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Brentuximab vedotin for the treatment of patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplantation

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Summary

Brentuximab vedotin (BV) is the first approved novel agent for salvage treatment of relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after autologous stem cell transplantation (ASCT). In this study, a literature-based analysis was undertaken to assess, via an indirect treatment comparison, the comparative efficacy of BV to salvage chemotherapy as treatment for R/R cHL patients following ASCT. This comparative effectiveness research was undertaken to support a reimbursement submission for BV to the Australian Pharmaceutical Benefits Advisory Committee. Retrospective analysis of individual patient data from four data sources demonstrated that the use of BV as first salvage treatment in cHL patients relapsing or progressing post-ASCT achieved improvements in both clinical response and overall survival. More specifically, BV was associated with an incremental improvement of 22% in overall response rate compared to salvage chemotherapy. Five-year overall survival and progression-free survival rates were 92·2% [95% confidence interval (CI): 85·5–99·3%] and 32·2% (95% CI: 19·1–54·6%) respectively for BV, compared to 30·5% (95% CI: 22·2–42·0%) and 3·2% (95% CI: 1·1–8·9%) respectively for salvage chemotherapy. The encouraging results from this conservative analysis have the potential to support informed clinical management and funding decisions for the first salvage of cHL patients demonstrating recurrence after ASCT.

Keywords: Hodgkin lymphoma, recurrence, autologous stem cell transplant, brentuximab vedotin, survival analysis.

Whilst the induction-remission chemotherapeutic regimens currently used to treat patients with classical Hodgkin lymphoma (cHL) result in high and prolonged progression-free survival (PFS) rates (up to 85–90%), considerable numbers of patients either do not respond to the initial chemotherapy (5–10%) or experience relapse (10–30%) after initially achieving a complete response (CR) to treatment (Evens *et al*, 2008). For patients with relapsed/refractory (R/R) disease who are fit enough to receive intensive chemotherapy, the contemporary management includes second line (salvage) chemotherapy, followed by autologous stem cell transplantation (ASCT), which results in long-term disease-free survival in 40–60% of patients (Linch *et al*, 1993; André *et al*, 1999; Schmitz *et al*, 2002). Patients displaying disease progression after ASCT, especially within the initial 12 months post-transplant, are considered to have a poor outcome, with a median overall survival (OS) not exceeding 2 years (Kewalramani *et al*, 2003; Moskowitz *et al*, 2009; Kaloyannidis *et al*, 2012; Arai *et al*, 2013), and the optimal treatment strategy in this setting remains unclear. While allogeneic stem cell transplantation (allo-SCT) still represents a curative option (Sarina *et al*, 2010), many cHL patients are unable to undergo this treatment for various reasons, including uncontrollable lymphoma, concomitant morbidities, lack of a suitable donor, older age and insufficient or inexperienced healthcare resources [as allo-SCT is an intensive procedure, it requires a high level of technical expertise and is associated with considerable costs in most developed countries (Blommestein *et al*, 2012; Majhail *et al*, 2013)]. Traditionally, many patients with R/R cHL after

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ASCT were treated with salvage chemotherapy, mostly with palliative intent (Devizzi *et al*, 1996; Santoro *et al*, 2000).

Histologically, cHL is characterised by the presence of a small number of malignant Reed-Sternberg cells, which consistently express the CD30 molecule, an activation marker belonging to the tumour necrosis factor receptor superfamily (Küppers *et al*, 1994; Küppers, 2009; Yurchenko & Sidorenko, 2010; Swerdlow *et al*, 2016). Brentuximab vedotin (BV) is a first-in class antibody-drug conjugate that targets malignant cells expressing the CD30 marker. It comprises an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). For patients with R/R cHL, novel agents such as BV offer an alternative, targeted treatment approach. BV's high efficacy and low toxicity profile have resulted in a plethora of clinical trials investigating its role either as monotherapy, or in combination with chemotherapy and/or newer agents in different treatment phases (including first-line treatment, and even after allo-SCT failure), as well as in other malignancies. Specifically regarding R/R cHL, BV has been approved by the Food and Drug Administration (FDA) in the USA (https://www.adcetris.com/presinfo/pi.pdf) for the treatment of patients with R/R HL either post-post-ASCT or after 2 lines of chemotherapy (for patients ineligible for ASCT), as well as by the European Medicines Agency (EMA) (conditional approval; https://www.medicines.org.uk/emc/medicine/27173) and the Australian Therapeutic Goods Administration (TGA) (https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&xml:id=CP-2014-PI-01042-1&d=201904051016933). BV has also been approved for R/R cHL by key reimbursement agencies, such as the National Institute for Health and Care Excellence (NICE) in the UK (NICE, 2018), the Scottish Medicines Consortium (SMC, 2014) and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) (Pharmaceutical Benefits Scheme, 2016).

This comparative effectiveness research study involved a literature-based analysis to assess, via an indirect comparison, the comparative efficacy of BV to the traditional treatment option of salvage chemotherapy for patients with progressing lymphoma following ASCT. The research was done to support a reimbursement submission to the PBAC, who advises on the reimbursement of drugs to be subsidised on Australia's national Pharmaceutical Benefits Scheme (PBS). In November 2016 the PBAC approved BV for the post-ASCT indication (Pharmaceutical Benefits Scheme, 2016). The strict guidelines for preparing a PBAC submission (Australian Government Department of Health, 2016) and associated peer-review validates both the approach as well as the quality of any analyses outlined. The study's findings can support informed clinical management and funding decisions at first salvage treatment of patients demonstrating lymphoma recurrence after ASCT.

Methods

The methodology described below outlines the analysis undertaken to support the reimbursement submission to PBAC for BV to be made available on the PBS for the post-ASCT R/R cHL population. This submission received a positive outcome in November 2016 (Pharmaceutical Benefits Scheme, 2016).

Identification of studies to inform an indirect treatment comparison

In the absence of direct comparative data investigating the efficacy of BV compared to salvage chemotherapy in the cHL post-ASCT setting [i.e., no randomised controlled trials (RCTs)], a systematic literature review was undertaken to identify relevant studies with R/R cHL post-ASCT patients exposed to treatment with either BV or with salvage chemotherapy regimens. The MEDLINE®, Embase® and Cochrane databases were searched, alongside clinical trial registries and grey literature, in order to move beyond traditional evidence in the published literature and identify all relevant data. The search terms used included Hodgkin disease, lymphoma, recurrence, salvage therapy and brentuximab vedotin. The searches were conducted initially in 2013 and updated in 2015/2016.

Two independent reviewers evaluated titles and abstracts of all citations; discrepancies were resolved by a third investigator. Articles deemed relevant from the information supplied in the abstract were chosen for full-text screening. The criteria for inclusion were:

1 The study intervention was BV (as a single agent) or a salvage chemotherapy regimen.
2 The patients had received a diagnosis of R/R cHL following ASCT.
3 The study reported one or more relevant endpoints for efficacy (OS; PFS; clinical response).

Full-text articles that met the inclusion criteria, and for which individual patient data (IPD) were available following a data sharing request, were included in this study. IPD were shared as de-identified information in Microsoft Excel.

Naïve indirect treatment comparison

Studies describing an intervention with BV were pooled together to form the intervention arm of the analysis while studies describing treatment with salvage chemotherapy were pooled together to form the comparator arm. These pooled datasets were used to assess the efficacy attributes of BV compared with salvage chemotherapy, unless otherwise specified.

Summary baseline characteristics of the pooled study arms. Patients characteristics at baseline (treatment initiation) were described by pooled treatment arm. Note that the term

"treatment line" relates specifically to the post-ASCT treatment line, and the numbering does not include any pre-ASCT treatments or ASCT itself. Variables with data for both arms were tested for heterogeneity using the chi-square test in R version 3.4 (R Core Team, 2018).

An evaluation of bias was performed by qualitative assessment comparing differences in characteristics and methodologies of the two pooled treatment arms.

Efficacy of BV compared with salvage chemotherapy: Survival analysis. Survival analyses were undertaken using Kaplan–Meier (KM) representations comparing BV and salvage chemotherapy. All analyses were performed using the survival package in R.

The survival outcomes of OS and PFS were compared across treatment arms using the pooled datasets described; to confirm consistency across data sources, these outcomes were also assessed using IPD. With the aim of capturing the full life expectancy of R/R cHL post-ASCT, outcomes were considered over a time horizon of 13 years, with this duration based on data demonstrating that OS exceeds 13 years in just 10% of patients (Pharmaceutical Benefits Scheme, 2016). Due to the short follow-up in the BV arm (5·9 years), an extrapolation was required. To align with the strict requirements of the PBAC guidelines, which state: "*economic claims based on models with very extended time horizons and predominantly extrapolated benefits will be less certain and are likely to be less convincing to the PBAC*", a conservative approach was adopted. Given that the available follow-up was considerably longer in the salvage chemotherapy arm compared with the BV arm (11·0 years vs. 5·9 years), proportional extrapolation was used to estimate outcomes of BV-treated patients over the "missing" follow-up period for this arm (i.e. between 5·9 and 11 years). Based on the proportional hazards approach employed for both OS and PFS, BV patients were assumed to decline at the same rate as that observed in patients treated with salvage chemotherapy (thus conservatively implying no incremental benefit of BV over salvage). After the last follow-up in patients treated with salvage chemotherapy, linear extrapolation was used over the last 2 years of the time horizon. This assumed survival in both the BV and salvage chemotherapy arms declined linearly at proportionally the same rate until no patients remained alive at the end of the 13-year time horizon. This extrapolation approach was deemed to be more conservative than traditional parametric extrapolations, as no additional BV benefit was assumed during the unobserved period beyond the follow-up available for BV-treated patients.

Survival at median, mean (restricted; at time of final patient follow-up within each pooled arm) and at 5 years across the un-extrapolated time horizon was evaluated. Wilcoxon and log-rank tests were used to determine if there were any significant differences in PFS and/or OS between the two pooled treatment arms.

Efficacy of BV compared with salvage chemotherapy: Clinical response. Clinical response was defined as the level of response achieved whilst on treatment using the revised response criteria for malignant lymphoma (Cheson *et al*, 2007). Overall response rate (ORR), defined as the sum of patients with CR and partial response (PR), was evaluated across pooled treatment arms for individual data sources that reported clinical response.

Results

Identification of studies to inform an indirect treatment comparison

The literature search identified 702 citations, of which a total of 690 data sources were excluded during the screening of titles and abstracts. Upon full-text assessment of the remaining 12 citations, 4 data sources of post-ASCT R/R cHL patients receiving either BV or conventional post-ASCT salvage chemotherapy treatments with IPD available were identified for the pooled indirect treatment comparison. The 4 data sources consisted of the registration study which was a single arm phase II study (ClinicalTrials.gov identifier NCT00848926; Chen *et al*, 2016), the control arm within an RCT (AETHERA; Moskowitz *et al*, 2015) and two country registries [Greece; (Kaloyannidis *et al*, 2012) and British Columbia (BC; Pharmaceutical Benefits Scheme, 2016)]. All four data sources reported OS outcomes, three reported PFS, and two reported clinical response (Table I).

The pooled BV arm consisted of two data sources: Chen *et al* (2016) ($n = 45$) and the phase III AETHERA trial (Moskowitz *et al*, 2015; $n = 62$). Chen *et al* (2016) reported the five-year survival data from a phase II single arm prospective cohort study in which BV was the first salvage treatment administered in 45 of the enrolled 102 cHL patients with disease progression after ASCT. This cohort was supplemented with a sub-population of patients ($n = 62$) within the placebo arm of the AETHERA trial (an RCT assessing the effect of BV consolidation after ASCT in cHL patients at increased risk for relapse or death) who received BV as the first salvage treatment following disease progression after ASCT. It is important to note that the AETHERA trial included only patients who were at high risk of relapse or death (Moskowitz *et al*, 2015), compared to the cohort of Chen *et al* (2016) where risk wasn't explicitly considered as an inclusion criterion, and as such is a limitation that could impact the outcomes within this arm.

A separate sub-population of 13 patients in the AETHERA trial received chemotherapy at first salvage after ASCT and were therefore included in the comparator (salvage chemotherapy) arm of the indirect treatment comparison, together with patients identified from two localised registries for R/R cHL that met the study inclusion criteria and for which IPD was available: Kaloyannidis *et al* (2012) ($n = 87$) and the BC registry (Pharmaceutical Benefits Scheme, 2016;

Table I. Studies included in the pooled indirect treatment comparison.

Source	Description	Outcome reported (yes/no)		
		OS	PFS	Clinical response
Treatment – BV (n = 107)				
Chen *et al* (2016)	A single arm Phase II non-comparative study for BV in R/R cHL after ASCT. 45 patients were enrolled at the first salvage after ASCT	Yes	Yes	Yes
AETHERA control arm (Moskowitz *et al*, 2015)	RCT assessing the efficacy of BV as a consolidation treatment after ASCT. Of the 85 patients who relapsed, 62 received BV as first salvage therapy after ASCT	Yes	No	No
Comparator – Salvage chemotherapy (n = 142)				
AETHERA control arm (Moskowitz *et al*, 2015)	RCT assessing the efficacy of BV as a consolidation treatment after ASCT. Of the 85 patients who relapsed, 13 received salvage chemotherapy as first salvage therapy after ASCT	Yes	No	No
Kaloyannidis *et al*, (2012)	Greek HL registry (n = 87)	Yes	Yes	Yes
BC registry (Pharmaceutical Benefits Scheme, 2016)	Canadian HL registry (n = 42)	Yes	Yes	No

ASCT, Autologous stem cell transplantation; BC, British Columbia; BV, Brentuximab vedotin; HL, Hodgkin lymphoma; OS, Overall survival; PFS, Progression-free survival; RCT, Randomised controlled trial; R/R, Relapsed or refractory.

n = 42). The addition of these two registries into the pooled comparator arm allowed for a comparison to be made within the study with reduced uncertainty.

Naïve indirect treatment comparison

Summary baseline characteristics of the pooled study arms. At post-ASCT relapse, a total of 107 and 142 patients received BV and salvage chemotherapy respectively as the first salvage treatment. The mean age of patients was 32·8 and 29·5 years for patients in the BV and salvage chemotherapy pooled treatment arms, respectively. Median age was lower at 29·0 *versus* 27·9 years, respectively. Males represented 58% of patients in the BV arm compared to 50% in the salvage chemotherapy arm. Whereas the majority of patients in the standard chemotherapy arm initiated treatment prior to and including 2008 (74·6%), all patients in the BV arm were treated post-2009. A significant difference was observed between the two arms based on current line of therapy (P = 0·01) with BV patients more likely to be on third or greater line of treatment (Table II). There was also a significant difference in the distribution of patients with stage IV disease between the treatment arms, with significantly more stage IV patients in the salvage chemotherapy arm compared with the BV arm (43% vs. 29%, P = 0·03). Lastly, where performance status was available, patients in the salvage chemotherapy arm were significantly less likely than BV-treated patients to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 (31% vs. 52%, P = 0·02) and significantly more likely to have an ECOG performance score of 2 (16% vs. 0%. P < 0·01), indicating better overall health of patients in the BV arm.

Patients in the standard chemotherapy arm most frequently received gemcitabine-based regimens (38–68%, depending on the source study). MOPP (mechlorethamine, vincristine, procarbazine, vincristine) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) variants, combining a nitrogen mustard (e.g. mechlorethamine, cyclophosphamide or chlorambucil) with a vinca alkaloid (e.g. vincristine), an alkylating agent (e.g. procarbazine) and a steroid (e.g. prednisone) were also commonly used in this setting (18–23%). Notably, in the Greek registry (Kaloyannidis *et al*, 2012), multiagent chemotherapy regimen was not specified for 24% of patients. Few patients received other regimens.

In the evaluation of bias comparing differences in characteristics and methodologies of the two pooled treatment arms, seven possible confounders were identified (Table III); three of which could have introduced bias towards BV: disease stage, frequency of second SCT and source study type. In addition, both the variation in geographical setting of the contributing datasets as well as the length of patient follow-up have potential to bias towards BV, however the actual effects cannot be ascertained. Difference between OS definitions was not considered a meaningful confounder. While OS was measured from date of treatment for all data sources in the BV arm, there were differences between OS definitions in the salvage chemotherapy arm: in the AETHERA control arm and in the Greek registry, OS was measured from date of treatment, but in the BC registry it was measured from date of progression after ASCT. However, as multiple relapsed HL is an aggressive disease, we did not anticipate the interval between relapse detection and start of treatment to meaningfully influence OS estimate. Finally, despite the significant difference in performance score favouring BV, it is

Table II. Baseline characteristics.

Treatment arm	BV	Salvage chemotherapy	*P*-value
n	107	142	-
Age (years), mean (median)	32·8 (29·0)	29·5 (27·9)	NE
Male, n (%)	62 (58%)	71 (50%)	$P = 0·22$
Number of lines of chemotherapy prior to first SCT, Median (range)	2 (NE)	NE	NE
By line of post-ASCT therapy			
1 or 2 lines of therapy, n (%)	52 (49%)	96 (68%)	$P = 0·01$
3 lines of therapy, n (%)	38 (36%)	28 (20%)	
4 lines of therapy, n (%)	12 (11%)	7 (5%)	
Greater than 5 lines of therapy, n (%)	5 (4%)	10 (7%)	
Unknown lines of therapy, n (%)	0 (0%)	1 (1%)	
Primary refractory, n (%)	47 (43·93)	NE	NE
Disease stage at initial diagnosis			
Stage I	5 (5%)	8 (6%)	$P = 0·96$
Stage II	41 (38%)	45 (32%)	$P = 0·34$
Stage III	29 (27%)	28 (20%)	$P = 0·22$
Stage IV	31 (29%)	61 (43%)	$P = 0·03$
Unknown	1 (1%)	0 (0%)	$P = 0·88$
B Symptoms at time of post-ASCT relapse	NE	NE	NE
ECOG performance status*			
ECOG score 0	56 (52·3%)	17 (30·9%)	$P = 0·02$
ECOG score 1	51 (47·7%)	29 (52·7%)	$P = 0·66$
ECOG score 2	0 (0·0%)	9 (16·4%)	$P < 0·01$
Calendar year of initialisation			
Pre-2008	0 (0·0%)	106 (74·6%)	$P < 0·01$
2009	45 (42·1%)	11 (7·8%)	$P < 0·01$
2010	1 (0·9%)	9 (6·3%)	$P = 0·07$
2011	20 (18·7%)	8 (5·6%)	$P < 0·01$
2012	29 (27·1%)	5 (3·5%)	$P < 0·01$
2013	9 (8·4%)	3 (2·1%)	$P = 0·046$
2014	3 (2·8%)	0 (0·0%)	$P = 0·16$

ASCT, Autologous stem cell transplantation; BV, brentuximab vedotin; ECOG, Eastern Cooperative Oncology Group; NE, not evaluated; SCT, stem cell transplantation.

*ECOG performance scores not available in Kaloyannidis *et al*, 2012.

difficult to assess if there was any resulting bias between the study arms, as ECOG performance score was only available for the minority of chemotherapy-treated patients (relevant information was not collected in the study reported by Kaloyannidis *et al*, 2012).

Efficacy of BV compared with salvage chemotherapy: Survival analysis. OS was defined as time from first post-ASCT salvage treatment initiation to death from any cause in all studies except in the analysis of the BC registry in which it was measured from date of progression after ASCT. PFS was defined as time from first post-ASCT salvage treatment initiation to progression for all studies.

Patients treated with BV achieved statistically improved OS outcomes compared to patients treated with salvage chemotherapy ($P < 0·001$ for both Log-rank and Wilcoxon tests) (Table IV, Fig 1). Five-year OS was 92·2% [95% confidence interval (CI): 85·5–99·3%] in the pooled BV arm compared to 30·5% (95% CI: 22·2–42·0%) in the pooled salvage chemotherapy arm. The median OS was not reached in the pooled BV arm and was 21·5 months (95% CI: 13·6–36·5 months) for the pooled salvage chemotherapy arm. When extrapolating OS, the median survival for BV was 114 months (a median gain of 92·5 months of OS compared to salvage chemotherapy).

The IPD for PFS was unavailable for the AETHERA trial (Moskowitz *et al*, 2015) and therefore the pooled comparisons omit this study from both arms. In addition, PFS could not be evaluated for patients with stable disease within the Kaloyannidis registry and, as such, these patients were assumed to progress at 15 days. Patients treated with BV achieved statistically improved PFS outcomes compared to patients treated with salvage chemotherapy ($P < 0·001$ for both Log-rank and Wilcoxon tests) (Table V, Fig 2). Five-year PFS rate was 32·2% (95% CI: 19·1–54·6%) in the pooled BV arm compared to 3·2% (95% CI: 1·1–8·9%) in the pooled salvage chemotherapy arm. The median PFS was 14·4 months (95% CI: 8·4 months – not reached) in the

Table III. Summary of bias evaluation.

Theme	BV	Salvage chemotherapy	Potential bias
Disease stage	29% had stage IV disease	43% of patients had stage IV disease	Towards BV
Time to relapse after ASCT	The median time to relapse after ASCT was 6·7 and 5·7 months for Chen *et al* (2016) and the sub-group of the AETHERA control arm (Moskowitz *et al*, 2015) who received BV as first salvage.	The median time to relapse after ASCT was approximately 11 months for registry based patients including Kaloyannidis *et al* (2012) and the BC registry (Pharmaceutical Benefits Scheme, 2016)	Against BV
Line of therapy	51% of patients were on at least their third line of therapy	32% of patients were on at least their third line of therapy	Against BV
Rate of second SCT	19% of patients were consolidated with a second SCT	13% of patients were consolidated with a second SCT	Towards BV
Geographical setting	The contributing data sources consists of patients from different regions and as such patients may follow different recommended treatment pathways	The contributing data sources consists of patients from different regions and as such patients may follow different recommended treatment pathways	Unknown
Time horizon	Patients were followed-up to a maximum of 72 months	Patients were followed-up to a maximum of 131 months	Unknown*
Data source (study type)	Clinical trial (100 % of patients)	Real-world registry studies (91% of patients), clinical trial (9% of patients)	Towards BV

ASCT, autologous stem cell transplant; BC, British Columbia; BV, brentuximab vedotin; OS, overall survival; SCT, stem cell transplantation.
*It is likely that a longer follow-up would result in more events resulting in poorer survival outcomes. However, it is unknown how this would compare against the extrapolation.

Table IV. Survival analysis (OS) – Pooled and by data source.

Study name	*n*	Total Follow-Up (months)	Median OS (months) (95% CI)	R-Mean (months)	Year 5 OS rate (95% CI)
BV					
Pooled population	107	72·0	NR	67·2	92·2% (85·5–99·3%)
Chen *et al* (2016)	45	72·0	NR	69·9	96·8% (90·8–100·0%)
AETHERA (Moskowitz *et al*, 2015)	62	40·2	NR	37·3	NR (NR-NR)
Salvage chemotherapy					
Pooled population	142	130·9	21·5 (13·6–36·5)	44·6	30·5% (22·2–42·0%)
Kaloyannidis *et al* (2012)	87	130·9	26·4 (15·5–40·7)	44·6	28·9% (19·3–43·2%)
BC registry (Pharmaceutical Benefits Scheme., 2016)	42	108·3	16·3 (8·0-NR)	40·9	34·7% (21·1–57·1%)
AETHERA (Moskowitz *et al*, 2015)	13	21·8	NR (6·9-NR)	16·6	NR (NR-NR)
BV vs. salvage chemotherapy					
Log-Rank	$P < 0·001$				
Wilcoxon	$P < 0·001$				

All analyses performed on non-extrapolated estimates.
BC, British Columbia; BV, Brentuximab vedotin; CI, Confidence interval; NR, not reached; OS, overall survival; R-Mean, Restricted mean.

pooled BV arm and 0·5 months (95% CI: 0·5–4·0 months) in the pooled salvage chemotherapy.

For each of the two treatment arms, individual data sources demonstrated similar trends in survival outcomes to each other and to the pooled dataset, for the non-extrapolated data (Figs S1 and S2).

Efficacy of BV compared with salvage chemotherapy: Clinical response. Due to the lack of reporting of clinical response in the AETHERA trial (Moskowitz *et al*, 2015) and the analysis of the BC registry, the response comparisons for the BV arm and the salvage chemotherapy arm were based on the study reported by Chen *et al* (2016) and the registry reported by Kaloyannidis *et al* (2012). The data demonstrated that BV was associated with an incremental improvement of 22% for ORR (consisting of 12% for CR and 10% for PR) compared to salvage chemotherapy (Table VI). An improvement of 9% for CR was also observed for those receiving BV within the study reported by Chen *et al* (2016) compared to the ITT population (CR: 42% vs. 33% respectively).

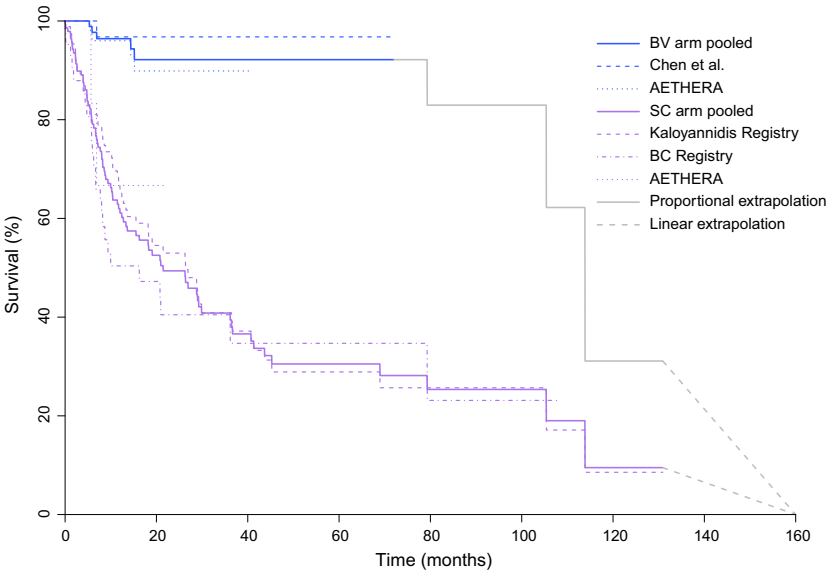

Fig 1. Survival analysis (OS) – Pooled (including extrapolation) and stratified by data source (without extrapolation). BV, Brentuximab vedotin; SC, salvage chemotherapy. [Colour figure can be viewed at wileyonlinelibrary.com]

Table V. Survival analysis (PFS) – Pooled and by data source.

Study name	*n*	Total follow-up (months)	Median PFS (months) (95% CI)	R-Mean (months)	Year 5 PFS rate (95% CI)
BV					
Pooled population	45	72·0	14·4 (8·4–NR)	30·3	32·2% (19·1–54·6%)
Chen *et al* (2016)	45	72·0	14·4 (8·4–NR)	30·3	32·2% (19·1–54·6%)
AETHERA (Moskowitz *et al*, 2015)	Not reported				
Salvage chemotherapy					
Pooled population	129	79·8	0·5 (0·5–4·0)	8·8	3·2% (1·1–8·9%)
Kaloyannidis *et al* (2012)*	87	34·9	0·5 (0·5–0·5)	4·1	NR (NR–NR)
BC registry (Pharmaceutical Benefits Scheme, 2016)	42	79·8	7·1 (5·2–14·5)	18·4	10·0% (3·7–26·8%)
AETHERA (Moskowitz *et al*, 2015)	Not reported				
BV vs. salvage chemotherapy					
Log-Rank	$P < 0·001$				
Wilcoxon	$P < 0·001$				

All analyses performed on non-extrapolated estimates.

BC, British Columbia; BV, Brentuximab vedotin; CI, Confidence interval; PFS, progression free survival; NR, not reached; R-Mean, Restricted mean.

*PFS is not able to be evaluated for patients with stable disease and it is assumed that those with stable disease have a PFS of 15 days.

Discussion

The decision regarding the choice of salvage treatment in patients with R/R cHL post-ASCT is becoming increasingly challenging in the era of novel agents, as there are no randomised studies to guide treatment choice. For studies where a relevant comparator is not available, it is possible to make indirect statistical comparisons from separate studies (Sutton *et al*, 2008). This can help with decision-making in clinical practice as well as in public health policy and funding decisions.

The present study, an evidence-based analysis of the comparative efficacy of BV to salvage chemotherapy for cHL patients experiencing relapse or progression following ASCT, was undertaken via an indirect treatment comparison, to support a reimbursement submission for BV to the PBAC. To address the limited availability of evidence that could negatively impact the outcome of the reimbursement submission (with this not being to the benefit of the patients) a thorough systematic review of the evidence was undertaken to identify appropriate registries and additional data sources, and move beyond the traditional evidence of published literature.

To our knowledge, this study is unique in assessing the impact of BV as first salvage treatment, compared with salvage chemotherapy, on clinical response and survival in patients with R/R cHL after ASCT. The results demonstrate that, compared to older salvage chemotherapy (as represented by a gemcitabine-vinorelbine-based multi-agent chemotherapy regimen), the use of BV as first salvage treatment in post-ASCT patients achieves improvements in both clinical response and survival. These results gain added prominence due to the

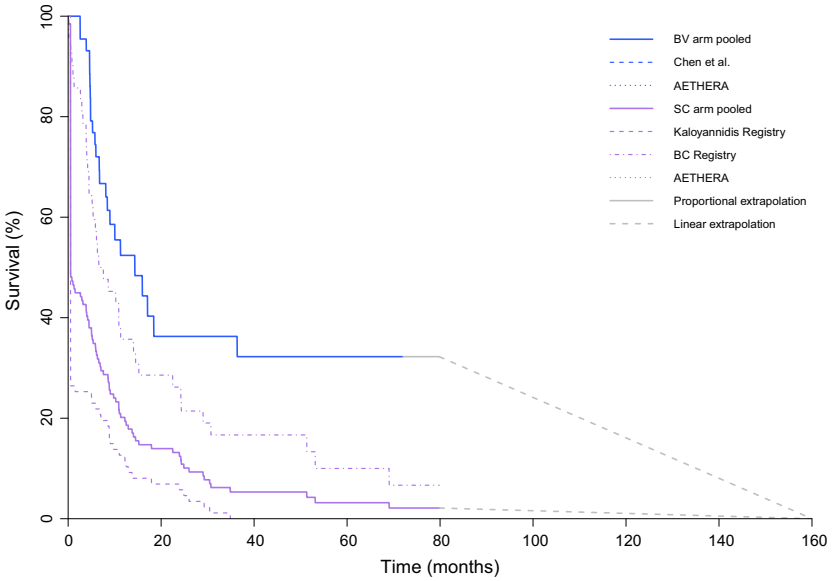

Fig 2. Survival analysis (PFS) – Pooled (including extrapolation) and stratified by data source (without extrapolation). BV, Brentuximab vedotin; SC, salvage chemotherapy. [Colour figure can be viewed at wileyonlinelibrary.com]

Table VI. Clinical response rates.

Study	*n*	ORR	CR	PR	SD	PD
BV treatment						
Pooled population	45	34 (75%)	19 (42%)	15 (33%)	11 (24%)	0 (0%)
Chen *et al* (2016)	45	34 (75%)	19 (42%)	15 (33%)	11 (24%)	0 (0%)
AETHERA (Moskowitz *et al*, 2015)	Not reported					
Salvage chemotherapy						
Pooled population	87	46 (53%)	26 (30%)	20 (23%)	41 (47%)	NA
Kaloyannidis *et al* (2012)	87	46 (53%)	26 (30%)	20 (23%)	41 (47%)	NA
BC registry (Pharmaceutical Benefits Scheme, 2016)	Not reported					
AETHERA (Moskowitz *et al*, 2015)	Not reported					

BC, British Columbia; BV, Brentuximab vedotin; CR, complete response; n, number of patients; ORR, overall response rate; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

conservative approach for BV adopted as per the PBAC submission guidelines (Pharmaceutical Benefits Scheme, 2016) to account for uncertainty within the pooled data.

Longer follow-up is required to determine whether these improvements in efficacy observed with BV will be maintained over longer periods of time. Since this study was completed, a 5-year follow-up of the phase 3 AETHERA trial has been published with the results demonstrating significant and sustained clinical benefit for patients treated with BV (Moskowitz *et al*, 2018).

Brentuximab vedotin is an antibody-drug conjugate which directly targets the malignant CD30-expressing Reed-Sternberg cells characteristic of cHL. A key advantage of targeted treatment with BV is limited drug exposure of normal tissues, and thus potentially fewer side effects and less debilitation compared to the various non-selective chemotherapy regimens currently employed as salvage therapy in this setting. Furthermore, BV's relatively simple and short mode of administration (a 30-min IV infusion once every three weeks) translates into a less onerous treatment schedule for the patient. Thus, BV can be considered an attractive option for cHL management. Furthermore, as indicated by the recommendations from NICE, SMC and the PBAC, the use of BV as a first salvage for patients with R/R cHL after ASCT could be considered an appropriate use of healthcare resources in the UK and Australia (Pharmaceutical Benefits Scheme, 2016, Parker *et al*, 2017).

Limitations of this study arise from confounding variables and the possibility of bias. Data sources utilised in this study were from non-randomised or observational research, which carry an inherent risk of bias, particularly as the proportion of patients from real-world studies was, by far, higher in the salvage chemotherapy group than the BV group. While clinical trials impose relatively strict eligibility criteria and usually guide patient management, registries generally provide information on unselected patient populations (some of whom could be ineligible for a trial due to age, comorbidities or other reasons) managed within routine care. Furthermore, one of the included registries, the Greek HL registry (Kaloyannidis *et al*, 2012), did not provide PFS information for patients with stable disease and these

patients were arbitrarily assigned a PFS of 15 days, which could somewhat impact the PFS assessment in this study. Overall, however, the incorporation of IPD strengthens the analysis as potential confounders could be examined at the individual patient level. Obtaining IPD enables the inclusion of studies that otherwise should be eliminated from a standard systematic review because they are either unpublished or do not report sufficient information to allow them to be included in the analyses, consequently avoiding publication bias. However, it is conceivable that by restricting analyses to those studies that can supply IPD, bias may be introduced through selective availability of study data and consequently the results of the study may not reflect the entire evidence base. Additional bias may be present in the survival analysis, as Kaplan–Meier plots were extrapolated beyond the last follow-up. However, the approach used is conservative and is likely to bias against BV. Despite the observed clear plateau of both PFS and OS curves which, as noted by Gopal *et al* (2015) when reporting the 3-year follow-up of the pivotal Phase II study, "*suggests that brentuximab vedotin may be curative in a fraction of patients*", the employed extrapolation method implies that the incremental benefit of treatment with BV (in terms of the substantial difference in OS and PFS) disappears immediately after the follow-up period, with the status of patients declining at the same rate as that in the salvage chemotherapy comparator arm, as well as being limited to a follow-up of 13 years. It is important to note, however, that the statistical analysis was performed only on the non-extrapolated data.

In conclusion, the data from this study demonstrated that treatment with BV as first salvage resulted in improved clinical response and survival rates in post-ASCT R/R cHL patients compared to those observed with conventional salvage chemotherapies. These are encouraging results, especially considering the conservative assumption surrounding the survival rates for BV, and are supported by the positive outcome of the PBAC submission, which validates the analysis, the results and the quality of the study. The findings have the potential to support informed decisions regarding the clinical management for first salvage treatment in patients with R/R cHL after ASCT, as well as to inform reimbursement decisions for healthcare payers.

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Conflicts of interest

K Webb, A Zomas and T Nikoglou are employees of Takeda Pharmaceuticals. JM Connors has received research support and honoraria from Seattle Genetics and Takeda Pharmaceuticals. R Schrover has received consultancy fees from Takeda Australia. M Hertzberg has received advisory/consultancy fees from Takeda, Gilead, Janssen, Roche and Sandoz and honoraria from Roche and Janssen. M Hurst and I Jacob are employees of Health Economics and Outcomes Research Ltd. and received funding from Takeda Pharmaceuticals to undertake the research outlined in this study. P Kaloyannidis has no conflicts of interest.

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K Webb, A Zomas, T Nikoglou, P Kaloyannidis, JM Connors and M Hertzberg conceptualised and designed the study. K Webb, R Schrover, M Hurst and I Jacob were responsible for data analysis. All authors contributed to interpretation of the results, preparation and review of the manuscript, and approval of the final manuscript for publication. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval to the version to be published.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Survival analysis (OS) – Pooled and stratified by data source (both including extrapolation).

Figure S2. Survival analysis (PFS) – Pooled and stratified by data source (both including extrapolation).

References

André, M., Henry-Amar, M., Pico, J.-L., Brice, P., Blaise, D., Kuentz, M., Coiffier, B., Colombat, P., Cahn, J.-Y. & Attal, M. (1999) Comparison of high-dose therapy and autologous stem-cell transplantation with conventional therapy for Hodgkin's disease induction failure: a case-control study. *Journal of Clinical Oncology*, **17**, 222–222.

Arai, S., Fanale, M., Devos, S., Engert, A., Illidge, T., Borchmann, P., Younes, A., Morschhauser, F., McMillan, A. & Horning, S.J. (2013) Defining a Hodgkin lymphoma population for novel therapeutics after relapse from autologous hematopoietic cell transplant. *Leukaemia & Lymphoma*, **54**, 2531–3.

Australian Government Department of Health (2016) Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory. Committee Available, https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf.

Blommestein, H., Verelst, S., Huijgens, P., Blijlevens, N., Cornelissen, J. & Uyl-De Groot, C. (2012) Real-world costs of autologous and allogeneic stem cell transplantations for haematological diseases: a multicentre study. *Annals of Hematology*, **91**, 1945–1952.

Chen, R., Gopal, A.K., Smith, S.E., Ansell, S.M., Rosenblatt, J.D., Savage, K.J., Connors, J.M., Engert, A., Larsen, E.K. & Huebner, D. (2016) Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*, **128**, 1562–1566.

Cheson, B., Pfistner, B., Juweid, M., Gascoyne, R., Specht, L., Horning, S., Coiffier, B., Ri, F., Hagenbeek, A., Zucca, E. & Rosen, S. (2007) Revised response criteria for malignant lymphoma. *Journal of clinical oncology*, **25**, 579–586.

R Core Team (2018) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

Devizzi, L., Santoro, A., Bonfante, V., Viviani, S. & Bonadonna, G. (1996) Vinorelbine: a new promising drug in Hodgkin's disease. *Leukemia and lymphoma*, **22**, 409–414.

Evens, A.M., Hutchings, M. & Diehl, V. (2008) Treatment of Hodgkin lymphoma: the past, present, and future. *Nature Reviews Clinical Oncology*, **5**, 543.

Gopal, A., Chen, R., Smith, S., Ansell, S., Rosenblatt, J., Savage, K., Connors, J., Engert, A., Larsen, E., Chi, X. & Sievers, E. (2015) Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. *Blood*, **125**, 1236–1243.

Kaloyannidis, P., Voutiadou, G., Baltadakis, I., Tsirigotis, P., Spyridonidis, A., Repousis, P., Balta, A., Tsimberis, S., Karakasis, D. & Sakellari, I. (2012) Outcomes of Hodgkin's lymphoma patients with relapse or progression following autologous hematopoietic cell transplantation. *Biology of Blood Marrow Transplantation*, **18**, 451–457.

Kewalramani, T., Nimer, S., Zelenetz, A., Malhotra, S., Qin, J., Yahalom, J. & Moskowitz, C. (2003) Progressive disease following autologous transplantation in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplantation*, **32**, 673.

Küppers, R. (2009) The biology of Hodgkin's lymphoma. *Nature Reviews Cancer*, **9**, 15.

Küppers, R., Rajewsky, K., Zhao, M., Simons, G., Laumann, R., Fischer, R. & Hansmann, M.-L. (1994) Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development. *Proceedings of the National Academy of Sciences, USA*, **91**, 10962–10966.

Linch, D., Goldstone, A., McMillan, A., Chopra, R., Hudson, G.V., Winfield, D., Hancock, B., Moir, D. & Milligan, D. (1993) Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *The Lancet*, **341**, 1051–1054.

Majhail, N., Mau, L., Denzen, E. & Arneson, T. (2013) Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: a study using a large national private claims database. *Bone Marrow Transplantation*, **48**, 294.

Moskowitz, A.J., Perales, M.A., Kewalramani, T., Yahalom, J., Castro-Malaspina, H., Zhang, Z., Vanak, J., Zelenetz, A.D. & Moskowitz, C.H. (2009) Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. *British Journal of Haematology*, **146**, 158–163.

Moskowitz, C.H., Nademanee, A., Masszi, T., Agura, E., Holowiecki, J., Abidi, M.H., Chen, A.I., Stiff, P., Gianni, A.M. & Carella, A. (2015) 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. *The Lancet*, **385**, 1853–1862.

Moskowitz, C.H., Walewski, J., Nademanee, A., Masszi, T., Agura, E., Holowiecki, J., Abidi, M.H., Chen, A.I., Stiff, P. & Viviani, S. (2018) Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood*, **132**, 2639–2642.

NICE (2018) Technology appraisal guidance [TA524]. Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma. National Institute for Health and Care Excellence, London, UK. Available. https://www.nice.org.uk/guidance/ta524.

Parker, C., Woods, B., Eaton, J., Ma, E., Selby, R., Benson, E., Engstrom, A., Sajosi, P., Briggs, A. & Bonthapally, V. (2017) Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma post-autologous stem cell transplant: a cost-effectiveness analysis in Scotland. *Journal of Medical Economics*, **20**, 8–18.

Pharmaceutical Benefits Scheme (2016) BRENTUXIMAB VEDOTIN, Powder for I.V. infusion 50 mg, Adcetris®, Takeda Pharmaceuticals Australia Pty Ltd. Public Summary Document – November 2016 PBAC Meeting. Available, http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/brentuximab-post-asct-psd-november-2016.pdf.

Santoro, A., Bredenfeld, H., Devizzi, L., Tesch, H., Bonfante, V., Viviani, S., Fiedler, F., Parra, H.S., Benoehr, C. & Pacini, M. (2000) Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study. *Journal of Clinical Oncology*, **18**, 2615–2619.

Sarina, B., Castagna, L., Farina, L., Patriarca, F., Benedetti, F., Carella, A.M., Falda, M., Guidi, S., Ciceri, F. & Bonini, A. (2010) Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. *Blood*, **115**, 3671–3677.

Schmitz, N., Pfistner, B., Sextro, M., Sieber, M., Carella, A.M., Haenel, M., Boissevain, F., Zschaber, R., Müller, P. & Kirchner, H. (2002) Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *The Lancet*, **359**, 2065–2071.

SMC (2014) Brentuximab vedotin (ADCETRIS®) 50mg powder for concentrate for solution for infusion. SMC No (845/12). Scottish Medicines Consortium. Glasgow, UK. Available.https://www.scottishmedicines.org.uk/media/1363/dad_brentuximab_vedotin__adcetris__final_sept_2014_amended_numbering_for_website.pdf.

Sutton, A., Ades, A., Cooper, N. & Abrams, K. (2008) Use of indirect and mixed treatment comparisons for technology assessment. *Pharmacoeconomics*, **26**, 753–767.

Swerdlow, S.H., Campo, E., Pileri, S.A., Harris, N.L., Stein, H., Siebert, R., Advani, R., Ghielmini, M., Salles, G.A., Zelenetz, A.D. & Jaffe, E.S. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, **127**, 2375–2390.

Yurchenko, M. & Sidorenko, S. (2010) Hodgkin's lymphoma: the role of cell surface receptors in regulation of tumor cell fate. *Experimental Oncology*, **32**, 214–223.

