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6.02 BRENTUXIMAB VEDOTIN, Powder for I.V. infusion 50 mg, ADCETRIS®, Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 Efficient Funding of Chemotherapy, Authority Required (Written) listing of brentuximab vedotin for use in the BrECADD regimen (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin and dexamethasone); for the first-line treatment of advanced stage CD30 positive Hodgkin lymphoma (HL). However, the requested restriction did not specify the BrECADD regimen and instead included the wording 'in combination with a multi-drug chemotherapy regimen'. CD30-positive Hodgkin Lymphoma is also referred to as classical Hodgkin lymphoma (cHL) and was described as such throughout the submission.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus eBEACOPP (escalated combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with previously untreated CD30+ advanced Hodgkin lymphoma, defined as stage IIB with large mediastinal mass and/or extranodal disease; stage III, or stage IV
Intervention	BrECADD[a] (21-day cycle): brentuximab vedotin 1.8 mg/kg (up to a maximum dose of 180 mg) to be used in combination with etoposide 150 mg/m2, cyclophosphamide 1250 mg/m2, doxorubicin 40 mg/m2, dacarbazine 250 mg/m2, and dexamethasone 40 mg
Comparator	eBEACOPP[1] (21-day cycle): bleomycin^ 10,000 IU/m2, etoposide 200 mg/m2, doxorubicin 35 mg/m2, cyclophosphamide 1,250 mg/m2, vincristine 1.4 mg/m2, prednisone~ 40 mg/m2, and procarbazine 100 mg/m2
Outcomes	Treatment-related morbidity, progression-free survival, complete response, overall survival, fertility, secondary primary malignancies, and patient-reported outcomes
Clinical claim	BrECADD is more effective than eBEACOPP at improving progression-free survival

Source: Table 1.1, p2 of the submission.
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin and dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and procarbazine.
[a] PET-adapted regimens where patients receive 2 cycles of treatment followed by an interim PET scan (iPET2). Patients who are iPET2 negative receive 2 subsequent cycles of treatment while patients who are iPET 2 positive receive 4 subsequent cycles.

2 Background

Registration status

2.1 Brentuximab vedotin was TGA registered in December 2025 for the treatment of adult patients with previously untreated CD30+ Stage IIB with large mediastinal mass and/or extranodal disease, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD).

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2.2 Brentuximab vedotin is TGA registered for the treatment of patients with previously untreated CD30+ Stage III or Stage IV HL in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

2.3 Brentuximab vedotin is also listed on the PBS for advanced cHL as part of the A+AVD regimen (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) following PBAC recommendation at the July 2025 meeting.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	**PBS item code**	**Dispensed Price Max Amt**	**Max. Amount**	**№.of Rpts**
BRENTUXIMAB VEDOTIN Injection	NEW (Public) NEW (Private)	Published Public: $17,780.23 Private: $18,073.54 Effective Public: $[redacted] Private: $[redacted]	180mg	11

Available brands	
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)	
Restriction Summary [new] / Treatment of Concept:	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 - Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ *Authority Required (telephone/online PBS Authorities system)* ☒~~Authority Required (in writing only via post/HPOS upload)~~
Prescribing rule level	**Administrative Advice:** No increase in the maximum *amount* ~~quantity~~ or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special Pricing Arrangements apply
	~~**Administrative Advice:**~~ ~~Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au~~ ~~Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)~~ ~~Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos~~ ~~Or mailed to:~~ ~~Services Australia~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~
	Administrative Advice:

		Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Episodicity: [blank]
		Severity: Advanced Stage
		Condition: CD30 positive Hodgkin lymphoma
		Indication: Advanced stage CD30 positive Hodgkin lymphoma
		Clinical criteria:
		The treatment must be for first line therapy for this condition.
		AND
		Clinical criteria:
		The treatment must be for curative intent.
		AND
		Clinical criteria:
		The patient must have either Stage IIB with large mediastinal mass and/or extranodal, Stage III or Stage IV disease
		AND
		Clinical criteria:
		The treatment must be in combination with a multi-drug chemotherapy regimen.
		AND
		Clinical criteria:
		The treatment must not be for more than 6 treatment cycles under this restriction in a lifetime.
		~~**Prescribing Instructions:**~~ ~~Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail.~~ ~~If the application is submitted through HPOS upload or mail, it must include:~~ ~~(a) details of the proposed prescription; and~~ ~~(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).~~
		Prescribing Instructions: *At the time of the authority application, medical practitioners must request the appropriate maximum amount and number of repeats to complete up to 6 cycles of treatment:* - *Up to a maximum of 180mg and 5 repeats may be requested where dosing is administered as part of the BrECADD regimen (in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone)* - *Up to a maximum of 120mg and 11 repeats may be requested where dosing is administered as part of the A+AVD regimen (in combination with doxorubicin, vinblastine and dacarbazine)*

3.2 The submission requested an Authority Required (in writing only via post/HPOS upload) Section 100 Efficient Funding of Chemotherapy listing of brentuximab vedotin 50 mg vial, reconstituted as a 5 mg/mL solution, and given as an intravenous (IV) infusion up to a maximum dose of 180 mg every 3 weeks for up to 6 cycles. The current 'Stage III or IV CD30 positive Hodgkin lymphoma' listings are Authority Required (telephone/online PBS Authorities system) due to simplicity of the criteria.

3.3 The submission requested a weighted price of $[redacted] across A+AVD and BrECADD (Table 2).

Table 2. Requested weighted price for brentuximab vedotin: A+AVD and BrECADD

	A+AVD	BrECADD
Population	1L stage III/IV cHL receiving brentuximab vedotin as part of A+AVD	1L stage IIB with large mediastinal mass and/or extranodal disease, III/IV cHL receiving brentuximab vedotin as part of BrECADD
Final AEMP per vial	$[redacted]	$[redacted] Weighted price based on A+AVD: $[redacted] (97,597 A+AVD vials, 48,799 scripts) BrECADD: $[redacted] (23,072 BrECADD vials, 7,691 scripts)

Source: Table 1-25, p55; of the submission and compiled from Sheet 'Intervention' of Excel workbook 'Adcetris (brentuximab vedotin) - FL HL – BrECADD.xlsb', Sheets '3a. Scripts – proposed', '3c. Impact proposed (eff)' of Excel workbook 'Adcetris (brentuximab vedotin) – FL HL – BrECADD – UCM.xlsx', Sheet '3c. Impact proposed (eff)' of Excel workbook 'Brentuximab vedotin – 07-2025 (7.01) – UCM vA.2 20250910.xlsx' (Attachment 19 of the submission

1L=first line; A+AVD=brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; cHL=classical Hodgkin lymphoma

3.4 The evaluation and the ESC considered that the estimated weighted price may not be reasonable as it was based on uncertain utilisation estimates for A+AVD and BrECADD. The number of vials was estimated from scripts for the corresponding treatment regimen, not just brentuximab vedotin, and multiplied by the expected number of vials of brentuximab vedotin per script (2 vials for A+AVD, 3 vials for BrECADD). The estimated numbers of scripts were based on estimated use over 5 years (2026-2030), with uptake for A+AVD assumed to be [redacted]%-[redacted]% per year while BrECADD uptake was [redacted]%-[redacted]% per year.

3.5 The ESC considered that since the March 2026 PBS listing of nivolumab for 'immunotherapy sensitive advanced or metastatic cancer', the vast majority of A+AVD would be replaced by nivolumab + AVD for patients with Stage IIB/III/IV disease. A+AVD would likely only be used in those with contraindications to immunotherapy, and who were considered unlikely to tolerate BrECADD. The ESC noted that if the majority A+AVD use was reduced the actual script ratio would shift heavily towards the lower priced BrECADD and hence the weighted price would be significantly decreased. Given expected changes in utilisation of A+AVD, the ESC considered that requesting a weighted price of $[redacted] was effectively assuming a much higher price of BrECADD than $[redacted] per 50 mg injection and recommended that the impact of using the requested weighted price on cost-effectiveness should be explored.

3.6 The proposed restriction was for brentuximab vedotin in combination with a multi-drug chemotherapy regimen to allow treatment with brentuximab vedotin for all treatment-naïve patients with advanced cHL. The PBAC previously considered it inappropriate for the restriction to be chemotherapy-agnostic, noting it would allow use of brentuximab vedotin in other regimens or combinations that had not been evaluated for efficacy, safety or cost effectiveness by PBAC (para 3.4, brentuximab vedotin, Public Summary Document [PSD], July 2025 PBAC meeting). The ESC considered that the restriction should specify the chemotherapy backbone (i.e. for use within the BrECADD regimen) as this is the evidence base for the submission. However, the ESC considered that it could be combined with the existing A+AVD restriction for first-line advanced cHL with both regimens specified within the listing.

3.7 The definition of advanced disease differed from the A+AVD restriction for first-line advanced cHL; the requested restriction included stage IIB with large mediastinal mass

and/or extranodal disease in addition to the previous definition of advanced disease, which included only stages III or IV. The pre-PBAC response accepted the ESC's advice that the term 'Advanced stage CD30 positive Hodgkin lymphoma' would be appropriate as the indication for a combined listing of both the currently listed A+AVD regimen and the proposed BrECADD regimen.

3.8 The submission was inconsistent regarding the target population's age; adult patients in the PICO (Table 1), patients ≤60 years in the financial estimates, and age-agnostic in the proposed restriction. The TGA indication was for adult patients only; however, the main trial only included patients aged 18 to 60 years, and the TGA delegate highlighted that the safety and efficacy of brentuximab vedotin as part of the BrECADD regimen have not been established in patients over the age of 60 years. The PSCR acknowledged differences in age across the populations who are eligible for treatment with BrECADD and A+AVD, and claimed that clinicians who treat cHL are experienced at identifying young, fit patients suitable for intensive therapies such as eBEACOPP and hence those who would be treated with BrECADD.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 HL is a B-cell lymphoid malignancy that accounts for approximately 15% of all lymphoma diagnoses. HL can be classified as either cHL or nodular lymphocyte predominant HL (NLPHL). cHL is characterised by the presence of abnormal lymphocytes, known as Hodgkin-Reed-Sternberg cells, which express the CD30 surface antigen and are unable to produce antibodies required for an effective immune response.

4.2 The most common clinical presentation is painless lymphadenopathy or mediastinal masses, which can grow quite large and indicate poorer prognosis in early-stage patients due to an increased risk of respiratory complications. Approximately 40% of patients present with B symptoms, which include unexplained high fever (> 38°C), night sweats, or significant weight loss (> 10% in 6 months preceding diagnosis).

4.3 The target population in the submission was patients with advanced stage cHL, defined as stage IIB with a large mediastinal mass and/or extranodal disease, stage III or stage IV. This definition aligns with the patient population in the clinical evidence presented in the submission (the HD21trial) and the TGA-approved indication.

4.4 The proposed clinical management algorithm (Figure 1) positioned brentuximab vedotin as part of the BrECADD regimen for first-line treatment of patients with advanced cHL aged ≤60 years. The evaluation considered that the proposed treatment algorithm was appropriate, but was not consistent with the proposed restriction, which was chemotherapy- and age-agnostic. The PBAC considered the proposed treatment algorithm did not reflect the recommended treatment options for first-line

advanced HL in European (European Society for Medical Oncology [ESMO] 2025[1]) and US (National Comprehensive Cancer Network [NCCN] 2026[2]) guidelines. The PBAC noted the ESMO guideline recommendations for first-line advanced HL had changed since 2018[3] with the key changes being:

- BrECADD (PET-adapted) the preferred treatment for fit patients aged ≤ 60 years;
- nivolumab + AVD as an alternative to BrECADD for patients aged ≤60 years and the favoured option for patients 60-80 years;
- A+AVD is a treatment option for patients ≤60 years where nivolumab + AVD is unavailable and BrECADD is clinically unsuitable; and
- ABVD or escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and dacarbazine (eBEACOPDac) if brentuximab vedotin and programmed cell death protein 1 (PD-1) inhibitors are not available. Previously ABVD was alternative to escalated BEACOPP.

The PBAC agreed with the ESC that, consistent with recent international guidelines, in Australian clinical practice nivolumab + AVD is now widely used in upfront treatment of advanced stage cHL, largely replacing A+AVD.

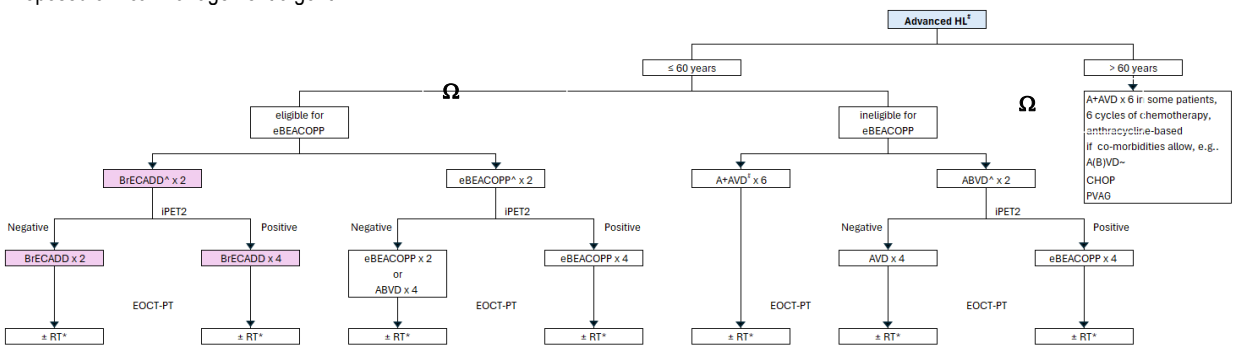
[1] Eyre et al. Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025 Nov;36(11):1263-1284

[2] Advani et al. Hodgkin Lymphoma, Version 1. J Natl Compr Canc Netw 2026;24(2):41–60

[3] Eichenauer et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018 Oct 1;29:iv19-29.

Figure 1: Proposed clinical management algorithm

Proposed clinical management algorithm



Source: Figure 1.18, p45 of the submission. Pink= proposed listing

AVD = doxorubicin, vinblastine, and dacarbazine; A+AVD = brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL = classical Hodgkin lymphoma; CHOP = doxorubicin, cyclophosphamide, vincristine, prednisolone; iPET = interim PET scan; eBEACOPP = escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; EOCT-PET = end of chemotherapy PET; EORTC = European Organisation for Research and Treatment of Cancer; GHSG = German Hodgkin Study Group; PVAG = prednisolone, vinblastine, doxorubicin, gemcitabine; RT = radiotherapy

Ω eBEACOPP is standard of care in a specific subgroup of cHL, used for at least the first 2 cycles for fit patients < 45 years (as noted by ESC, see para 5.5, brentuximab vedotin, PSD, March 2024). The Australian consensus statement (Cochrane et al. 2021) recommended the following PET-adapted strategies for fit patients younger than 60: i) ABVD x2, escalating to eBEACOPP if iPET2 is positive, or continuing with AVD if iPET2 is negative; ii) eBEACOPP x2, continuing to 4 instead of 6 cycles of eBEACOPP if iPET2 is negative; iii) eBEACOPP x2, de-escalating to additional ABVD x4 if iPET2 is negative.

4.5 Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent (monomethyl auristatin E [MMAE]), resulting in death of the CD30-expressing tumour cells in cHL. Brentuximab vedotin binds to CD30 on the cell surface, the ADC-CD30 complex enters the cell and MMAE is released, leading to cell cycle arrest and apoptotic death of the CD30-expressing tumour cell.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated positron emission tomography (PET)-adapted eBEACOPP as the main comparator. The evaluation and the ESC considered that (PET)-adapted eBEACOPP was the appropriate comparator for first-line treatment with BrECADD in patients with advanced cHL aged <60 years. This was consistent with Australian guidelines, which recommend that eBEACOPP should not be used in patients older than 60 years.

5.2 The submission did not consider nivolumab as a near-market comparator stating it was neither TGA approved nor under evaluation for the first-line treatment of cHL (although it was submitted for this indication in January 2026[4]). The evaluation noted that nivolumab was listed on the PBS for the treatment of 'immunotherapy sensitive advanced or metastatic cancer' in March 2026 (which would allow use for the first line

[4] OPDIVO Bristol-Myers Squibb Australia Pty Ltd | Therapeutic Goods Administration (TGA)

treatment of cHL). Therefore, the evaluation considered nivolumab + AVD may be considered a relevant comparator.

5.3 The ESC considered that with the March 2026 nivolumab listing the majority of fit patients <60 years eligible for eBEACOPP would continue to receive eBEACOPP and hence this remained the treatment most likely to be replaced by BrECADD. However, nivolumab + AVD may also be considered a relevant comparator for some patients, though it was unclear what proportion of patients who would currently receive eBEACOPP may be treated with nivolumab + AVD.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (6) and organisations (4) via the Office of Health Technology Assessment Consultation Hub. The input from health care professionals highlighted a range of benefits of treatment with brentuximab vedotin in the BrECADD regimen including improved progression-free survival with the potential for a shorter duration of therapy with a PET-adapted approach. Safety was a key consideration, with health care professionals comparing the toxicity profile of BrECADD and currently available treatment options. Compared with escalated BEACOPP, BrECADD was reported to have reduced toxicity, particularly in relation to fertility, secondary malignancies, pulmonary toxicity and treatment-related infections. Adverse effects associated with BrECADD were also reported, including peripheral neuropathy related to brentuximab vedotin, and the risk of neutropenia requiring growth factor support. Health care professionals emphasised the importance of preserving quality of life for patients with Hodgkin lymphoma, many of whom are diagnosed at a young age and may experience treatment-related consequences for decades after achieving remission. Health care professional input also noted that the treatment landscape had changed with the introduction of nivolumab + AVD which was identified as a preferred or emerging standard treatment option for many patients.

6.3 The PBAC also noted input from Rare Cancers Australia and Lymphoma Australia, highlighting the substantial physical, emotional, social and financial burden of Hodgkin lymphoma and its treatment, particularly in younger patients. They emphasised the importance of achieving durable remission with first-line therapy and reducing long-term toxicity, including impacts on fertility and quality of life.

6.4 The PBAC noted the advice received from the Haematology Society of Australia and New Zealand (HSANZ) and from the Australasian Leukaemia and Lymphoma Group (ALLG). Input from HSANZ highlighted that this condition affects a predominately

young patient population in whom the goal of first-line treatment is cure. HSANZ considered the BrECADD regimen represents a clinically meaningful advance because it preserves the curative intent of intensive first-line therapy while reducing toxicity. Input from ALLG emphasised that the first-line treatment landscape for advanced cHL has evolved substantially in recent years with the emergence of nivolumab + AVD. ALLG's position was that BrECADD and nivolumab + AVD address overlapping but clinically distinct patient populations, and that both have a legitimate place in the contemporary management of this condition. Acknowledging that populations in the trials were not directly comparable and no head-head trials have been conducted, ALLG considered that BrECADD achieved the highest medium-term disease-free survival rates of any regimen tested in this population. ALLG advised that BrECADD would likely be reserved for a well-defined subgroup of younger, fit patients with high International Prognostic Scores who are suitable for intensive PET-adapted induction therapy. They highlighted that nivolumab + AVD was the preferred first-line treatment option patients for whom an AVD-based regimen is appropriate, including older and lower-risk patients. They considered that A+AVD would be reserved for patients unable to receive nivolumab.

Clinical trial

6.5 The submission was based on one head-to-head trial comparing BrECADD to eBEACOPP as first-line therapy for patients with advanced cHL (HD21).

6.6 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HD21 (NCT02661503)	Treatment Optimization Trial in the First-Line Treatment of Advanced-Stage Hodgkin lymphoma; Comparison of 4-6 Cycles of Escalated BEACOPP With 4-6 Cycles of BrECADD	Primary CSR, 19 March 2024
	Treatment Optimization Trial in the First-Line Treatment of Advanced Stage Hodgkin Lymphoma; Comparison of 4-6 Cycles of Escalated BEACOPP With 4-6 Cycles of BrECADD	CSR Addendum, 7 November 2024
	Borchmann P, Ferdinandus J, Schneider G et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial.	The Lancet 2024; 404(10450), p341-352
	Ferdinandus J, Schneider G, Moccia A et al. Fertility in patients with advanced-stage classic Hodgkin lymphoma treated with BrECADD versus eBEACOPP: a secondary analysis of the multicentre, randomised, parallel, open-label, phase 3 HD21 trial.	Lancet Oncology 2025; 26(8), p1081-1090
	Kristo F, Mazerolle F, Alin T et al. Patient perspective on chemotherapy-induced peripheral neuropathy (CIPN) in advanced-stage classic Hodgkin lymphoma treated with multiagent chemotherapy regimens in the HD21 trial.	Clin Lymphoma Myeloma Leuk 2026; 2026 Mar 17:S2152-2650(26)00074-1
	Khair WAM. Progress in the Treatment of Advanced-Stage Classical Hodgkin Lymphoma in the PET-Adapted Era.	Oncology (Williston Park) 2025; 39 (9): p424-430
	Li DH, Zhang WH, Ding Y et al. Treatment efficacy for advanced-stage classic Hodgkin lymphoma: a systematic review and meta-analysis of randomised controlled trials.	HemaSphere 2025; 9, p1137-1139
	Vinsentin A, Cellini A, Angotzi F et al. BrECADD: the optimal treatment for advanced-stage hodgkin lymphoma - a metanalysis and an indirect comparison with individual patient data extraction	HemaSphere 2025; 9, p294-295

Source: Table 2.3, p64 of the submission.
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CIPD=chemotherapy-induced peripheral neuropathy; CSR=clinical study report; eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GHSG=German Hodgkin study group; PET=positron emission tomography

6.7 The key features of the HD21 trial are summarised in Table 4.

Table 4: Key features of the HD21 trial

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
BrECADD[a] vs. eBEACOPP[b]						
HD21	1500 Enrolled July 2016 – Aug 2020	P3, MC, R, OL Median follow up (months) BrECADD[a] vs eBEACOPP[b] arms; 40.6 vs 40.4 (interim analysis), 50.8 vs 51.1 updated analysis Ongoing longer-term follow up	Moderate	Age: 18 – 60 years, Advanced cHL. ECOG performance status 0-2,	TRMB, PFS, OS, CRR rate, infertility at 1-year, second malignancies, AE, SAE, HRQoL	PFS, AE, HRQoL

Source: Figure 2.1 p68; pp73,75 of the submission.
AE=adverse event; ASCT=autologous stem cell transplant; CRR=complete remission rate; DB=double blind; ECOG=Eastern Cooperative Oncology Group; HRQoL=health-related quality of life; MC=multi-centre; OL=open label; OS=overall survival; P3=phase 3; PFS=progression-free survival; R=randomised; SAE=serious adverse event; TRMB=treatment related morbidity.
[a] Regimen for BrECADD includes 4-6 cycles (2+2 or 2+4 cycles, PET adaptive) of brentuximab vedotin + cyclophosphamide + etoposide/etoposide phosphate + doxorubicin + dacarbazine + dexamethasone
[b] Regimen for eBEACOPP includes 4-6 cycles of (2+2 or 2+4 cycles, PET adaptive) of cyclophosphamide + doxorubicin + etoposide/etoposide phosphate + procarbazine + prednisone + vincristine + bleomycin

6.8 The HD21 trial enrolled participants aged 18 to 60 years with untreated advanced cHL, defined as stage IIB with large mediastinal mass/extranodal disease, or stages III/IV. Patients in both arms received either 4 or 6 cycles of treatment, based on a computed tomography/positron emission tomography (CT/PET) assessment after 2 cycles (21-days each) of treatment (iPET2); iPET2-positive patients received 4 additional cycles, and iPET2-negative patients received 2 additional cycles of treatment. The ESC considered that the trial was well balanced with robust patient numbers.

6.9 The submission stated the analysis of trial outcomes was investigator assessed, but an independent central review panel blinded to treatment assignment of the study participants, performed the review of tumours, including staging and restaging. The open-label design and investigator-assessed outcomes increased the risk of bias due to potential detection bias. As opposed to a blinded independent central review (BICR), which usually evaluates all patient data, the independent central panel review only reviewed tumour samples, not health related quality of life (HRQoL) or AEs, potentially overestimating the effectiveness and safety of brentuximab vedotin. Even though identified tumours were confirmed by an independent review panel, the panel would have only assessed the tumours identified by the investigators, potentially missing disease progression. The trial had two co-primary outcomes: progression-free-survival (PFS) and treatment-related morbidity (TRMB). The efficacy analysis was conducted as intention to treat (ITT), and the safety analysis included patients with at least one dose of treatment.

6.10 TRMB included clinically relevant toxicities arising in previous studies of eBEACOPP and toxicities associated with brentuximab vedotin; these included acute haematological toxicities of Grade 4 (i.e., anaemia, thrombocytopenia, or infections) and acute organ toxicities of Grade 3-4 (i.e., cardiac, gastrointestinal [GI], hepatobiliary, nervous system, renal or urinary, and respiratory or thoracic or mediastinal disorders), occurring from treatment initiation to 30 days after completion of chemotherapy. TRMB was investigator assessed. Antibiotic prophylaxis

was only given to patients in the BrECADD arm, which could bias the TRMB outcome, favouring BrECADD by reducing infection risk in the BrECADD arm only.

6.11 There were a series of protocol and statistical analysis plan (SAP) amendments to the HD21 trial, including:

- Reversal of testing hierarchy following review of safety data by the independent data monitoring committee, from initially specifying that PFS-non-inferiority would be tested first, to requiring TRMB superiority before PFS non-inferiority (SAP amendment 1).
- The SAP amendment 1 also pre-specified PFS non-inferiority as an absolute difference of less than 6% at 5 years (hazard ratio (HR) < 1.69), requiring a total of 154 progression events to achieve 90% power at a two-sided significance level of 0.05. However, at the interim (data cut-off 31 Dec 2022) and updated (data cut-off October 2023) analyses, only 101 and 109 progression events were reported, respectively, substantially reducing the statistical power.
- At the interim analysis (36 months estimated follow-up), PFS non-inferiority analysis was demonstrated, with Type-I-error controlled using O'Brien–Fleming boundaries with a Lan–DeMets spending function. However, the target number of events was not reached. After 48 months of follow-up, reaching 154 progression events during the trial was deemed unachievable. Based on alpha spent at the interim analysis, and an actual information rate of 71%, a two-sided significance level of 0.0392 remained for the updated non-inferiority analysis of PFS.
- Following evidence of non-inferiority, the protocol was further amended (version 10, 8th December 2023) to conduct a superiority analysis for PFS in accordance with EMA scientific guidelines; however, this superiority analysis was not included in the SAP amendment 1.

6.12 Although type-I-error control was maintained, the substantially reduced number of PFS events limits the precision of both the non-inferiority and superiority estimates. The evaluation and the ESC considered that the timing of the protocol amendments, made after review of emerging TRMB data, introduced uncertainty about whether the revised analyses may have been influenced by accumulating information. The PSCR acknowledged shortcomings in trial execution, but reiterated that the amendments were made in accordance with EMA guidance on interpreting a non-inferiority trial as a superiority trial, and maintained that the published HR of 0.66 (95% CI 0.45, 0.97, p = 0.035) was appropriate.

6.13 The TGA clinical evaluation report (CER) considered that the data were adequate to support the conclusion that BrECADD was non-inferior to the eBEACOPP regimen in terms of efficacy. The PSCR argued that the TGA was not provided with the later superiority test. However, the ESC noted the test for superiority was not incorporated in the modified SAP provided by the submission. The ESC considered that the inclusion of a superiority analysis in the protocol amendment but not in the SAP was not consistent with good statistical practice.

6.14 The final analysis after 5 years of follow-up was not discussed in the submission, although a conference abstract[5] was included in the reference list.

Comparative effectiveness

6.15 Table 5 and Figure 2 summarise the PFS and OS outcomes in HD21. The median follow-up was 40.6 months for BrECADD and 40.4 months for eBEACOPP at the interim analysis; and 50.8 and 51.1 months, respectively, at the updated analysis.

Table 5: Summary of progression-free survival and overall survival outcomes (ITT population).

Trial ID	Interim Analysis data cut-off: Dec 2022		Updated Analysis data cut-off: Oct 2023	
	BrECADD	eBEACOPP	BrECADD	eBEACOPP
Progression-free survival				
Events n/N (%) Median TTE (95% CI)	39/751 (5.2%) NE (NE, NE)	62/749 (8.3%) NE (NE, NE)	44/751 (5.9%) NE (NE, NE)	65/749 (8.7%) NE (NE, NE)
HR (95%)	**0.619 (0.415, 0.925)** [a]		**0.664 (0.453, 0.973)** [b]	
HR (98.87%)	**0.619 (0.369, 1.040)** [c]		-	
HR (98.46%)	-		**0.664 (0.414, 1.065)** [d]	
Overall survival				
Events n/N (%) Median TTE (95% CI)	- -	- -	12/751 (1.6%) NE (NE, NE)	13/749 (1.7%) NE (NE, NE)
HR (95%)[a]	-		0.919 (0.419, 2.015) [e]	

Source: Table 2.21, p96; Table 2.22, p97; Figure 2.4, p98 of the submission.
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CI=confidence interval; eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; HR=hazard ratio; ITT=intention to treat; N=total participants in group; n=number of participants with event; NE=not estimable; TRMB=treatment-related morbidity; TTE=time to event

[a] Non-inferiority analysis at interim analysis; the hazard ratio was derived from an unstratified Cox proportional hazards model.

[b] Superiority analysis at updated analysis; the hazard ratio was derived from an unstratified Cox proportional hazards model; see Table 2.23 of the submission where it is called final analysis; p = 0.035, also reported in Borchmann et al. 2024.

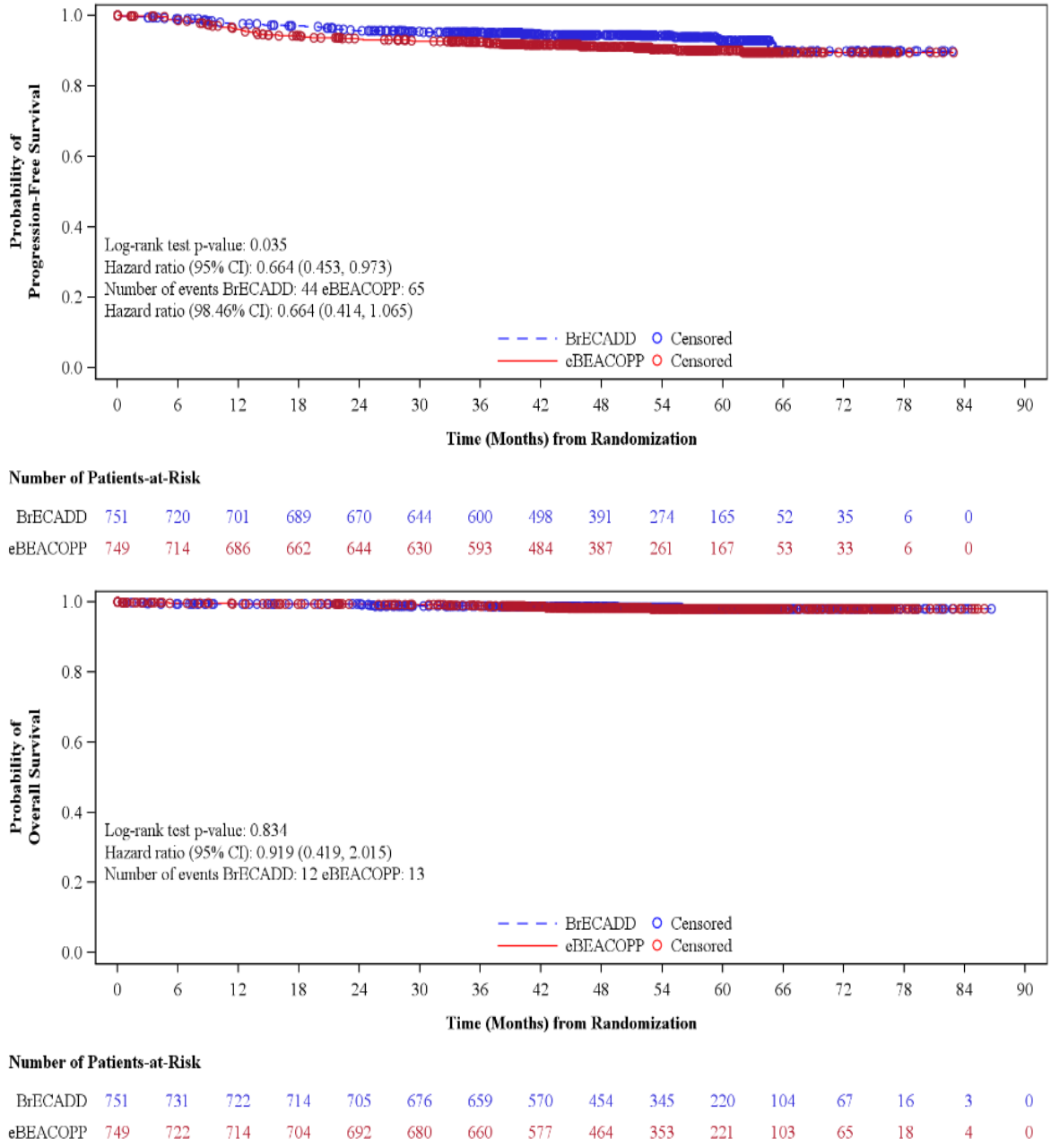
[c] Non-inferiority analysis at interim analysis; as 101 out of the 154 prespecified progression events occurred (65.6% information fraction), the level of the confidence interval was adjusted (98.87%) using the O'Brien-Fleming method to control type I error.

[d] Non-inferiority analysis at updated analysis; as 109 out of the 154 prespecified progression events occurred (70.8% information fraction), the level of the confidence interval was adjusted (98.46%) using the O'Brien-Fleming method to control type I error

[e] The hazard ratio was derived from an unstratified Cox proportional hazards model; see Table 2.24 of the submission; p = 0.834.

[5] Ferdinandus et al. 2025. Final analysis of the Phase III GHSG HD21 trial: PET-guided brecadd vs. ebeacopp in advanced-stage classical Hodgkin lymphoma. Blood 2025; 146 (Supplement 1): 152.

Figure 2: Kaplan-Meier curves for progression free survival and overall survival (ITT population, Updated Analysis)



Source: Figure 2.4, p102; Figure 2.6, p102 of the submission.
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

6.16 The submission stated that PFS results at both the interim analysis (HR: 0.619; 98.87% CI: 0.369, 1.040) and updated analysis (HR: 0.664; 98.46% CI: 0.414, 1.065) demonstrated that BrECADD was non-inferior to eBEACOPP.

6.17 The superiority analysis at the updated analysis reported a significantly reduced risk of progression in the BrECADD arm (HR: 0.664; 95% CI: 0.453, 0.973).

6.18 Overall, PFS data were immature due to the small number of progression events over 51 months (4.25 years) of follow-up. The final 5-year PFS results were presented in a conference abstract (Ferdinandus et al. 2025[6]), but not included in the submission or the clinical study report (CSR). The PFS HR after a median follow-up of 60 months was 0.64 (95% CI: 0.44, 0.93) favouring BrECADD. Noting the wide confidence intervals for estimated HR, the ESC considered the magnitude of PFS benefit was uncertain.

6.19 The ESC noted that Ferdinandus et al. 2025 reported that salvage therapies were similar across treatment arms: most patients with progression or relapse received autologous stem cell transplantation (52/61 (82%) after eBEACOPP vs 29/38 (76%) after BrECADD). The ESC considered that similar use of subsequent therapies suggests there may not be meaningful downstream clinical benefits associated with BrECADD.

6.20 There were no significant differences in OS between BrECADD and eBEACOPP (HR: 0.919; 95% CI: 0.419, 2.015). The final analysis reported that OS remained at 98% in both arms at 5 years of follow-up.

6.21 There were no statistically significant differences between the BrECADD and eBEACOPP arms for the secondary outcomes of overall response rate (ORR), complete response (CR), PET status at treatment cycle 2, rates of radiotherapy and health-related quality of life (HRQoL). Duration of response (DOR) was significantly higher in the BrECADD arm, but the median DOR was not estimable for both arms.

Comparative harms

6.22 Table 6 summarises the co-primary outcome of TRMB and adverse events (AEs) in HD21 for the safety population (data cut-off 31 Dec 2022).

6.23 The TGA CER highlighted that some AEs were not included in the TRMB outcome: Grade 1, 2, or 3 haematologic toxicities were considered manageable and therefore excluded; similarly, Grade 4 neutropenia was expected to occur in nearly all patients treated with eBEACOPP and was not included. The evaluation considered that given the significantly higher incidence of febrile neutropenia in the BrECADD arm (Table 6), exclusion of these events from the TRMB outcome seems inappropriate.

[6] Ferdinandus et al. 2025. Final analysis of the Phase III GHSG HD21 trial: PET-guided BrECADD vs. eBEACOPP in advanced-stage classical Hodgkin lymphoma. Blood 2025; 146 (Supplement 1): 152.

Table 6: Summary of key adverse events in HD21 (interim analysis: data cut-off 31 Dec 2022).

Outcome	BrECADD N=747	eBEACOPP N=741	RR (95% CI)
TRMB	315 (42.2%)	435 (58.7%)	**0.72 (0.65, 0.79)**
Any TEAE	745 (99.7%)	741 (100%)	0.997 (0.993, 1.002)
Any Grade ≥3 TEAE	682 (91.3%)	717 (96.8%)	**0.944 (0.920, 0.968)**
Any SAE	328 (43.9%)	310 (41.8%)	1.050 (0.933, 1.180)
SAE leading to treatment discontinuation	15 (2.0%)	15 (2.0%)	0.992 (0.489, 2.015)
AE leading to dose modification	300 (40.2%)	486 (65.6%)	**0.612 (0.553, 0.678)**
Grade 5 TEAE	4 (0.5%)	3 (0.4%)	1.323 (0.297, 5.889)
CTCAE toxicity grade ≥3 (> 5% of patients)			
Leukopenia	646 (86.5)	698 (94.2)	**0.918 (0.888; 0.949)**
Thrombocytopaenia	411 (55.0)	533 (71.9)	**0.765 (0.707; 0.828)**
Anaemia	220 (29.5)	435 (58.7)	**0.502 (0.442; 0.569)**
Infection	210 (28.1)	183 (24.7)	1.138 (0.960; 1.350)
Febrile neutropenia	198 (26.5)	145 (19.6)	**1.355 (1.122; 1.636)**
GI disorders (excl. nausea, vomiting, mucositis)	58 (7.8)	33 (4.5)	**1.744 (1.151; 2.641)**
Hepatobiliary disorders	37 (5.0)	22 (3.0)	**2.338 (1.396; 3.916)**
Mucositis	33 (4.4)	43 (5.8)	0.761 (0.490; 1.185)

Source: Table 2.31, p118; Table 2.32, p120; Table 2.33, p122 of the submission
AE=adverse event; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CI=confidence interval; eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GI=gastrointestinal; N=total participants in group; n=number of participants reporting data; RR=relative risk; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRMB= treatment-related morbidity.

6.24 TRMB at the interim analysis was significantly lower in BrECADD compared to eBEACOPP (relative risk [RR]: 0.72, 95% CI: 0.65, 0.79). Of the AEs included in TRMB, the submission noted that BrECADD resulted in lower rates of acute haematological toxicity compared to eBEACOPP (31.2% vs 52.1%, respectively). However, the rates of febrile neutropenia, as well as gastrointestinal and hepatobiliary disorders, were higher in the BrECADD arm (Table 6).

6.25 The submission did not present any safety data for the updated analysis, except for secondary malignancy, citing no change to the safety outcomes between the two cutoff dates. There were no significant differences in the incidence of secondary malignancy between BrECADD and eBEACOPP at the interim analysis (2.3% vs. 1.6%, RR: 1.405; 95%CI: 0.676, 2.9220) or updated analysis (2.4% vs. 2.2%, RR: 1.116; 95% CI: 0.573, 2.172).

6.26 There were significantly lower Grade ≥3 AEs, and AEs leading to dose modifications in the BrECADD arm. There were no significant differences in serious adverse events (SAEs) leading to discontinuations; however, only SAEs leading to discontinuations were reported, rather than all AEs leading to discontinuation.

6.27 The ESC noted that rates of infertility 1-year post-treatment, assessed by FSH measurements, were lower for females in the BrECADD treatment arm (26.5%) than females in the eBEACOPP arm (46.1%). Similarly, infertility was lower in males following BrECADD treatment (53.7%), compared to eBEACOPP (80.5%). The ESC noted that after therapy, the 5-year incidence of parenthood was significantly higher in men (9.3%, 95% CI 6.0, 14.5 vs 3.3%, 95% CI 1.7, 6.5, p=0.014) but not significantly

higher in women (19.3%, 95% CI, 13.7, 27.3 vs 17.1%, 95% CI 11.9, 24.6, p=0.53) with BrECADD versus eBEACOPP.[7]

6.28 The PBAC noted Ferdinandus et al. 2025[6] reported the rates of secondary malignancy were 2.8% and 2.1% at 60 months in the BrECADD and eBEACOPP arms, respectively. There were more cases of acute myeloid leukaemia (AML) and myelodysplastic neoplasms (MDS) in the eBEACOPP arm (6 vs 1) and more cases of non-Hodgkin Lymphoma (NHL) in the BrECADD arm (8 vs 2).

6.29 The TGA CER and delegate highlighted that 'the safety and efficacy of the BrECADD regimen has not been established in subjects over the age of 60 years.' Safety results from an open-label study, single-arm feasibility study of BrECADD in patients aged 61 to 75 years (Ferdinandus et al., 2025)[8], showed that more patients in the older cohort developed TRMB (80%) than in the younger cohort (42.2%), and experienced considerably higher rates of AEs Grade≥3 and secondary malignancy. This trend suggests higher toxicity of BrECADD in older patients, which is consistent with clinical guideline[9] recommendations for BrECADD to be used in the treatment of fit patients ≤ 60 years.

Benefits/harms

6.30 A summary of the comparative benefits and harms for BrECADD versus eBEACOPP is presented in Table 7.

[7] Ferdinandus J. et al. Fertility in patients with advanced-stage classic Hodgkin lymphoma treated with BrECADD versus eBEACOPP: a secondary analysis of the multicentre, randomised, parallel, open-label, phase 3 HD21 trial. Lancet Oncol. 2025; 26:1081-1090

[8] Ferdinandus J. et al. Positron Emission Tomography-Guided Brentuximab Vedotin, Etoposide, Cyclophosphamide, Doxorubicin, Dacarbazine, and Dexamethasone in Older Patients With Advanced-Stage Classic Hodgkin Lymphoma: A Prospective, Multicenter, Single-Arm, Phase II Cohort of the German Hodgkin Study Group HD21 Trial. J Clin Oncol. 2025 Sep 20;43(27):2974-2985.

[9] Eyre et al. Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025 Nov;36(11):1263-1284.

Table 7: Summary of comparative benefits and harms for BrECADD and eBEACOPP

Benefits				
Event	**BrECADD**	**eBEACOPP**	**Absolute Difference**	**HR (95% CI)**
Progression-free survival[a] (median duration of follow up, BrECADD: 50.8 months; eBEACOPP: 51.1 months)				
Progressed, n/N (%)	44/751 (5.9%)	65/749 (8.7%)		**0.664 (0.453, 0.973)**
Median PFS, months (95% CI)	50.8 (49.15, 51.35)	51.1 (49.84, 51.91)	-0.3 months	
% not progressed at 12 months (95% CI)	97.5 (96.1, 98.4)	96 (94.3, 97.2)	1.5 (-0.35, 3.35)	
% not progressed at 24 months (95% CI)	95.7 (93.9, 96.9)	93.3 (91.2, 94.9)	2.4 (0.02, 4.78)	
Overall survival[a] (median duration of follow up, BrECADD: 52.6 months; eBEACOPP: 53.2 months)				
Deaths, n/N (%)	12/751 (1.6%)	13/749 (1.7%)		0.919 (0.419, 2.015)
Median OS, months (95% CI)	52.6 (51.15, 54.18)	53.2 (52.14, 54.51)	-0.6 months	
% Alive at 12 months (95% CI)	99.5 (98.6, 99.8)	99.5 (98.5, 99.8)	0 (-0.88, 0.88)	
% Alive at 24 months (95% CI)	99.3 (98.4, 99.7)	99.3 (98.4, 99.7)	0 (-0.92, 0.92)	

Harms						
	BrECADD	**eBEACOPP**	**RR (95% CI)**	**Event rate/100 patients[b]**		**RD (95% CI)**
				BrECADD	**eBEACOPP**	
TRMB n/N	315/747	435/741	**0.72 (0.65, 0.79)**	42.2	58.7	**-16.5 (-21.6, -11.4)**
Any TEAE n/N	745/747	741/741	0.99 (0.99, 1)	99.7	100	- 0.003 (-0.007, 0.002)
Grade ≥3 TEAE n/N	682/747	717/741	**0.94 (0.92, 0.97)**	91.3	96.8	**- 0.055 (-0.079, -0.031)**
Any SAE n/N	328/747	310/741	1.05 (0.93, 1.18)	43.9	41.8	0.021 (-0.030, 0.071)
SAE leading to treatment discontinuation n/N	15/747	15/741	0.99 (0.49, 2.02)	2	2	<0.001 (-0.014, 0.014)
AE leading to dose modification n/N	300/747	486/741	**0.61 (0.55, 0.68)**	40.2	65.6	**-0.254 (-0.303, -0.205)**
Grade 5 TEAE n/N	4/747	3/741	1.32 (0.30, 5.89)	0.5	0.4	0.001 (-0.005, 0.007)
CTCAE toxicity grade ≥3 of interest						
Febrile neutropenia	198/747	145/741	1.36 (1.12; 1.64)	26.5	19.6	6.9 (2.6, 11.2)
Gastrointestinal disorders (excl. nausea, vomiting, mucositis)	58/747	33/741	1.74 (1.15; 2.64)	7.8	4.5	3.3 (0.9, 5.7)
Hepatobiliary disorders	37/747	22/741	2.34 (1.40; 3.92)	5.0	3.0	2.1 (0.06, 4.1)

Source: Table 2.22, pp97-98; Table 2.25, p102; Table 2.30, p115; Table2.31, p118 of the submission
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CI=confidence interval; CTCAE=common terminology criteria for adverse events; eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; N=total participants in group; n=number of participants reporting data; OS=overall survival; PFS=progression-free survival; RD=risk difference; RR=relative risk; TEAE=treatment-emergent adverse event; TRMB=treatment-related morbidity
[a] 31 October 2023 data cut-off
[b] 31 December 2022 data cut-off
Bold= statistically significant

6.31 On the basis of direct evidence presented by the submission, for every 100 patients treated with BrECADD in comparison to eBEACOPP:

- Approximately 2 additional patients will remain progression free after 24 months, however, there would be no difference in overall survival;
- Approximately 17 fewer patients will experience TRMB; e.g., anaemia, infection, cardiac, gastrointestinal, kidney, respiratory, or nervous system disorders;
- Approximately 5 fewer patients will experience a TEAE of Grade ≥ 3, however, there would be no difference in overall occurrence of TEAEs;

- Approximately 7 additional patients would experience febrile neutropenia of Grade ≥ 3 severity;
- Approximately 3 additional patients would experience gastrointestinal disorders (excluding nausea, vomiting and mucositis) of Grade ≥ 3 severity;
- Approximately 2 additional patients would experience hepatobiliary of Grade ≥ 3 severity;
- Approximately 2 more patients will experience a SAE, however, there would be no difference in SAEs leading to discontinuation of treatment.

Clinical claim

6.32 The submission claimed BrECADD as superior in terms of effectiveness and safety compared to eBEACOPP.

6.33 The evaluation considered the evidence supporting the superior effectiveness of BrECADD versus eBEACOPP for PFS outcomes was unclear, due to:

- The PFS data in HD21 were immature (<10% events), with median PFS not reached in either treatment arm.
- The HD21 trial considered its target of 154 progression events to achieve 90% power of analysis to be unachievable, and the test for non-inferiority was modified. The test for superiority on the PFS outcome was introduced following evidence of non-inferiority at the interim analysis, only after multiple protocol amendments. The ESC considered this introduced uncertainty about whether the revised analyses may have been influenced by accumulating information.
- The assessment of PFS was led by investigators unblinded to treatment, rather than BICR. While the investigator assessments of progression in HD21 were confirmed by a central pathology review, the TGA CER noted that 'non-progression' would not have been subject to blinded review and could present a source of bias.

6.34 Regarding the claim of superior safety for patients undergoing first-line therapy for advanced cHL, the evaluation and the ESC noted that the TRMB outcome consisted of select toxicities and TEAEs associated with eBEACOPP, and may not represent the full spectrum of risks associated with the treatment. Furthermore, the incidence of febrile neutropenia, gastrointestinal and hepatobiliary disorders was higher in BrECADD versus eBEACOPP. However, the ESC also noted the data suggesting improved fertility outcomes for BrECADD (see paragraph 6.27) was likely to be important to patients. The ESC considered that while the safety claim was uncertain, it was likely that BrECADD was at least noninferior to eBEACOPP.

6.35 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.36 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data. The PBAC considered a claim of non-inferior comparative safety was appropriate.

Economic analysis

6.37 The submission presented a cost-utility analysis of BrECADD versus eBEACOPP for previously untreated advanced cHL based on trial evidence from HD21 and further informed by the previous brentuximab vedotin model for A+AVD versus ABVD (described in Table 8, brentuximab vedotin, PSD, July 2025).

6.38 Table 8 presents a summary of the key model features.

Table 8: Summary of model structure, key inputs and rationale

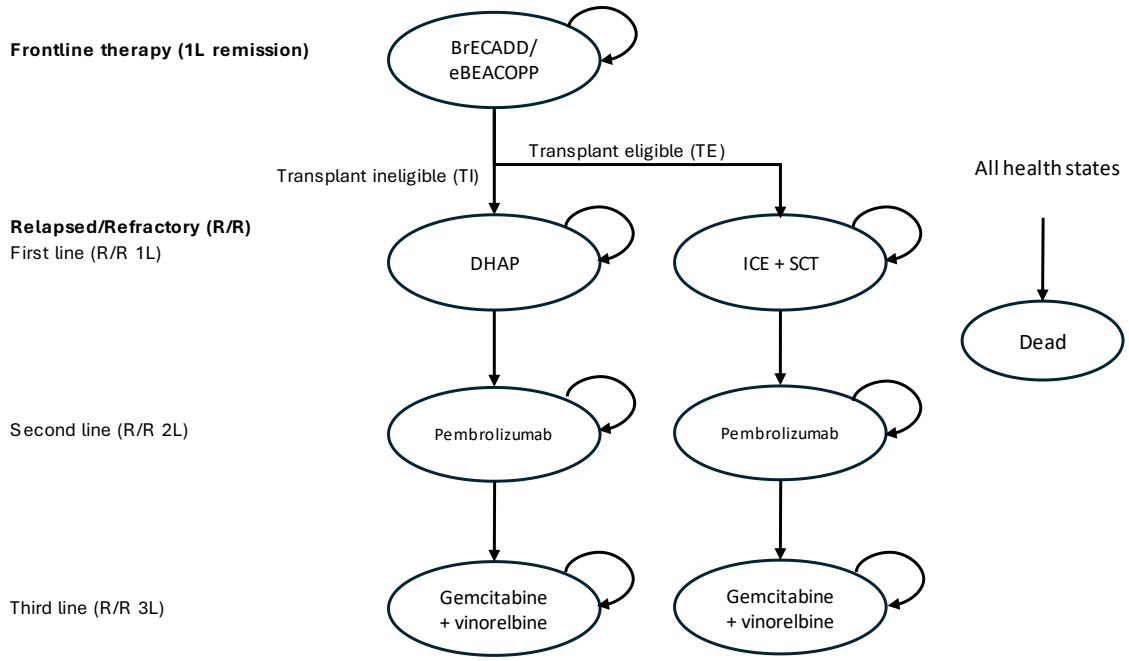
Component	Summary
Treatments	BrECADD vs eBEACOPP.
Time horizon	The PBAC previously considered a 65-year time horizon reasonable for cHL (para 7.8, brentuximab vedotin, PSD, July 2025). However, given the shorter follow up of HD21 (84 months) compared to ECHELON-1 (97 months), and fewer progression events in HD21 (~10% in both BrECADD and eBEACOPP arms) compared to ECHELON-1 (29% ABVD, 21% A+AVD), the uncertainty of extrapolating to 65 years was greater in the current submission.
Outcomes	Costs, life years gained (LYG), quality-adjusted life years (QALYs).
Methods used to generate results	Cohort model, using mixture-cure (weighted curves based on statistically cured and uncured fractions) and standard parametric survival models. The approach was the same as that presented in the brentuximab vedotin July 2025 submission.
Health states	A total of 8 health states defined by line of treatment and SCT eligibility: • 1L Remission (BrECADD or eBEACOPP) • R/R 1L SCT eligible (ICE + ASCT) • R/R 1L not-SCT eligible (DHAP) • R/R 2L after SCT (pembrolizumab) • R/R 2L no prior SCT (pembrolizumab) • R/R 3L, with or without prior SCT (GemVino). • Dead Patients progressed sequentially through the lines of treatment (i.e., patients could not transition from 1L to 3L without going through 2L). The health states were the same as presented in the brentuximab vedotin July 2025 A+AVD versus ABVD submission. No downstream brentuximab vedotin was included in either arm, although it is available on the PBS for R/R disease.
Cycle length	3 weeks, which was in line with treatment cycles of BrECADD. The submission inconsistently applied half cycle correction; half cycle correction was removed during the evaluation.

Component	Summary
Allocation to health states	**Progression free:** **1L Remission**: HD21 KM data to 62 months, dependent mixture-cure Weibull extrapolations thereafter. **R/R 1L SCT eligible**: pooled Brockelmann 2022 (autologous [A]SCT without consolidation subgroup) and Viviani 2024 KM data to 84 months, mixture cure log-normal extrapolation thereafter. If standard parametric survival modelling was selected for SCT (Cell G68 of Sheet 'Settings', Excel workbook 'Adcetris (brentuximab vedotin) - FL HL – BrECADD.xlsb'), health state allocation exceeded 100% of the population, and negative occupancy of the R/R post SCT health states could occur. This could not be corrected during the evaluation, but it did not appear to affect the base case model. **R/R 1L not-SCT eligible**: Brockelmann 2022 (no SCT subgroups) KM data to 108 months, log-normal extrapolation thereafter. **R/R 2L after SCT**: Younes 2012 KM data to 20 months PFS, Weibull extrapolations thereafter. **R/R 2L no prior SCT**: Brockelmann 2017 PFS KM data to 21 months, Weibull extrapolation thereafter **R/R 3L (with or without prior ASCT):** survival minus other health states **Mortality:** proportion of patients who die from 1L to R/R 1L based on proportion of patients who die in PF from HD21, mortality from R/R 2L-3L based on Younes 2012 and Brockelmann 2017 in line with PFS. Background mortality equal to SMR 2.2 applied to general population mortality. This was not a significant driver of the model. **Probability of SCT eligibility and type (auto or allo)** were based on HD21 data. **Time on treatment** was based on the recommended treatment duration for each therapy, with costs applied according to time in state. Eligible patients were assumed to receive SCT after 10 weeks in R/R 1L (i.e., 3 model cycles). The approach to transitions not from HD21 was unchanged from the brentuximab vedotin July 2025 submission and similar to that submission, downstream modelling beyond R/R 1L had little impact on the ICER, as there was very little allocation to these health states. 75% of QALYs, 87% LYGs (and 32% of costs) occur in the extrapolated period.
Health related quality of life	From HD21 EORTC-QLQ-C30 cross-walked to EQ-5D-3L with UK preference weights **1L on BrECADD**: 0.688; **1L on eBEACOPP**: 0.678; **1L off treatment**: 0.806 From Delea 2019 applied to HD21, with BrECADD anchored to A+AVD **R/R 1L with SCT**: 0-6m: 0.324, 6m+: 0.749; **R/R 1L no SCT**: 0.574; **R/R 2L, 3L (with/without SCT):** 0.574 Age-based utility adjustment using Clemens 2014 (Queensland general population HRQoL) 35-44 yrs: 1 (mean age at baseline=33.5 yrs), 45-54 yrs: 0.955, 55-64 yrs: 0.955, 65-74 yrs: 0.921, 75+ years: 0.899
Adverse events	Costs (BrECADD: $15,274.42, eBEACOPP: $16,260.78) and QALY loss (BrECADD: -0.0106, eBEACOPP: -0.0122) associated with grade ≥3 TEAEs from HD21 were applied in the first cycle of the model. AEs were a significant cost offset in the model (-$986, or -19.7% incremental cost), but were not a driver of the incremental QALYs. QALY losses were likely underestimated, given events were assumed to occur only once in each patient and for maximum 16.1 days. Long-term AEs were not included in the model.
Cost of SCT	$65,878, cost of ASCT and allo-SCT based on AR-DRG codes R06A/B/C and R05A/B and weighted by proportion of ASCT in BrECADD arm of HD21. If weighting of SCT cost by treatment arm as per HD21, the ICER increased to $[redacted][1] per QALY gained compared to $[redacted][1] in the base case. However, the evaluation considered it may be more reasonable to pool SCT data from HD21, given the small number of patients who progressed in either arm.

Source: compiled during the evaluation
1L=first line; 2L=second line; 3L=third line; AE=adverse event; allo = allogeneic; AR-DRG=Australian Refined Diagnosis Related Groups; ASCT=autologous stem cell transplant; auto = autologous; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; cHL=classic Hodgkin lymphoma; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ICER=incremental cost-effectiveness ratio; KM=Kaplan Meier; PFS=progression free survival; QALY=quality adjusted life-year; R/R=relapse/refractory ; SC=stem cell; SCT= stem cell transplant (auto/allo); SMR=standardise mortality ratio
The redacted values correspond to the following ranges:
[1] $55,000 to < $75,000

6.39 3 presents an overview of the model structure.

Figure 3: Model diagram

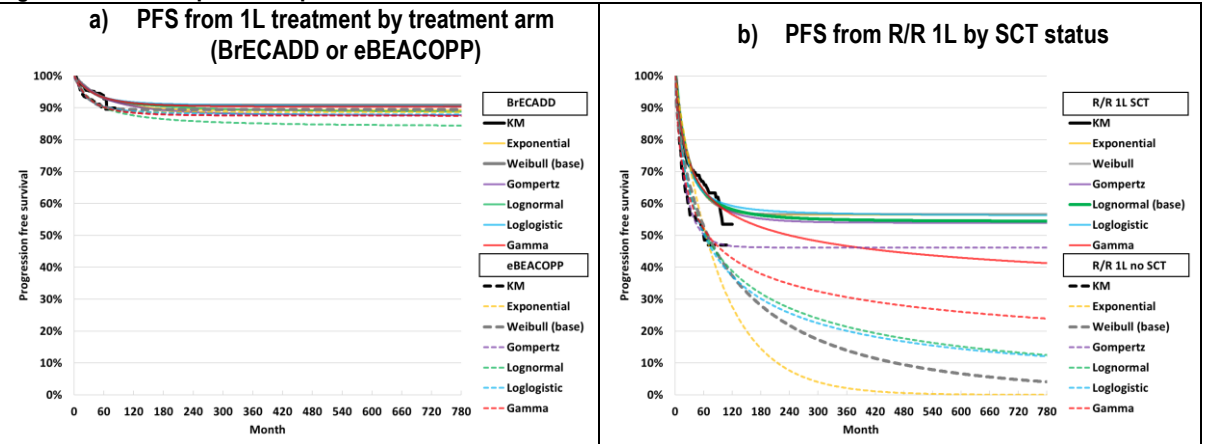


Source: adapted from Figure 3-5, p168 of the submission
1L=first line; 2L=second line; 3L=third line; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; DHAP=dexamethasone, high-dose cytarabine, cisplatin; ICE=ifosfamide, carboplatin, etoposide; R/R=relapse/refractory; SCT=stem cell transplant (auto or allo)

6.40 All patients entering the model received first-line treatment with either BrECADD or eBEACOPP. Each cycle, patients could remain in the same health state, experience progression to relapse/refractory (R/R) disease or die. Patients who experienced disease progression received subsequent therapy in accordance with SCT eligibility. Patients in R/R disease could experience up to three lines of therapy: R/R 1L ICE (ifosfamide, carboplatin, etoposide) plus stem cell transplant (SCT) or DHAP (dexamethasone, high-dose cytarabine, cisplatin), followed by pembrolizumab in R/R 2L, followed by GemVino (gemcitabine plus vinorelbine) in R/R 3L. Patients in R/R 3L could only remain in that health state or die. Although not included in the model diagram, the model tracked time from entry into subsequent treatment health states to implement time-dependent probabilities of disease progression or death.

6.41 PFS extrapolations for 1L remission and R/R 1L are presented in Figure .

Figure 4: PFS extrapolations presented in the submission



KM data from HD21

R/R 1L SCT KM data pooled from Figure 3A Brockelmann 2022 (subgroup 4. ASCT with watch+wait), and Figure 1A from Viviani 2024 (all patients who received ASCT)
R/R 1L no SCT KM data pooled from Figure 3A Brockelmann 2022 (subgroups 1, 2, 3: low risk, high age/comorbidities, and salvage/stem cell failure)

Source: compiled from Sheet 'Clinical – KM', 'Clinical – Parametrics' of Excel workbook Adcetris (brentuximab vedotin) – FL HL – BrECADD.xlsb'
1L=first line; 2L=second line; ASCT=autologous stem cell transplant; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; cHL=classic Hodgkin lymphoma; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; KM=Kaplan Meier; PFS=progression free survival; R/R=relapse/refractory; SCT= stem cell transplant (auto/allo)

6.42 The model base case used KM data from HD21 for the first 62 months for both arms, when around 20% of patients remained at risk. This cut-off occurred before convergence of the PFS KM curves (Figure a), and the overall PFS data were immature. Dependent mixture-cure models were used to extrapolate from Month 62 onwards. Independent mixture-cure and standard parametric models were also fitted but not used in the base case. The Weibull function was chosen for the base case based on clinical plausibility, visual fit and estimated cure fractions, rather than statistical fit. Although mixture-cure models (Figure a) were similar across parametric functions and independent/dependent fits, the ICER was highly sensitive to the selected extrapolation. The evaluation considered that while cure after frontline treatment for cHL may be clinically plausible, limited evidence of a cure was available from the HD21 PFS KM data, as neither arm had established a plateau. The evaluation noted that if extrapolations were applied any time from Month 66 (rather than Month 62 as per the base case), the BrECADD arm was dominated by the eBEACOPP arm (less effective and more costly). The evaluation considered that, given the convergence of the PFS KM data, it may also be reasonable to consider independent extrapolations. The PSCR noted that the proportion of patients that remained at risk declined to 10% at around 64.5 months in both treatment arms with an incremental difference in PFS of 3.22 percentage points. The PSCR argued that as the convergence in PFS KM data from HD21 occurred when <10% of patients remained at risk the sensitivity analysis extrapolating from this point, which resulted in the eBEACOPP arm dominating BrECADD, was inappropriate.

6.43 The ESC agreed with the evaluation that, while the mixture-cure models (Figure a) were similar across parametric functions, the ICER was highly sensitive to the selected extrapolation and KM truncation point (Table 13). The ESC considered it unclear from a statistical point of view when the data becomes unreliable and noted the PSCR statement that HD21 has concluded with no further data expected. The ESC considered that 48 months was a clinically plausible cure point for this indication. However, the ESC noted that around 50% of the population remained at risk at that point and considered it was preferrable to use as much KM data as possible. The ESC noted that the mixture cure approach used in the submission effectively assumed the absolute PFS difference remains at 3.22% and hence assumed a permanent cure fraction advantage for BrECADD. The ESC considered that, given a cure was clinically plausible from 48 months, it was uncertain but likely reasonable to assume a small cure fraction advantage for BrECADD. The ESC considered that the convergence of the PFS KM data observed from Month 66 was likely an artefact of the small number of patients at risk and agreed with the PSCR that extrapolation from this point was not appropriate. Overall, the ESC considered that the clinical benefit modelled was uncertain and sensitive to factors influencing extrapolation.

6.44 The proportion of patients who progressed and were eligible to receive SCT in R/R 1L were based on patients receiving subsequent therapy in HD21: 68.6% and 80.6% of patients with subsequent treatment in BrECADD and eBEACOPP arms respectively. Fewer than 10% of patients in HD21 received subsequent therapy, and the submission provided no clinical justification for why SCT eligibility after progression would differ by treatment arm. Overall, SCT estimates were uncertain and were a key driver of the ICER. The PSCR acknowledged that a maximum difference of 3.22 percentage points in PFS is unlikely to result in a near four-fold incremental difference (12 percentage points) in the proportion of patients receiving SCT following BrECADD and eBEACOPP. Instead, the PSCR suggested that it may be more reasonable to assume the proportion of patients receiving SCT is the same for BrECADD and eBEACOPP, based on the pooled proportions from both treatment arms in HD21 (75.4%). The PSCR also acknowledged that there are no data from HD21 to support a difference in the proportion of allogeneic versus autologous SCT between arms. The PSCR therefore suggested that it may be more appropriate to assume that the distribution is the same based on the pooled proportions from both treatment arms (i.e. 89.9%). The ESC considered these amendments appropriate.

6.45 The approach to modelling all transitions post-1L was identical to the July 2025 submission for A+AVD versus ABVD. For R/R 1L eligible for SCT, PFS extrapolation used KM data from Viviani et al., 2024[10] (ASCT after first R/R with or without consolidation,

[10] Viviani S, Vanazzi A, Frassoni S, Rusconi C, Rossi A, Romano A, Patti C, Schiavotto C, Sorasio R, Marasco V, Lissandrini L, Rapezzi D, Gottardi D, Cocito F, Mulè A, Leotta S, Gini G, Sorio M, Derenzini E, Rambaldi A, Bagnardi V, Tarella C. High-dose chemotherapy and autologous stem cell transplant as first salvage treatment for relapsed or refractory Hodgkin Lymphoma in the era of PET-adapted strategies. Leuk Lymphoma. 2024 Apr;65(4):460-471. doi: 10.1080/10428194.2023.2298273

N=220) and Brockelmann et al.,2022[11] (ASCT without consolidation subgroup, n=211) for the first 84 months, followed by a log-normal mixture-cure extrapolation. As with 1L treatments, there was limited evidence of a cure plateau effect in the SCT data (Figure b). Furthermore, there was high uncertainty in the extrapolation as a result of: i) combining the two data sources with different baselines, ii) different maximum follow up, and iii) substantial heterogeneity in disease progression for patients with cHL across the subgroups. Uncertainty in the underlying pooled data and extrapolation estimates could not be sufficiently quantified, particularly because switching the model to use standard parametric extrapolations (i.e., not a mixture-cure model) led to model errors (negative health state occupancy in alive states and occupancy of the dead state greater than 100%).

6.46 For R/R 1L not eligible for SCT, PFS extrapolation used pooled KM data from Brockelmann et al., 2022, including patients not intended to undergo ASCT (due to low risk; or increased age or co-morbidities); and patients intended to undergo ASCT but failing due to insufficient response to salvage treatment or stem cell mobilisation. These KM data were then applied for the first 108 months, followed by a Weibull extrapolation using a standard parametric approach. Figure b demonstrates that most extrapolations fitted the KM data well but had varying long-term extrapolations. Gompertz had the best statistical fit (lowest AIC and BIC).

6.47 OS data from HD21 were immature, with no OS benefit observed for BrECADD over eBEACOPP over the 83-month follow up. In the model, mortality was applied both as disease progression mortality, and as background cHL mortality; as previously described in the July 2025 submission comparing A+AVD to ABVD. Disease progression mortality from 1L remission or R/R 1L was estimated as the proportion of death events from HD21 applied to the proportion of patients progressing from these health states each cycle. For death from 1L remission, the proportions differed by arm (16% events in BrECADD arm and 12% in eBEACOPP arm); while for death from R/R 1L, with or without SCT, this was pooled across treatment arms (14% events in both arms). Probability of death from 1L remission was a key driver of the ICER.

6.48 Time on first line treatment with BrECADD or eBEACOPP was modelled according to the recommended number of cycles from HD21 by PET status, applied to the proportion of patients remaining in 1L remission each cycle, resulting in a mean of 4.79 cycles of BrECADD and 4.80 cycles of eBEACOPP modelled. The evaluation considered it may be more accurate to model time to treatment discontinuation as explicitly experienced in HD21, but this approach was generally reasonable.

[11] Bröckelmann, P.J., Müller, H., Gillessen, S. et al. Clinical outcomes of relapsed and refractory Hodgkin lymphoma patients after contemporary first-line treatment: a German Hodgkin Study Group analysis. Leukemia 36, 772–780 (2022). https://doi.org/10.1038/s41375-021-01442-8

6.49 EORTC-QLQ-C30 data were collected in HD21 and mapped to EQ-5D-3L with UK valuations (Young et al., 2015[12]). A repeated-measure mixed effects model was used to estimate least-square (LS) mean utility values for progression free patients on and off first treatment (BrECADD or eBEACOPP). Off-treatment utility from the BrECADD arm of HD21 (0.806) was applied for both arms, while on treatment utility was assumed to differ between BrECADD (0.688) versus eBEACOPP (0.678). The submission attributed the lower on treatment utility for eBEACOPP to higher AE rates, although AE QALY losses were also modelled separately. The ICER was not sensitive to the on-treatment utility. Unadjusted utilities were slightly higher on treatment with eBEACOPP compared to BrECADD (0.689 versus 0.685), but lower off treatment while progression free (0.796 versus 0.820); suggesting uncertainty in the 1L utility estimates. Off-treatment utility in 1L remission was also lower than in the March 2024 submission comparing A+AVD to ABVD (0.806 versus 0.843).

6.50 The approach to utilities in the other health states was unchanged from the July 2025 submission, comparing A+AVD to ABVD. Utility values from Delea et al., 2019[13] , a US cost-effectiveness analysis of A+AVD versus ABVD, were multiplicatively applied to the BrECADD on-treatment utility to estimate downstream health state utilities. These estimates were highly uncertain, given differences in patient characteristics, disease status and treatments received across the studies informing Delea et al. 2019, (ECHELON-1, Swinburn et al., 2015[14], Ramsey et al., 2016[15]). As R/R 1L post-SCT occupancy was a driver of the ICER, the ICER was sensitive to utility in this state. The PSCR acknowledged the uncertainty and argued that utilities in the progressed disease states may be better informed by assuming the ratio of eBEACOPP on treatment from HD21 to ABVD from Delea et al., 2019 (in the submission BrECADD on treatment from HD21 was anchored to A+AVD from Delea et al., 2019). The ESC considered this approach to be reasonable.

6.51 QALY losses from AEs during 1L treatment were estimated based on published literature and assumptions, consistent with the brentuximab vedotin July 2025 PBAC submission for A+AVD versus ABVD. Disutility estimates and assumed event duration were poorly documented. Overall, the approach resulted in AE QALY losses of -0.011 and -0.012 in the BrECADD and eBEACOPP arms, respectively, equivalent to full loss of health for 3.9 days and 4.4 days. These losses were likely underestimated, despite

[12] Young TA, Mukuria C, Rowen D, Brazier JE, Longworth L. Mapping Functions in Health-Related Quality of Life: Mapping from Two Cancer-Specific Health-Related Quality-of-Life Instruments to EQ-5D-3L. Med Decis Making. 2015 Oct;35(7):912-26. doi: 10.1177/0272989X15587497. Epub 2015 May 21. PMID: 25997920; PMCID: PMC4574084.

[13] Delea TE, Sharma A, Grossman A, Eichten C, Fenton K, Josephson N, Richhariya A, Moskowitz AJ. Cost-effectiveness of brentuximab vedotin plus chemotherapy as frontline treatment of stage III or IV classical Hodgkin lymphoma. J Med Econ. 2019 Feb;22(2):117-130. doi: 10.1080/13696998.2018.1542599.

[14] Swinburn P, Shingler S, Acaster S, et al. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Leuk Lymphoma 2015;56:1839-45

[15] Ramsey SD, Nademanee A, Masszi T, et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. Br J Haematol 2016;175:860-7

double-counting with the on-treatment utility decrement, as events were assumed to occur only once per patient and for a maximum of 16.1 days.

6.52 The submission used 2026 costs, except for SCT and AEs, which were sourced from the 2022-23 NHCDC public sector costs reports and not inflated. The costs of vincristine, pegfilgrastim and pembrolizumab did not align with current (April 2026) costs, but were not key drivers of the ICER, so were not updated during the evaluation.

6.53 The submission estimated drug costs associated with BrECADD and eBEACOPP, with doses for each agent based on a mean weight of 76.2 kg and a mean body surface area (BSA) 1.91 m^2 from HD21.

6.54 BrECADD cost was $[redacted] per cycle ($[redacted] in Cycle 1 with pre-treatment dexamethasone), which included $[redacted] brentuximab vedotin (based on assumed effective $[redacted] per vial, with dose 1.8 mg/kg equal to total dose 137 mg =3 x 50 mg vials, assuming full vial wastage and mark ups). The ESC noted the submission requested a weighted price of $[redacted] as part of a combined A+AVD and BrECADD restriction (See paragraph 3.4). The weighted price assumed a continued 80.5% use of A+AVD, which ESC considered was not reasonable given the changing frontline treatment landscape. The ESC considered that given the expected changes in utilisation of A+AVD, the submissions requested weighted price was effectively assuming a much higher price of BrECADD than $[redacted] per vial. When evaluated at the requested weighted price, the ICER increased from $55,000 to < $75,000 to $155,000 to < $255,000 per QALY gained.

6.55 eBEACOPP cost was $1,565.76 per cycle. 1L drug costs were applied to 100% of patients in Cycles 1 to 4, then reduced in Cycles 5 and 6 to reflect the 58.1% and 57.7% PET-negative patients in the BrECADD arm and eBEACOPP arm who received only 4 cycles of treatment, respectively. All BrECADD patients continued to receive trimethoprim + sulfamethoxazole costs across Cycles 5 and 6. As this was a small cost ($4.94 per week), it was not a driver of the ICER. The evaluation considered that aside from slight overestimates in the costs of vincristine and pegfilgrastim, eBEACOPP costing was generally reasonable. The PSCR considered the cost of trimethoprim + sulfamethoxazole should be removed from Cycles 5 and 6 for PET-negative patients. The ESC noted this was a small cost and was not a driver of the ICER.

6.56 The submission did not include costs for dacarbazine as part of BrECADD, or procarbazine as part of eBEACOPP, as these drugs are not PBS-listed. This approach was not appropriate as there will still be a cost to the healthcare system, however, as costs were excluded from both arms of the model, the impact on the incremental costs was limited.

6.57 Choice and costing of subsequent treatments in the submission were informed by the July 2025 submission for A+AVD versus ABVD, with costs updated, and patient characteristics and proportion of patients receiving SCT based on HD21 rather than ECHELON-1. The submission assumed separate treatment pathways for R/R disease depending on SCT eligibility. SCT eligible patients received ICE for up to 3 cycles followed by SCT in R/R 1L, followed by pembrolizumab in R/R 2L, and GemVino in R/R 3L. SCT ineligible patients received DHAP in R/R 1L, followed by pembrolizumab in R/R

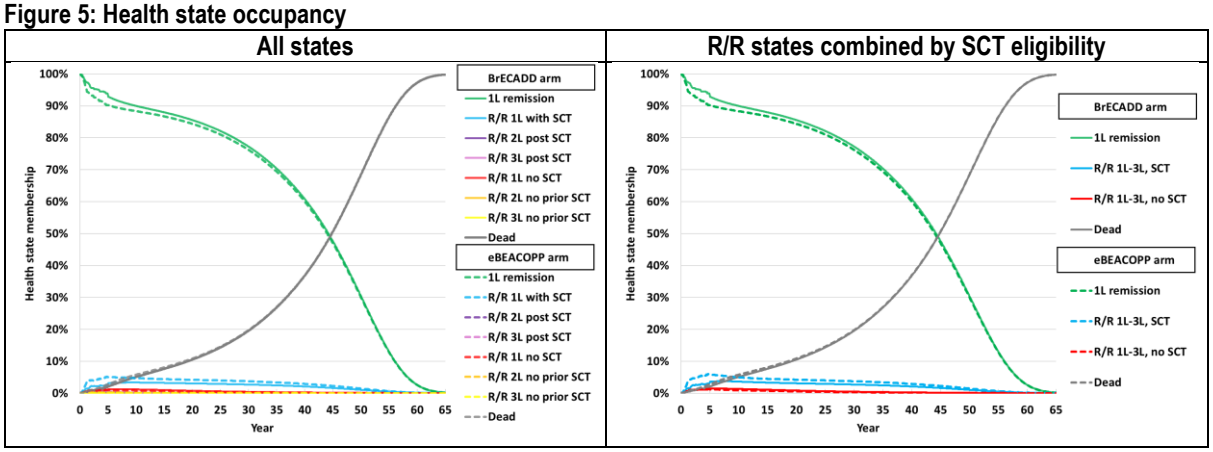
2L, and GemVino in R/R 3L. The evaluation considered that the subsequent therapies were unlikely to reflect current practice and were inconsistent with the data used to inform transition probabilities. SCT was considered only at initial progression to R/R disease, and the submission did not include costs for radiotherapy or immunotherapies as consolidation therapies (including brentuximab or nivolumab in R/R disease). The main cost driver in the subsequent therapies was SCT, with all other treatment costs equating to -2.5% of the incremental costs.

6.58 The cost of SCT was inconsistent, with the probability of any SCT estimated by treatment arm from HD21 (for patients receiving subsequent therapy, 68.6% received SCT in the BrECADD arm, 80.6% in the eBEACOPP arm), but the proportion of SCTs that were autologous was based only on the BrECADD arm (85.7%, based on 30/35 patients receiving SCT). This was lower than the probability of ASCT in the eBEACOPP arm (92.6%, based on 50/54 patients receiving SCT) and therefore resulted in a higher weighted SCT cost, as ASCT is less expensive than allogeneic SCT. The ESC noted the relatively small number of progression events in the trial and considered that different proportions and types of SCT being applied for each arm was not clinically justified. As previously discussed, the evaluation and the ESC considered it may be more reasonable to pool SCT data from HD21.

6.59 AE costs were applied as a one-off cost in the first model cycle ($15,274.42 in the BrECADD arm, $16,260.78 in the eBEACOPP arm). Costs were based on incidence in HD21 and 2022-23 NHCDC public sector costs weights. AE costs were likely underestimated as they included only hospital costs, not ongoing costs that may be associated with some AEs. Furthermore, no costs for AE associated with subsequent therapy or long-term AEs, such as secondary malignancies, were included in the model. Despite having a limited impact on incremental QALYs, AEs were a significant driver of the incremental costs, favouring the BrECADD arm. It was not possible for the evaluation to explore ongoing AE costs (which may affect survival and quality of life).

6.60 Figure 5 presents model traces for all health states and a simplified trace that combines R/R states by SCT eligibility. Across the time horizon, the majority of patients remained in 1L remission until death, with 1L remission occupancy exceeding all other states until Year 44. More patients in the BrECADD arm remained progression free than in the eBEACOPP arm, though the 1L remission occupancy converged by about Year 35. Health state occupancy in the R/R 1L with SCT states was slightly higher in the eBEACOPP arm (based on a higher percentage of SCT in HD21, and a higher proportion of patients progressing to R/R for eBEACOPP than BrECADD). Survival was similar in both arms across time, with a slight persistent survival benefit in the BrECADD arm.

Figure 5: Health state occupancy



Source: compiled from Sheets 'Results', 'Trace – BrECADD', and 'Trace – eBEACOPP' of Excel workbook 'Adcetri (brentuximab vedotin) – FL HL – BrECADD.xlsb'.

1L=first line; 2L=second line; 3L=third line; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; R/R=relapse/refractory; SCT= stem cell transplant

6.61 A summary of the key drivers of the model is presented in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact: Revised[a] base case: $[redacted][1]/QALY gained
1L remission extrapolation	State occupancy was based on HD21 PFS KM data to Month 62 followed by dependent Weibull mixture-cure extrapolations. The HD21 data were immature, and the BrECADD and eBEACOPP PFS KM data curves converged after the extrapolation point. As such, the ongoing benefit was uncertain. The ICER was very sensitive to the choice of extrapolation method and KM truncation point. The ESC considered that the convergence of the PFS KM data observed was likely an artefact of the small number of patients at risk but agreed with the evaluation that the clinical benefit modelled was uncertain and not robust to factors influencing extrapolation.	High, favoured the BrECADD arm. When BrECADD benefit only accrued in the first 83 months, the ICER increased to $[redacted][2]/QALY gained. When the extrapolations with the best statistical fit were chosen (exponential, lowest BIC; loglogistic, lowest AIC) the ICER ranged from $[redacted][3] to $[redacted][4]/QALY gained.
Utilities in R/R 1L	R/R 1L with SCT 0-6 months: 0.324, 6 months onwards: 0.749; R/R 1L no SCT: 0.673 based on Delea 2019 applied to HD21 estimated with BrECADD utility anchored to A+AVD. The PSCR proposed a revision assuming the ratio of eBEACOPP on treatment from HD21 to ABVD from Delea et al., 2019. The ESC considered the approach proposed in the PSCR to be reasonable.	High, favoured the BrECADD arm. When the utility after 6 months in R/R 1L was set equal to utility in 1L remission (0.806) the ICER increased to $[redacted][5].
Utilities in 1L off treatment	1L remission off treatment: 0.806 based on HD21 EORTC-QLQ C30 mapped to EQ-5D-3L and a repeated measure mixed effects model was used to estimate least-square mean utility values for progression free patients on and off first line treatment (BrECADD or eBEACOPP).	High, uncertain effect. If utility was altered by +/-10% (0.887, 0.725), the ICER ranged from $[redacted][6] to $[redacted][5]/QALY.
SCT	SCTs were associated with significant cost and life year offsets in the model, driven by the probability and type of SCT from HD21. The submission was inconsistent in its modelling of SCT, with the probability of any SCT based on the individual arms of HD21, but the autologous/allogeneic split was informed only by the BrECADD arm. The PSCR proposed amendments to the approach taken which the ESC considered were reasonable (see paragraph 6.44).	High, favoured the eBEACOPP arm. When the HD21 data were pooled across arms, the ICER reduced to $[redacted][6]/QALY gained.
Probability of death from 1L remission	The probability of death from 1L remission was based on the proportion of events due to death from HD21, BrECADD arm 16%, eBEACOPP arm 12%.	High, favoured eBEACOPP arm. When the HD21 data were pooled across arms, the ICER reduced to $[redacted][6]/QALY gained.
AE costs	AE costs were applied as a one-off cost in the first model cycle ($15,274.42 in the BrECADD arm, $16,260.78 in the eBEACOPP arm). Costs were based on incidence in HD21 and 2022-23 NHCDC public sector costs weights.	High, uncertain effect. When the costs were removed (i.e., assume no difference in incremental AEs) ICER increased to $[redacted][5]/QALY gained. If costs were doubled, ICER decreased to $[redacted][6]/QALY gained

Source: compiled during the evaluation.

1L=first line; 6m=6 months; AE=adverse event; ASCT=autologous stem cell transplant; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ICER=incremental cost-effectiveness ratio; KM=Kaplan-Meier; PFS=progression free survival; QALY=quality-adjusted life-year; SCT=stem cell transplant (allo/auto).

[a] half cycle correction removed

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$155,000 to < $255,000*

[3] *$25,000 to < $35,000*

[4] *$95,000 to < $115,000*

[5] *$75,000 to < $95,000*

[6] *$45,000 to < $55,000*

6.62 The results of the stepped economic analysis in the submission, and the revised base case with the half-cycle correction removed, are presented in Table 10.

Table 10: Results of the stepped economic evaluation

Step and component	Revised (no half cycle correction)		
	BrECADD arm	eBEACOPP arm	Increment
Step 1: time horizon 83 months (maximum PFS KM follow up from HD21, other transitions modelled from literature, no background mortality), 1L treatment and administration costs, discounting 5% costs and outcomes			
Costs	$[redacted]	$9,927	$[redacted]
LYG	5.941	5.920	0.021
Incremental cost/extra LYG gained			$[redacted][1]
Step 2: time horizon 65 years (62 months of PFS KM follow up from HD21, other transitions modelled as Step 1, background mortality included), 1L treatment and administration costs, discounting 5% costs and outcomes			
Costs	$[redacted]	$9,927	$[redacted]
LYG	17.261	17.185	0.076
Incremental cost/extra LYG gained			$[redacted][2]
Step 3: time horizon 65 years (62 months of PFS KM follow up from HD21, other transitions modelled as Step 1, background mortality included), all costs (1L and subsequent treatment, administrations, disease monitoring and adverse events), discounting 5% costs and outcomes			
Costs	$[redacted]	$44,355	$[redacted]
LYG	17.261	17.185	0.076
Incremental cost/extra LYG gained			$[redacted][3]
Step 4: time horizon 65 years (62 months of PFS KM follow up from HD21, other transitions modelled as Step 1, background mortality included), all costs (1L and subsequent treatment, administrations, disease monitoring and adverse events), utility weights applied, discounting 5% costs and outcomes			
Costs	$[redacted]	$44,355	$[redacted]
QALYs	13.153	13.076	0.077
Incremental cost/extra QALY gained (base case)			**$[redacted][3]**

Source: Table 3-26, p227 and compiled during the evaluation from Sheet 'Results' of Excel workbook 'Adcetris (brentuximab vedotin) – FL HL – BrECADD.xlsb'.

1L=first line; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; KM=Kaplan-Meier; LYG=life-year gain; PFS=progression free survival; QALY=quality-adjusted life-year

The redacted values correspond to the following ranges:

[1] *$355,000 to < $455,000*

[2] *$115,000 to < $135,000*

[3] *$55,000 to < $75,000*

6.63 These results were based on the price of the components of BrECADD, eBEACOPP and the published price of subsequent therapies. The revised base case ICER was $55,000 to < $75,000 per QALY, representing an incremental cost of $5,000 to < $15,000 per 0.077 QALYs gained for BrECADD versus eBEACOPP, which was similar to the cost per LY gained ($55,000 to < $75,000, incremental cost $5,000 to < $15,000 per 0.076 LYs gained).

6.64 Undiscounted disaggregated costs are presented in Table 11. The drug costs for BrECADD were the main driver of the undiscounted incremental costs, equal to $[redacted]. The majority of this cost ($[redacted]) was for brentuximab vedotin. The main cost-offsets were drug costs for eBEACOPP, incremental cost of SCT, incremental cost of AEs associated with 1L treatment, and incremental cost of administration of 1L treatments.

6.65 Undiscounted disaggregated health outcomes are presented in Table 12. Incremental LYs (0.149 undiscounted) and QALYs (0.139 undiscounted) were primarily driven by additional time in 1L remission for BrECADD arm over eBEACOPP. The main LY and QALY offsets were in the R/R 1L with SCT, with 0.569 incremental undiscounted LYs and 0.394 incremental QALYs.

Table 11: Health care resource items: disaggregated summary of cost impacts (undiscounted, revised base case)

Resource item	BrECADD arm	eBEACOPP arm	Incremental cost
1L treatment			
1L drug costs	$[redacted]	$7,509	$[redacted]
Administration	$1,807.51	$2,417.20	-$609.69
Adverse events	$15,274.42	$16,260.78	-$986.36
Monitoring	$9,719.25	$9,610.64	$108.61
Total	$[redacted]	$35,798.07	$[redacted]
R/R 1L			
ICE	$287.31	$397.35	-$110.04
SCT	$3,588.06	$4,962.23	-$1,374.16
DHAP	$190.53	$138.77	$51.77
Administration	$98.94	$112.59	-$13.65
Monitoring	$2,435.93	$2,595.52	-$159.59
Total	$6,600.78	$8,206.45	-$1,605.67
R/R 2L total	$6,493.10	$6,567.58	-$74.48
R/R 3L total	$332.25	$376.81	-$44.55
Overall total	**$[redacted]**	**$50,948.91**	**$[redacted]**

Source: compiled during the evaluation from Sheet 'Results' of Excel workbook 'Adcetris (brentuximab vedotin) – FL HL – BrECADD.xlsb'.
1L=first line; 2L=second line; 3L=third line; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; KM=Kaplan-Meier; LYG=life-year gain; PFS=progression free survival; QALY=quality-adjusted life-year

Table 12: Disaggregated summary of health outcomes included in the economic evaluation (undiscounted, revised base case)

Outcome	BrECADD arm	eBEACOPP arm	Incremental outcome
LYs			
1L remission	39.523	38.876	0.646
R/R 1L with SCT	1.330	1.899	-0.569
R/R 1L no SCT	0.303	0.224	0.080
R/R 2L	0.057	0.057	0.001
R/R 3L	0.032	0.040	-0.008
Total	**41.245**	**41.096**	**0.149**
QALYs			
1L remission	29.718	29.225	0.493
R/R 1L with SCT	0.925	1.319	-0.394
R/R 1L no SCT	0.164	0.122	0.043
R/R 2L	0.031	0.031	0.000
R/R 3L	0.018	0.022	-0.005
Adverse events	-0.011	-0.012	0.002
Total	**30.845**	**30.707**	**0.139**

Source: compiled during the evaluation from Sheet 'Results' of Excel workbook 'Adcetris (brentuximab vedotin) – FL HL – BrECADD.xlsb'.
1L=first line; 2L=second line; 3L=third line; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; KM=Kaplan-Meier; LYG=life-year gain; PFS=progression free survival; QALY=quality-adjusted life-year; SCT=stem cell transplant (allo/auto)

6.66 The results of key sensitivity analyses are summarised in Table 13. The ICER was most sensitive to assumptions around 1L PFS extrapolation, including the time point at

which the extrapolation was applied, the probability and type of SCT in each arm, utilities and AE costs.

Table 13: Sensitivity analyses

Analyses	Incr. cost	Incr. QALY	ICER	% change
Base case (revised, no half cycle correction)	**$[redacted]**	**0.077**	**$[redacted]**	**-**
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes	$[redacted]	0.139	$[redacted]	-[redacted]%
• 3.5% costs and outcomes	$[redacted]	0.089	$[redacted]	-[redacted]%
Time horizon (base case 65 years)				
• 10 years	$[redacted]	0.051	$[redacted]	[redacted]%
• 25 years	$[redacted]	0.072	$[redacted]	[redacted]%
1L PFS extrapolation (base case dependent mixture-cure model, Weibull, from Month 62)				
• dependent mixture-cure model, Weibull, from Month 83	$[redacted]	-0.020	Dominated	NE
• dependent mixture-cure model, Weibull, from Month 66	$[redacted]	-0.037	Dominated	NE
• dependent mixture-cure model, Weibull, from Month 65	$[redacted]	0.110	$[redacted]	-[redacted]%
• dependent mixture-cure model, Weibull, from Month 48	$[redacted]	0.108	$[redacted]	-[redacted]%
• dependent mixture-cure model, exponential, from Month 62[a]	$[redacted]	0.050	$[redacted]	[redacted]%
• dependent mixture-cure model, exponential, from Month 48[a]	$[redacted]	0.083	$[redacted]	-[redacted]%
• dependent mixture-cure model, loglogistic, from Month 62[b]	$[redacted]	0.124	$[redacted]	-[redacted]%
• dependent mixture-cure model, loglogistic, from Month 48	$[redacted]	0.167	$[redacted]	-[redacted]%
• independent mixture-cure model, BrECADD lognormal, eBEACOPP gamma, from Month 62	$[redacted]	0.023	$[redacted]	[redacted]%
• independent mixture-cure model, BrECADD lognormal, eBEACOPP gamma, from Month 48	$[redacted]	0.067	$[redacted]	[redacted]%
Probability of death from 1L (base case BrECADD arm 16%, eBEACOPP arm 12%)				
• pooled across arms (14%)	$[redacted]	0.100	$[redacted]	-[redacted]%
R/R 1L with SCT PFS extrapolation (base case mixture-cure model, lognormal[a])				
• mixture-cure model, gamma[b]	$[redacted]	0.086	$[redacted]	-[redacted]%
R/R 1L no SCT PFS extrapolation (base case standard parametric extrapolation, Weibull)				
• Gompertz[a,b]	$[redacted]	0.081	$[redacted]	-[redacted]%
Probability of SCT and type (base case BrECADD 68.6%, eBEACOPP 80.6%; with 85.7% ASCT in both arms)				
• Pooled HD21 arms (75.4% SCT of which 89.9% ASCT)	$[redacted]	0.111	$[redacted]	-[redacted]%
• As HD21 (BrECADD 68.6% SCT, of which 85.7% ASCT, eBEACOPP 80.6% SCT, of which 92.6% ASCT)	$[redacted]	0.077	$[redacted]	[redacted]%
R/R 2L post-SCT OS extrapolation (base case standard parametric extrapolation, Weibull)				
• exponential	$[redacted]	0.070	$[redacted]	[redacted]%
• lognormal	$[redacted]	0.073	$[redacted]	[redacted]%
Utilities (base case: BrECADD on treatment 0.688; eBEACOPP on treatment 0.678; 1L off treatment 0.806; R/R 1L with SCT first 6m 0.324, post-6m 0.749; all other states 0.574)				
• HD21 observed (BrECADD on/off treatment 0.685/0.820; eBEACOPP on/off treatment 0.689/0.796, rest as base case)	$[redacted]	0.443	$[redacted]	-[redacted]%
• R/R 1L with SCT post-6m equal to 1L off-treatment (0.806, rest as base case)	$[redacted]	0.064	$[redacted]	[redacted]%
• 1L off-treatment 0.725 (-10%)	$[redacted]	0.053	$[redacted]	[redacted]%
• 1L off-treatment 0.887 (+10%)	$[redacted]	0.101	$[redacted]	-[redacted]%
AE costs, QALY loss (base case: BrECADD arm $15,274, -0.01065 QALYs; eBEACOPP arm $16,261, -0.01215 QALYs)				
• No AE disutilities	$[redacted]	0.076	$[redacted]	[redacted]%
• No AE costs	$[redacted]	0.077	$[redacted]	[redacted]%
• Double AE costs	$[redacted]	0.077	$[redacted]	-[redacted]%
Max 6 cycles of BrECADD and eBEACOPP (base case mean 4.8 in both arms)	$[redacted]	0.077	$[redacted]	[redacted]%

Analyses	Incr. cost	Incr. QALY	ICER	% change
Base case (revised, no half cycle correction)	**$[redacted]**	**0.077**	**$[redacted][1]**	**-**
Brentuximab vedotin vial cost (base case $[redacted]) • $[redacted] per brentuximab vedotin vial as per requested weighted price	$[redacted]	0.077	$[redacted][5]	[redacted]%
Multivariate analyses				
MA1: all post-1L transitions simplified (exponential extrapolations from time 0)	$[redacted]	0.072	$[redacted][1]	[redacted]%
MA2: MA1 and pooled SCT data from HD21	$[redacted]	0.111	$[redacted][6]	-[redacted]%
MA3: BrECADD benefit only first 83 months (KM data to Month 83, extrapolation equal to eBEACOPP after, pooled SCT data from HD21))	$[redacted]	0.034	$[redacted][5]	[redacted]%
MA4: MA3 and $[redacted] per brentuximab vedotin vial	$[redacted]	0.111	$[redacted][7]	[redacted]%
PSCR revised analyses and base case				
PSCR A: Corrected base case (half cycle applied as described in submission plus cost of trimethoprim + sulfamethoxazole removed from Cycle 5 and 6 in PET-ve patients)	$[redacted]	0.077	$[redacted][1]	-[redacted]%
PSCR B: A + Pooled SCT data from HD21[d]	$[redacted]	0.111	$[redacted][2]	-[redacted]%
PSCR C: A + Downstream utilities from eBEACOPP vs ABVD[e]	$[redacted]	0.088	$[redacted][1]	-[redacted]%
PSCR revised base case: PSCR A + B + C (brentuximab vedotin vial cost - $[redacted])	**$[redacted]**	**0.119**	**$[redacted][6]**	**-[redacted]%**
PSCR revised base case with $[redacted] per brentuximab vedotin vial as per requested weighted price	$[redacted]	0.119	$[redacted][7]	[redacted]%

Source: Table 3-20, pp230-231 and compiled during the evaluation from Excel workbook 'Adcetris (brentuximab vedotin) – FL HL – BrECADD.xlsb'.

1L=first line; 2L=second line; 6m=6 months; AE=adverse event; ASCT=autologous stem cell transplant; BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ICER=incremental cost-effectiveness ratio; incr.=incremental; KM=Kaplan-Meier; MA=multivariate analysis; NE=not estimable; OS=overall survival; PFS=progression free survival; QALY=quality-adjusted life-year; SCT=stem cell transplant (allo/auto); SMR=standardised mortality ratio

[a] lowest BIC

[b] lowest AIC

[c] SCT type refers to allogeneic and autologous SCT

[d] 75.4% SCT of which 89.9% ASCT, versus submission base case SCT BrECADD 68.6%, eBEACOPP 80.6%; with 85.7% ASCT in both arms

[e] Utilities in R/R 1L with SCT first 6m 0.304, post-6m 0.702; all other states 0.538 versus submission base case R/R 1L with SCT first 6m 0.324, post-6m 0.749; all other states 0.574

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$45,000 to < $55,000*

[3] *$5,000 to < $15,000*

[4] *$75,000 to < $95,000*

[5] *$155,000 to < $255,000*

[6] *$35,000 to < $45,000*

[7] *$135,000 to < $155,000*

6.67 The PSCR presented a revised base which applied the half-cycle correction as described in the submission and corrected the cost of trimethoprim + sulfamethoxazole (paragraph 6.55). In addition, the revised PSCR base case pooled SCT data from HD21 (paragraph 6.44) and incorporated downstream utilities from eBEACOPP vs ABVD (paragraph 6.50). The revised base case presented in the PSCR reduced the ICER from $55,000 to < $75,000 per QALY gained to $35,000 to < $45,000 per QALY gained.

6.68 As outlined in paragraph 6.44 and paragraph 6.50, the ESC considered the pooling of SCT data from HD21 and the approach taken to applying downstream utilities outlined in the PSCR were appropriate. However, the ESC advised that the PSCR revised base case did not address all of the underlying uncertainty in the long-term PFS extrapolation from HD21. In addition, the ESC noted that when the requested brentuximab vedotin weighted price of $[redacted] per vial was used in the PSCR revised base case the ICER increased to $135,000 to < $155,000 per QALY gained.

6.69 The pre-PBAC response stated that a brentuximab vedotin AEMP of $[redacted] per 50 mg injection was offered for both BrECADD and A+AVD indications. The pre-PBAC response noted that this represented a price reduction for the current A+AVD indication (vial price reduced from $[redacted] per 50 mg injection to $[redacted] per 50 mg injection). The pre-PBAC response argued that the corresponding reduction in the ICER for A+AVD using the July 2025 economic model with the reduced brentuximab vedotin vial price offered for this indication had not been considered. The pre-PBAC response argued that, incorporating an AEMP of $[redacted] across both indications and assuming a distribution of A+AVD:BrECADD of 86.4%:13.6%, returned a weighted ICER of $55,000 to < $75,000 per QALY gained. The pre-PBAC response stated that revising the distribution to 69% A+AVD to 31% BrECADD returned a weighted ICER of $55,000 to < $75,000 per QALY gained.

BrECADD cost/patient/course

6.70 A summary of the drug doses and costs across the submission is presented in the following table, disaggregated into the components of BrECADD and eBEACOPP. The costs presented assume a brentuximab vedotin effective AEMP of $[redacted] per 50 mg injection.

Table 14: Drug cost per patient for proposed and comparator drugs

	BrECADD			eBEACOPP		
	HD21 dose and duration	**Model**	**Financial estimates**	**HD21 dose and duration**	**Model**	**Financial estimates**
Total mean dose (mg)[a]						
Brentuximab vedotin	626.54	719.42	719.42			
Cyclophosphamide	10,860.01	11,990.25	11,990.25	10,539.31	12,009.25	12,009.25
Etoposide	3,894.88	4,316.49	4,316.49	5,033.35	5,764.44	5,764.44
Doxorubicin	355.35	479.61	479.61	307.88	480.37	480.37
Dacarbazine	4,449.57	0	0	NA	NA	NA
Vincristine	NA	NA	NA	8.71	9.61	9.61
Bleomycin	NA	NA	NA	82.98	144.11	144.11
Procarbazine	NA	NA	NA	6,127.94	0	0
Dexamethasone	750.84	927.38	927.38	NA	NA	NA
Trimethoprim + sulfamethoxazole	NR	8,496 + 42,480	6,906 + 34,532	NA	NA	NA
Pegfilgrastim	NR	28.78	28.78	NR	28.82	28.82
Prednisone	NA	NA	NA	4,971.40	5,124.62	5,124.62
Mean duration (3-week cycles)	**PET+ 5.9, PET– 4.0**	**PET+ 5.9, PET– 4.0**	**PET+ 5.9, PET– 4.0**	**PET+ 5.9, PET– 4.0**	**PET+ 5.9, PET– 4.0**	**PET+ 5.9, PET– 4.0**
Cost/patient/course						
Brentuximab vedotin		$[redacted]	$[redacted]		-	-
Cyclophosphamide		$746.78	$748.99		$749.01	$750.18
Etoposide		$3,290.79	$3,300.52		$3,861.05	$3,867.07
Doxorubicin		$725.75	$727.89		$727.91	$729.05
Dacarbazine		$0.00	$0.00		-	-
Vincristine		-	-		$625.88	$626.86
Bleomycin	-	-	-	-	$961.56	$963.06
Procarbazine		-	-		$0.00	$0.00
Dexamethasone		$146.78	$121.73		-	-
Trimethoprim + sulfamethoxazole		$88.67	$71.13		-	-
Pegfilgrastim		$466.89	$468.27		$468.28	$469.01
Prednisone					$115.77	$114.13
Total	**-**	**$[redacted]**	**$[redacted]**	**-**	**$7,509.46**	**$7,519.35**

Source: compiled during the evaluation from Table 15.3.7.1 of HD21 CSR Addendum, and Excel workbooks 'Adcetris (brentuximab vedotin) – FL HL – BrECADD.xlsb' and 'Adcetris (brentuximab vedotin) – FL HL – BrECADD – UCM.xlsx'

BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

a Total mean dose from HD21 reported for safety population (BrECADD N=747, eBEACOPP N=741). For economic and financial estimates, total dose includes full vial wastage over mean number of cycles.

6.71 Generally, costs were similar across the economic analysis and financial estimates, with differences apparently due to rounding and, in the case of trimethoprim + sulfamethoxazole, due to use across all patients in all cycles in the economic analysis but following the number of cycles by PET status in the financial estimates. Usage was higher in the economic analysis and financial estimates than reported in HD21 due to assumed vial wastage and the absence of relative dose intensity in the economic analysis. The submission did not include the cost of dacarbazine or procarbazine.

6.72 The pre-PBAC response offered a brentuximab vedotin effective AEMP of $[redacted] per 50 mg injection.

Estimated PBS usage & financial implications

6.73 This submission was not considered by DUSC.

6.74 The submission estimated the financial implications of the proposed listing using an epidemiological approach, based on an incident population of adults with CD30+ Stage IIB with a large mediastinal mass and/or extranodal disease, Stage III or Stage IV cHL who are aged ≤ 60 years and sufficiently fit to be able to tolerate PET-adapted eBEACOPP.

6.75 Table 15 summarises the key inputs and calculations of the number of patients likely to receive brentuximab vedotin and number of scripts dispensed.

Table 15: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incident patients with Hodgkin lymphoma	Yr 1: 644 Yr 2: 651 Yr 3: 658 Yr 4: 664 Yr 5: 670 Yr 6: 675	Calculated by applying incidence rate of HL to the ABS population: ▪ ABS population aged ≤ 60 years ▪ Incidence of HL: 3/100K (Table 15, brentuximab vedotin PSD, July 2025)	Incident patients included children; estimates were based on the ABS population, including all people ≤60. This is inconsistent with the TGA-approved indication for adult patients. The proposed restriction was not limited to patients <60, although BrECADD is not recommended in older patients (>60).
Eligible patients with advanced cHL	Yr 1: 48 Yr 2: 49 Yr 3: 50 Yr 4: 50 Yr 5: 50 Yr 6: 51	Calculated by applying to the incident HL patients: ▪ % of cHL: 94.2% (average of Cochrane et al., 2021, Eichenauer et al 2018, and Cancer Council NSW, 2023) ▪ % Advanced cHL: 62.63% (290/463) (Nguyen 2023) ▪ Eligible for eBEACOPP: 12.8% (37/290) (Nguyen 2023)	DUSC previously considered 94.2% reasonable. The PBAC agreed with DUSC that this was reasonable. The PBAC also considered the % with advanced cHL was reasonable. The PBAC considered the population eligible for eBEACOPP was underestimated with the actual percentage eligible much higher. In addition, the PBAC considered there would be some use of BrECADD in patients who would have used nivolumab + AVD, A+AVD or other regimens. Overall, the PBAC considered that an assumption of 70% eligibility would be more applicable to the population aged ≤ 60 years.
Treatment utilisation			
Uptake rate	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Submission's assumptions.	DUSC previously considered the uptake of A+AVD of [redacted]% in Year 1, range increasing by [redacted]% per year and remaining steady at [redacted]% would be more appropriate (Table 12, brentuximab vedotin PSD, March 2024). The PBAC considered the uptake rates appropriate.

Data	Value	Source	Comment
PET assessment after 2 cycles and number of cycles	<table><tr><td></td><td colspan="2">BrECADD</td><td colspan="2">eBEACOPP</td></tr><tr><td></td><td>%</td><td>cycles</td><td>%</td><td>cycles</td></tr><tr><td>PET+</td><td>41.9</td><td>5.9</td><td>42.3</td><td>5.9</td></tr><tr><td>PET-</td><td>58.1</td><td>4.0</td><td>57.7</td><td>4.0</td></tr></table>	HD21 CSR Addendum, p39, pp83-84	This was used to calculate the number of proposed/affected scripts per year and treatment duration. The PBAC agreed with the evaluation that this was reasonable.
Number of patients treated with BrECADD	<table><tr><td></td><td>Total</td><td>PET+</td><td>PET-</td></tr><tr><td>Y1</td><td>[redacted][1]</td><td>[redacted][1]</td><td>[redacted][1]</td></tr><tr><td>Y2</td><td>[redacted][1]</td><td>[redacted][1]</td><td>[redacted][1]</td></tr><tr><td>Y3</td><td>[redacted][1]</td><td>[redacted][1]</td><td>[redacted][1]</td></tr><tr><td>Y4</td><td>[redacted][1]</td><td>[redacted][1]</td><td>[redacted][1]</td></tr><tr><td>Y5</td><td>[redacted][1]</td><td>[redacted][1]</td><td>[redacted][1]</td></tr><tr><td>Y6</td><td>[redacted][1]</td><td>[redacted][1]</td><td>[redacted][1]</td></tr></table>	Based on the number of eligible patients and assumed uptake rate. PET status, based on above cell, was used to calculate duration of treatment.	The PBAC considered the number of patients treated with BrECADD was underestimated as the proportion eligible for eBEACOPP was much lower than would be expected and there would be some uptake from patients who would have used nivolumab + AVD, A+AVD or other regimens. .
Scripts dispensed	Yr 1: [redacted][2] Yr 2: [redacted][2] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][2] Yr 6: [redacted][2]	Number of scripts were based on the PET status and number of cycles for BrECADD patients.	Dexamethasone pre-treatment was given at each cycle, instead of at initial treatment. That was incorrect, it should be tablets per year, not per cycle/month.
Scripts displaced	Yr 1: [redacted][2] Yr 2: [redacted][2] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][2] Yr 6: [redacted][2]	Number of scripts were based on the PET status and number of cycles for eBEACOPP patients.	This was reasonable.
PBS/RPBS Costs[a, b]			
BrECADD cost per cycle	<table><tr><td>**DPMQ**</td><td>**Published**</td><td>**Effective**</td></tr><tr><td colspan="3">**Brentuximab vedotin (136 mg)**</td></tr><tr><td>Public</td><td>$13,357.98</td><td>$[redacted]</td></tr><tr><td>Private</td><td>$13,589.38</td><td>$[redacted]</td></tr><tr><td>Weighted</td><td>$13,465.95</td><td>$[redacted]</td></tr><tr><td colspan="3">**Cyclophosphamide (2365 mg)**</td></tr><tr><td>Public</td><td>$134.58</td><td>-</td></tr><tr><td>Private</td><td>$180.86</td><td>-</td></tr><tr><td>Weighted</td><td>$156.17</td><td>-</td></tr><tr><td colspan="3">**Etoposide (283 mg)**</td></tr><tr><td>Public</td><td>$207.33</td><td>-</td></tr><tr><td>Private</td><td>$254.63</td><td>-</td></tr><tr><td>Weighted</td><td>$229.40</td><td>-</td></tr><tr><td colspan="3">**Doxorubicin (76 mg)**</td></tr><tr><td>Public</td><td>$130.21</td><td>-</td></tr><tr><td>Private</td><td>$176.43</td><td>-</td></tr><tr><td>Weighted</td><td>$151.77</td><td>-</td></tr><tr><td colspan="3">**Dexamethasone (40 mg)**</td></tr><tr><td>Public</td><td>$19.04</td><td>-</td></tr><tr><td>Private</td><td>$19.04</td><td>-</td></tr><tr><td>Weighted</td><td>$19.04</td><td>-</td></tr></table>	Effective and published DPMA were calculated by multiplying the AEMP by the number of vials/units per cycle and the pharmacy markup (private); and adding fees for drug preparation and distribution. Doses per cycle were based on the recommended dose, mean bodyweight (76.20 kg) or body surface area (1.91 m^2), and relative dose intensity (99.1%, 99.3%, 99.2%, 99.1%, 100% for each of BrECADD components, respectively) in the HD21 trial. The DPMQs for trimethoprim/sulfamethoxazole ($16.48) and pegfilgrastim (public=$91.63, private=$104.51, weighted=$97.64) were also added.	The submission assumed the cost of dacarbazine to be zero as it was not PBS-listed. Given that procarbazine costs were also excluded from the comparator arm, this may not have a substantial impact on the estimates. Trimethoprim/sulfamethoxazole was added to the BrECADD regimen but not to eBEACOPP. The submission did not explain why, although the low cost of this antibiotic would not significantly impact the estimates.

Data	Value		Source	Comment
eBEACOPP cost per cycle	**DPMQ**	**Published**	Calculations done as above. The relative dose intensities were: Bleomycin 92.2% Etoposide: 99.1% Doxorubicin: 99.1% Cyclophosphamide: 99.3% Vincristine: 93.0% Prednisone: 98.4% The DPMQ for pegfilgrastim was also added (public=$91.63, private=$104.51, weighted=$97.64)	The submission assumed the cost of procarbazine to be zero as it was not PBS-listed. Given that dacarbazine costs were also excluded from the comparator arm, this may not have a big impact on the estimates.
	Bleomycin (17,555 mg)			
	Public	$178.61		
	Private	$225.50		
	Weighted	$200.49		
	Etoposide (378 mg)			
	Public	$246.03		
	Private	$293.87		
	Weighted	$268.35		
	Doxorubicin (66 mg)			
	Public	$130.21		
	Private	$176.43		
	Weighted	$151.77		
	Cyclophosphamide (2365 mg)			
	Public	$134.58		
	Private	$180.86		
	Weighted	$156.17		
	Vincristine (2 mg)			
	Public	$109.07		
	Private	$154.99		
	Weighted	$130.50		
	Prednisone (75 mg)			
	Public	$16.97		
	Private	$16.97		
	Weighted	$16.97		
MBS costs				
Parenteral administration of antineoplastic agent	$126		MBS item 13950 was applied once per administration, irrespective of the number of medicines administered on the same day. The use of this item was calculated using etoposide scripts in BrECADD; etoposide and bleomycin were used in eBEACOPP.	MBS item 13950 was correctly applied to both regimens using the recommended 80% fee. The use of etoposide and bleomycin scripts to calculate the use scripts was reasonable.

Source: compiled during the evaluation from pp.232-244 and financial model (excel file 'Adcetris (brentuximab vedotin) – FL HL – BrECADD-UCM.xlsx')

Abbreviations: A+AVD=brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; cHL=classic Hodgkin lymphoma; CSR=clinical study report; eBEACOPP=escalated regimen with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and procarbazine; BrECADD=Brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin and dexamethasone; DUSC=drug utilisation subcommittee; MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Scheme; PET=positron emission tomography

[a] The submission presented PBS dispensing data for eBEACOPP: etoposide, cyclophosphamide, vincristine, doxorubicin, bleomycin, prednisone and pegfilgrastim (PBS items: 4428C, 7237X, 4327R, 7226H, 4619D, 7262F, 4361M, 7229L, 4433H, 7244G, 1936X, 6363X, 9514R) in calendar year 2025, which gave a split PBS 98.37%: RBPS 1.63%, but inappropriately did not use these values.

[b] The public/private split was based on a general chemotherapy code administered in hospital. Given eBEACOPP is an intensive regimen for advanced disease, it might not be directly applicable. Using the public/private split for eBEACOPP components would have been more reasonable.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

6.76 Table 16 summarises the estimated net financial implications to the PBS/RPBS and the Government health budget for the proposed listing of brentuximab vedotin over the first six years (assumed as 2027 to 2032).

Table 16: Estimated use and financial implications at the effective price of $[redacted] per vial

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Estimation of number of patients (treatment-naïve advanced cHL ≤ 60 years)							
Incident HL patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Eligible advanced cHL	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
BrECADD-treated patients	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total scripts dispensed PBS							
BrECADD scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][3]
BrECADD Net Cost to PBS							
Total net cost less copay	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted]	$[redacted][4]
Estimation of changes in use and financial impact of currently listed treatments (eBEACOPP) PBS							
Scripts net change	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][3]
Total net cost less copay	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Estimated financial implications for the PBS and the health budget							
Net cost to PBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost MBS	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net cost to Government Health budgets	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]

Source: compiled during the evaluation from pp.232-251 and financial model (excel file "Adcetris (brentuximab vedotin) – FL HL – BrECADD- UCM.xlsx")

cHL=classic Hodgkin lymphoma; eBEACOPP=escalated regimen with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and procarbazine; BrECADD=Brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin and dexamethasone; HL=Hodgkin lymphoma; MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *< 500*

[3] *5,000 to < 10,000*

[4] *$0 to < $10 million*

[5] *net cost saving*

6.77 The total cost to the PBS of listing brentuximab vedotin was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing. The evaluation considered that these financial estimates were highly uncertain.

6.78 The submission estimates were underestimated due to the use of an effective price per vial of $[redacted] as part of the BrECADD regimen, instead of the requested effective weighted price of $[redacted] per vial for the chemotherapy-agnostic indication. The proposed $[redacted] AEMP was calculated as a weighted average of the AEMP for A+AVD ($[redacted]) and BrECADD ($[redacted]), based on the estimated total number of scripts for each of the combinations from 2026 to 2030. The evaluation considered that this approach was highly uncertain, and if the use of brentuximab vedotin in the BrECADD setting versus the A+AVD setting was to increase, the cost in the BrECADD setting and financial estimates would be further underestimated. The ESC considered that with the March 2026 listing of nivolumab for 'immunotherapy sensitive advanced or metastatic cancer', the vast majority of A+AVD would be replaced by nivolumab + AVD for patients with Stage IIB/III/IV disease. As outlined in paragraph 3.4, the ESC considered that given the expected changes in utilisation of A+AVD, the submission's request for a weighted price of $[redacted] was effectively assuming a much higher price of BrECADD than

$[redacted] per 50 mg injection and agreed with the evaluation that the estimates were underestimated. If a price of $[redacted] per 50 mg injection was assumed the total cost to the PBS of listing brentuximab vedotin was estimated to be $0 to < $10 million in Year 6, and a total of $$0 to < $10 million in the first 6 years of listing.

6.79 The PBAC considered financial estimates underestimated the population with advanced cHL eligible for BrECADD for the follow reasons:

- The submission used LaRDR data (Nguyen et al. 2023) from patients with advanced cHL receiving eBEACOPP (12.8%) to estimate the proportion of eligible patients to receive BrECADD, but LaRDR data fluctuated considerably over 7 years (from 8.1% to 27%, Wellard et al. 2023).;
- The submission underestimated eBEACOPP use in patients aged ≤60 years because it applied the percentage of eBEACOPP use in the whole population (12.8%) and applied it to the population aged ≤ 60 years. This underestimated use in the as eBEACOPP is not recommended for patients aged over 60 years;
- Regimens other than eBEACOPP (e.g. ABVD, A+AVD and now nivolumab + AVD) would have been used for advanced cHL to preserve fertility; and
- The LaRDR data may be incomplete and not representative of the population.

Therefore, the PBAC considered it would be more reasonable to assume 70% of patients with advanced cHL would be eligible to use BrECADD (rather than 12.8%). The PBAC noted the pre-PBAC response proposed a price of $[redacted] for brentuximab vedotin. The PBAC noted that incorporating these changes increased the net cost to government health budgets over 6 years to $20 million to < $30 million (Table 17).

Table 17: Revised estimated use and financial implications at the effective weighted price of $[redacted] per vial

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Estimation of number of patients (treatment-naïve advanced cHL ≤ 60 years)							
Incident HL patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Eligible advanced cHL [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]
BrECADD-treated patients	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]
Total scripts dispensed PBS/RPBS							
BrECADD scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]
BrECADD Net Cost to PBS/RPBS							
Total net cost less copay	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][7]
Estimation of changes in use and financial impact of currently listed treatments (eBEACOPP) PBS							
Scripts net change	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][4]	-[redacted][5]
Total net cost less copay	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]
Estimated financial implications for the PBS and the health budget							
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][9]
Net cost MBS	-$[redacted][8]	-$[redacted]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]
Net cost to Government Health budgets	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][9]

Source: from pp.232-251 and financial model (excel file "Adcetris (brentuximab vedotin) – FL HL – BrECADD- UCM.xlsx")
cHL=classic Hodgkin lymphoma; eBEACOPP=escalated regimen with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and procarbazine; BrECADD=Brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin and dexamethasone; MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Scheme; Repatriation Pharmaceutical Benefits Scheme.
[a] 70% of patients with advanced stage cHL (Stage IIB-IV) eligible for BrECADD (submission base case 12.8%).
The redacted values correspond to the following ranges:
[1] 500 to < 5,000

[2] *< 500*
[3] *5,000 to < 10,000*
[4] *10,000 to < 20,000*
[5] *50,000 to < 60,000*
[6] *$10 million to < $20 million*
[7] *$30 million to < $40 million*
[8] *net cost saving*
[9] *$20 million to < $30 million*

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended expanding the Section 100 Efficient Funding of Chemotherapy, Authority Required listing of brentuximab vedotin for the first-line treatment of advanced CD30 positive classical Hodgkin lymphoma (cHL) to include use of the BrECADD regimen (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin and dexamethasone). The PBAC was satisfied that BrECADD provides, for some patients, a significant improvement in efficacy over eBEACOPP (escalated combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). The PBAC's recommendation for listing was based on, among other matters, its assessment that the expanded listing for advanced cHL, which includes BrECADD and the A+AVD regimen (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine), would be acceptably cost-effective at the price per brentuximab vedotin 50 mg injection proposed in the pre-PBAC response.

7.2 The PBAC noted the input from health care professionals, Rare Cancers Australia, Lymphoma Australia, the Haematology Society of Australia and New Zealand (HSANZ) and the Australasian Leukaemia and Lymphoma group (ALLG) supporting the listing. The PBAC considered the input highlighted the need for treatments that improve outcomes of first-line treatment while reducing short-term and long-term treatment toxicity. The PBAC noted concerns about long term toxicities of treatment including infertility, secondary cancers, neuropathy and lung damage. The PBAC considered the input from health professionals and ALLG was informative for understanding the clinical place of the BrECADD regimen in the context of rapidly changing treatment options for first-line cHL. The PBAC noted advice that nivolumab + AVD is now considered the preferred first-line treatment option for patients for whom an AVD-based regimen was appropriate, including older and lower-risk patients. The PBAC noted ALLG input that A+AVD would be reserved for patients unable to receive nivolumab. The PBAC acknowledged that there was a clinical need for more effective treatments with lower toxicity, as long-term treatment-related adverse events are a major cause of morbidity in cHL.

7.3 The PBAC provided the following advice on the proposed restriction:

- The existing brentuximab vedotin listing for Stage III or IV CD30 positive Hodgkin lymphoma (as part of A+AVD) be amended. Patients will be able to access the A+AVD or the BrECADD regimens with the recommended listing in paragraph 8.1.
- An Authority Required (Telephone/Online) listing was appropriate due to simplicity of the criteria.
- Advanced stage CD30 positive Hodgkin lymphoma was appropriate as an indication for the recommended listing.
- Clinical criteria stating that the treatment must be in combination with a multi-drug chemotherapy regimen was appropriate.
- Clinical criteria specifying that the patient must have either Stage IIB with large

mediastinal mass and/or extranodal, Stage III or Stage IV disease was not required.

- A prescribing instruction with maximum amounts and repeats specified for the BrECADD (180 mg and 5 repeats) and A+AVD (120 mg and 11 repeats) regimens was appropriate.
- The listing should be age-agnostic.
- The existing relapsed or refractory HL listings (with or without previous autologous stem cell transplant) allow re-treatment for patients who had responded to first-line brentuximab vedotin with a lifetime maximum of 16 treatment cycles. The PBAC considered this remained appropriate.

7.4 The PBAC considered the proposed clinical place of BrECADD was appropriate and advised that, consistent with international guidelines (see paragraph 4.4), it would be used as the preferred treatment in fit, younger (≤ 60 years) patients with cHL. The PBAC acknowledged that the clinical place of first-line treatments for cHL had changed rapidly with the introduction of newer regimens such as nivolumab + AVD for advanced cHL. The PBAC noted advice that nivolumab + AVD was now a preferred treatment option for patients who would use an AVD-based regimen.

7.5 The PBAC considered that PET-adapted eBEACOPP was an appropriate main comparator as it is the treatment most likely to be replaced. However, the PBAC considered that in clinical practice, BrECADD may also replace some use of other therapies such as ABVD, A+AVD and nivolumab + AVD (refer to paragraphs 6.79 and 7.9).

7.6 The PBAC noted the clinical evidence was from the HD21 clinical trial which compared BrECADD to eBEACOPP in adults aged 18 to 60 years. The PBAC noted a 36% reduction in the risk of progression with BrECADD (progression-free survival (PFS) hazard ratio (HR) after a median follow-up of 60 months was 0.64 (95% CI: 0.44, 0.93)). The PBAC noted that overall survival was similar in both arms at 60 months median follow-up, however differences in overall survival would be difficult to detect due to the good prognosis following first-line treatment for advanced cHL. The PBAC considered that the claim of superior comparative effectiveness was reasonable.

7.7 The PBAC noted that fewer patients in the BrECADD arm experienced treatment-related morbidity and treatment-related adverse events (Grade ≥ 3), however more patients in the BrECADD arm experienced febrile neutropenia and serious adverse events. The PBAC considered secondary malignancies are an important safety outcome because cHL has high cure rates. People treated for cHL have a high incidence of secondary cancers and are more likely to die from secondary malignancy in the longer term (> 20 years after diagnosis) than from Hodgkin lymphoma. The PBAC noted rates of secondary malignancy were 2.8% and 2.1% at 60 months in the BrECADD and eBEACOPP arms of the HD21 clinical trial, respectively. There were more cases of acute myeloid leukaemia (AML) and myelodysplastic neoplasms (MDS) in the eBEACOPP arm (6 vs 1) and more cases of non-Hodgkin Lymphoma (NHL) in the BrECADD arm (8 vs 2). The PBAC considered there was not enough evidence to determine whether the rates of secondary malignancy differed between the

treatments. The PBAC noted that rates of infertility at 1-year post-treatment, assessed by FSH measurements, were lower in the BrECADD arm for both males and females. The PBAC considered this may suggest the potential for improved fertility outcomes following BrECADD and noted this was an important outcome for patients. The PBAC considered that the claim of superior comparative safety was not fully supported based on the available data. The PBAC considered a claim of non-inferior comparative safety was appropriate.

7.8 The PBAC noted that the submission presented a cost-utility analysis. The PBAC considered the structure of the economic model was appropriate. The PBAC noted the key uncertainties related to the modelling of long-term outcomes, particularly the selected extrapolation and Kaplan Meier truncation point. The PBAC noted the revised base case ICER presented in the Pre-Sub-Committee Response was $35,000 to < $45,000 per QALY gained using the effective brentuximab vedotin price of $[redacted] per vial for the BrECADD regimen. The PBAC considered that this ICER was underestimated as the submission had requested a weighted brentuximab vedotin vial price of $[redacted] as part of a combined A+AVD and BrECADD listing and the weighted price assumed a continued 80.5% use of A+AVD. The PBAC noted that the brentuximab vedotin AEMP of $[redacted] per 50 mg injection was offered for both BrECADD and A+AVD indications, and acknowledged with this price the ICER for the A+AVD regimen would be reduced (brentuximab vedotin PSD, July 2025 PBAC meeting).

7.9 The PBAC considered the A+AVD use assumed in the submission to be overestimated as nivolumab + AVD was now widely used in Australian clinical practice, largely replacing A+AVD for patients who would use an AVD-based regimen. The PBAC considered the rapid changes in the first-line treatment options for cHL made it difficult to reliably estimate a weighted price for brentuximab vedotin between the BrECADD and A+AVD regimens.

7.10 The PBAC noted that in HD21, both BrECADD and eBEACOPP achieved higher rates of PFS than A+AVD and ABVD in the ECHELON-1 trial (brentuximab vedotin PSD, July 2025 PBAC meeting). The PBAC noted that guidelines recommended BrECADD as the preferred treatment regimen for fit patients aged ≤ 60 years with this condition (see paragraph 4.4). The PBAC acknowledged the clinical need and noted that with the revisions to the patient population outlined in paragraph 7.11, the estimated treated population remained small. The PBAC considered the cost per course of currently reimbursed first line treatment options for advanced cHL and advised that the proposed cost per course of BrECADD was consistent with existing regimens. In addition, the PBAC acknowledged the proposed price was lower than the current price for the existing brentuximab vedotin listing for the A+AVD regimen and hence there would be a reduction in the cost of this regimen. Overall, the PBAC considered the expanded listing for advanced cHL, which includes BrECADD and A+AVD, was acceptably cost-effective for the first line treatment of advanced CD30 positive cHL at a price per brentuximab vedotin 50 mg injection of $[redacted].

7.11 The PBAC considered the submission's financial estimates underestimated the size of

the population eligible for BrECADD. The submission assumed 12.8% of patients aged ≤ 60 years with advanced cHL would be eligible for BrECADD based on the proportion of patients who used eBEACOPP in the LaRDR data. The PBAC considered this was an underestimate as the submission incorrectly estimated the proportion of patients who used eBEACOPP and there were limitations with the LaRDR data (see paragraph 6.79). In addition, the PBAC considered there would be some use of BrECADD in patients who would have used A+AVD, nivolumab + AVD or other regimens. The PBAC considered it would be reasonable to assume 70% of patients with advanced HL aged ≤ 60 years would be eligible for BrECADD. The PBAC noted the revised financial estimates (Table 17) were substantially higher because it assumed a larger eligible population and used the higher vial price of $[redacted]. The PBAC considered the revised financial estimates were appropriate.

7.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for brentuximab vedotin:

a) The treatment is expected to provide a clinically relevant improvement in efficacy over alternative therapies, however, the improvements in PFS were not sufficiently large in magnitude to be classified as substantial;

b) The treatment is not expected to address a high and urgent unmet clinical need, as while the PBAC acknowledged there was an unmet need it was not considered high and urgent due to the availability of other therapies;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.13 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing of brentuximab vedotin for Stage III or IV CD30 positive Hodgkin lymphoma as follows:
Additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	№.of Rpts
BRENTUXIMAB VEDOTIN Injection	15098P (Public) 15080Q (Private)	~~120~~ *180mg*	11
Available brands			
Adcetris (brentuximab vedotin 50 mg injection, 1 vial)			
Edit Restriction Summary / ToC			
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 - Efficient Funding of Chemotherapy- Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)		
Prescribing rule level	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).		
	Administrative Advice: ~~No increase in the maximum quantity or number of units may be authorised.~~ *No increase in the maximum amount or number of units may be authorised.*		
	Administrative Advice: No increase in the maximum number of repeats may be authorised		
	Administrative Advice: Special Pricing Arrangements apply		
	Episodicity: [blank]		
	Severity: Advanced Stage		
	Condition: CD30 positive Hodgkin lymphoma		
	Indication: ~~Stage III or IV CD30 positive Hodgkin lymphoma~~ *Advanced stage CD30 positive Hodgkin lymphoma*		
	Clinical criteria:		
	The treatment must be for first line therapy for this condition.		
	AND		
	Clinical criteria:		
	The treatment must be for curative intent.		
	~~**AND**~~		
	~~**Clinical criteria:**~~		
	~~The treatment must be in combination with at least the following: (i) doxorubicin, (ii) vinblastine~~		
	~~**AND**~~		
	~~**Clinical criteria:**~~		
	~~The treatment must not be in combination with (i) etoposide, (ii) cyclophosphamide~~		
	AND		
	Clinical criteria:		
	The treatment must be in combination with a multi-drug chemotherapy regimen.		
	AND		
	Clinical criteria:		
	The treatment must not be for more than 6 treatment cycles under this restriction in a lifetime.		

	Prescribing Instructions: *At the time of the authority application, medical practitioners must request the appropriate maximum amount and number of repeats to complete up to 6 cycles of treatment based on the following:* • *Up to a maximum of 180 mg and 5 repeats may be requested where dosing is administered as part of the BrECADD regimen (i.e. in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone); or* • *Up to a maximum of 120 mg and 11 repeats may be requested where dosing is administered as part of the A+AVD regimen (i.e. in combination with doxorubicin, vinblastine and dacarbazine)*

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.