treatment with brentuximab vedotin and established risk factors (covariates, n=18)[iv] were examined, and showed that the most significant treatment and covariate interaction was the subgroup of patients with 1 versus ≥2 risk factors, with greater

[iv] Risk factors (covariates) included in the Cox proportional hazards model were: age, sex, weight, geographic region, initial disease stage, time from initial diagnosis, number of treatments pre-ASCT, chemosensitivity, response to frontline and salvage therapy, prior radiotherapy, extranodal disease pre-ASCT, ASCT conditioning regimen, B symptoms at pre-ASCT relapse, pre-existing peripheral neuropathy, baseline ECOG status, baseline lesions, and number of risk factors (which included: relapsed <12 months or refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, 2 or more salvage therapies).

treatment PFS benefit associated with patients in the ≥2 risk factor category (PFS by IA, HR=0.42). A sensitivity analysis with this covariate removed found no other covariate interaction to be significant, suggesting that the number of risk factors versus specific risk factors was predictive of treatment benefit.

Table 15: Post-hoc analysis of PFS by number of risk factors in the AETHERA trial.[1,12,14]

PFS by Number of Risk Factors	N	Hazard ratio (95% CI)
PFS[a] by Independent Review[1,14]		
ITT (all patients)	329	0.58 (0.41-0.81)
≥3	166	0.43(0.27-0.68)
≥2	280	0.49 (0.34-0.71)
≥1	329	0.57 (0.40-0.81)
1[b]	49	1.65 (0.60-4.55)[14]
PFS [a] by Investigator Assessment[12,14]		
ITT (all patients)	329	0.50 (0.36-0.70)
≥3	166	0.38 (0.25-0.58)
≥2	280	0.40 (0.28-0.57)
≥1	329	0.50 (0.36-0.70)
1[c]	49	2.75 (0.99-7.59)[14]
Abbreviations: BSC - best supportive care; CI - confidence interval; IA - investigator assessment; IR - independent review; ITT - intent-to-treat; NE - not estimable; NR - not reported; PFS - progression-free survival.		
Notes: [a] Based on primary analysis of PFS (data cut-off August 18, 2014). PFS by IR reflects regular scheduled CT scans up to 24 months, with CT scans performed at the discretion of investigators beyond 24 months. PFS by IA reflects CT scans/clinical assessment up to 24 months, with scheduled clinical assessments only beyond 24 months. [b] Analyses of the 1 risk factor group were unstratified due to small sample size. [c] This treatment effect estimate is based on 3-year PFS data, which includes five additional PFS by IA events observed during the third year follow-up period.		

7.1.3 Summary

Post-hoc analyses of the AETHERA trial data were performed to gain insight into whether the PFS improvement with brentuximab vedotin was clinically meaningful in the absence of an OS and QOL benefit; and further, to assess if subgroups of the trial population, based on number of risk factors present, benefited more or less from consolidation treatment. The post-hoc analyses performed included assessment of time-to-treatment failure (TTF), time-to-next treatment (TTNT), and PFS analyzed by number of risk factors. These analyses were exploratory and should be interpreted with caution since the trial was not powered to detect relative differences between the treatment groups for these additional endpoints and subgroups. Refer to Section 7 for an explanation of outcome definitions and the biases associated with each analysis.

Time-to-treatment failure was similar between the treatment groups (median TTF of 11 months in both groups; HR=0.86, 95% CI, 0.65-1.13 by IR assessment).[11] The Kaplan Meier curves demonstrated TTF favoured brentuximab vedotin during the first 12 months following randomization (treatment phase) with no difference between groups during the follow-up phase of the trial.

There were 52% (n=85) and 31% (n=51) of patients in the placebo and brentuximab vedotin treatment groups, respectively, who received subsequent treatment.[11] The median TTNT was

20.9 months in the placebo group and not reached in the brentuximab vedotin group, demonstrating a reduced risk of receiving subsequent treatment with brentuximab vedotin (HR=0.45 (95% CI, 0.32-0.64).

Eligibility criteria for the AETHERA trial required patients have at least one of the following risk factors: refractory HL, relapsed HL within <12 months of frontline treatment, and extranodal involvement at the time of pre-ASCT relapse. In the post-hoc risk factor analysis,[1,6,12-14] additional risk factors for which data were available for all patients were also examined and included best response to most recent salvage therapy, B symptoms at relapse, and two or more prior salvage therapies. The results showed a trend for improved PFS (by independent review) by increasing number of risk factors [for patients with ≥1, ≥2, and ≥3 risk factors, HRs were 0.57 (95% CI, 0.40-0.81), 0.49 (95% CI, 0.34-0.71), and 0.43 (0.27-0.68), respectively] but not for patients with only one risk factor (HR=1.65, 95% CI, 0.60-4.55).[11,14] The small number of patients in the one risk factor subgroup (n=49) should be considered when interpreting the result for this subgroup, as small sample size can produce an unreliable and inprecise treatment estimate.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were identified during development of the pCODR review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma Tumour Group Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on brentuximab vedotin (Adcetris) for Hodgkin Lymphoma (HL) (post-ASCT consolidation). Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The pCODR Lymphoma Tumour Group Clinical Guidance Panel is comprised of 3 medical oncologists.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. a) Original Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2016, **Embase** 1974 to 2016 April 14, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Brentuximab* or Adcetris* or Adtsetrys* or SGN-35 or SGN35 or 914088-09-8 or 7XL5ISS668).ti,ab,ot,kf,hw,rn,nm.	2057
2	Hodgkin Disease/ or Hodgkin*.ti,ab,kf. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignant).ti,ab,kf.	211279
3	1 and 2	1334
4	3 use pmez	241
5	3 use cctr	17
6	4 or 5	258
7	*Brentuximab vedotin/ or (brentuximab* or Adcetris* or Adtsetrys* or SGN-35 or SGN35 or 7XL5ISS668).ti,ab,kw.	1377
8	Hodgkin Disease/ or Hodgkin*.ti,ab,kw. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignant).ti,ab,kw.	213094
9	7 and 8	969
10	9 use oemezd	711
11	6 or 10	969

12	limit 11 to English language	932
13	remove duplicates from 12	703

Literature search via PubMed
A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#15	Search **#14 AND publisher[sb]** Filters: **English**	10
#14	Search **#12 AND #13** Filters: **English**	254
#13	Search **Hodgkin Disease[mh] OR Hodgkin*[tiab] OR ((lymphoma*[tiab] OR lymphogranuloma*[tiab] OR granuloma*[tiab]) AND malignant[tiab]))** Filters: **English**	68380
#12	Search **cAC10-vcMMAE [Supplementary Concept] OR Brentuximab*[tiab] OR Adcetris*[tiab] OR SGN-35[tiab] OR SGN35[tiab] OR 914088-09-8[rn] OR 7XL6ISS668[tiab]** Filters: **English**	392

b) Updated Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials July 2017, Embase 1974 to 2017 August 24, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Line #	Searches	Results
1	(Brentuximab* or Adcetris* or adtsetrys* or SGN-35 or SGN35 or 914088-09-8 or 7XL5ISS668).ti,ab,ot,kf,hw,rn,nm.	3169
2	Hodgkin Disease/ or Hodgkin*.ti,ab,kf. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignant).ti,ab,kf.	225165
3	1 and 2	2044
4	3 use pmez	405
5	3 use cctr	102
6	4 or 5	507
7	*Brentuximab vedotin/ or (brentuximab* or adcetris* or adtsetrys* or SGN-35 or SGN35 or 7XL5ISS668).ti,ab,kw.	2139
8	Hodgkin Disease/ or Hodgkin*.ti,ab,kw. or ((lymphoma* or lymphogranuloma* or granuloma*) and malignant).ti,ab,kw.	227150
9	7 and 8	1498

10	9 use oemezd	1026
11	6 or 10	1533
12	limit 11 to english language	1474
13	limit 12 to yr="2016 -Current"	541
14	remove duplicates from 13	360

Literature search via PubMed
A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#6	Search #1 AND #2 AND publisher[sb] Filters: Publication date from 2016/01/01; English	12
#5	Search #1 AND #2 Filters: Publication date from 2016/01/01; English	124
#4	Search #1 AND #2 Filters: Publication date from 2016/01/01	127
#3	Search #1 AND #2	361
#2	Search Hodgkin Disease[mh] OR Hodgkin*[tiab] OR ((lymphoma*[tiab] OR lymphogranuloma*[tiab] OR granuloma*[tiab]) AND malignant[tiab])	91663
#1	Search cAC10-vcMMAE [Supplementary Concept] OR Brentuximab*[tiab] OR Adcetris*[tiab] OR adtsetrys*[tiab] OR SGN-35[tiab] OR SGN35[tiab] OR 914088-09-8[rn] OR 7XL6ISS668[tiab]	580

2. Cochrane Central Register of Controlled Trials (Central)
Searched via Ovid

3. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Adcetris/Brentuximab, Hodgkin disease

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Adcetris/brentuximab, Hodgkin disease

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Adcetris/brentuximab, Hodgkin disease - last 2 years

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017Aug24) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017Aug24) via Ovid; The Cochrane Central Register of Controlled Trials (July 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Adcetris, brentuximab and Hodgkin disease.

No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, published between 1974 and December 31, 2017.

The search is considered up to date as of December 31, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last two years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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