

**6.03 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 (Telephone/Online) listing for the first line treatment of advanced classical Hodgkin lymphoma.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus ABVD (doxorubicin, bleomycin, vincristine and dacarbazine) as a proxy for positron emission tomography (PET)-adapted ABVD.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Adult patients with previously untreated CD30+ advanced (Ann Arbor Stage III or IV) Hodgkin lymphoma
Intervention	Brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine (A+AVD), for 6 x 28-day cycles
Comparator	<p><u>Main comparator:</u> PET-adapted ABVD regimen consisting of ABVD for the first 2 x 28-day cycles followed by:</p> <ul style="list-style-type: none"> • AVD for a further 4 x 28-day cycles in iPET2-negative patients, or • eBEACOPP for a further 4 x 21-day cycles in iPET2-positive patients <p><u>Supplementary comparator:</u> PET-adapted eBEACOPP regimen consisting of eBEACOPP for the first 2 x 21-day cycles followed by:</p> <ul style="list-style-type: none"> • eBEACOPP for a further 2 x 21-day cycles or ABVD for 4 x 28-day cycles in iPET2-negative patients, or • eBEACOPP for a further 4 x 21-days cycles in iPET2-positive patients
Outcomes	Improved modified progression-free survival, overall survival, and health-related quality of life
Clinical claim	A+AVD is superior in terms of efficacy but inferior in terms of safety compared to PET-adapted ABVD No clinical claim was made in terms of efficacy for A+AVD versus PET-adapted eBEACOPP A+AVD is superior in terms of safety compared to PET-adapted eBEACOPP

Source: Table 1.1.1, p17 of the submission

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; AVD, doxorubicin, vinblastine and dacarbazine; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; iPET2, interim positron emission tomography after 2 cycles of chemotherapy; PET, positron emission tomography

Note: Australian guidelines (Cochrane 2021) note that trial definitions of response based on the iPET2 may differ. The cut-off for negative iPET2 is based on a Deauville Score (5-point scale) of either ≤ 2 or ≤ 3 .

2 Background

Registration status

2.1 Brentuximab vedotin is TGA-approved for the following indications:

- Hodgkin lymphoma
 - Treatment of adult patients with CD30+ Hodgkin lymphoma at higher risk of relapse or progression following autologous stem cell transplant (ASCT).
 - Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma following ASCT; or following at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
- Peripheral T-cell lymphoma
 - Treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma in combination with cyclophosphamide, doxorubicin and prednisone.
 - Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma.
- Cutaneous T-cell lymphoma
 - Treatment of adult patients with CD30+ cutaneous T-cell lymphoma after at least 1 prior systemic therapy.

2.2 The current submission was lodged under the TGA/PBAC parallel process for a new indication that was TGA-approved in January 2024: Treatment of patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).

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	PBS item code	Dispensed Price Max Amt	Max. Amount	No. of Rpts
BRENTUXIMAB VEDOTIN (50 mg injection, 1 vial)	NEW (Public) NEW (Private) MP	Published price Public: \$ 1 Private: \$ 1 Effective price Public: \$ 1 Private: \$ 1	150 120 mg	11
Available brands				
ADECTRIS (brentuximab vedotin 50 mg injection, 1 vial)				
Restriction Summary [new] / Treatment of Concept: [new] [number – For. Dept. use]: Authority Required				

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	<p>Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals</p> <p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p> <p>Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised</p>
	<p>Administrative Advice: Special Pricing Arrangements apply</p>
	<p>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</p>
	<p>Episodicity: [Blank]</p>
	<p>Severity: [Blank]</p>
	<p>Condition: Stage III or IV CD30 positive classical Hodgkin lymphoma.</p>
	<p>Indication: Stage III or IV CD30 positive classical Hodgkin lymphoma.</p>
	<p>Treatment Phase: Initial PBS subsidised treatment</p>
	<p>Clinical criteria:</p>
	<p>The treatment must be for first line therapy for this condition.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The treatment must be for curative intent.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The treatment must be in combination with <i>at least the following:</i> (i) doxorubicin, (ii) vinblastine-doxorubicin, vinblastine and dacarbazine.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have a WHO performance status of 2 or less.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The treatment must not be for more than 6 treatment cycles under this restriction in a lifetime.</p>
	<p>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) a completed authority prescription form; 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).</p>
	<p>Administrative Advice: A patient may only qualify for PBS subsidised treatment under this restriction once</p>

- 3.2 The submission proposed a special pricing arrangement with an effective AEMP of \$| per vial and a published AEMP of \$| per vial. For the treatment of adult patients with relapsed or refractory Hodgkin lymphoma who are ASCT naïve or post ASCT the effective AEMPs for these indications are \$| per vial and \$| per vial respectively.
- 3.3 The requested restriction is silent on age. The submission claimed that this allows for the use of brentuximab vedotin in rare instances of advanced stage disease in adolescents. A recently published phase III trial indicated that brentuximab vedotin in combination with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide resulted in superior efficacy compared to doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide, when used as first-line treatment for paediatric high-risk Hodgkin lymphoma (Castellino 2022). The ESC considered it was appropriate for the requested restriction to be silent on age.
- 3.4 The submission claimed there is an unmet clinical need for treatments in older patients with advanced disease and that A+AVD would be suitable for fit patients in this age group. However, the submission acknowledged concerns regarding the risk-benefit balance in patients aged ≥ 60 years and noted that the sponsor is amenable to an age restriction if needed. The clinical evidence suggested uncertainty in terms of treatment benefit but increased toxicities in patients aged ≥ 60 years.
- 3.5 The requested restriction does not include criteria relating to patient fitness. The submission acknowledged that this was inconsistent with the eligibility criteria in the key trial, ECHELON 1, that required patients to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 . However, the submission claimed that this was consistent with the PBS listing of brentuximab vedotin for treatment of CD30 positive peripheral T-cell lymphoma despite the key trial requiring patients to have an ECOG performance status of ≤ 2 . The ESC considered that a criterion regarding ECOG performance status was not required in the restriction.
- 3.6 The submission noted that doxorubicin and vinblastine have unrestricted listings on the PBS/RPBS, while dacarbazine is neither TGA-approved (indicated for metastatic malignant melanoma and various sarcomas only) nor listed on the PBS for treatment of Hodgkin lymphoma. Based on information in the eviQ guidelines and Lymphoma Australia website, dacarbazine is available to patients at no cost in public settings. Patient information on the Lymphoma Australia website notes that dacarbazine is not funded in private settings, with varying levels of coverage through private insurers or out-of-pocket costs of approximately \$800 per treatment cycle. The lack of full coverage of these costs in private settings may lead to equity of access issues for the A+AVD regimen although this would also apply to the nominated main comparator, ABVD.
- 3.7 The submission also proposed amendments to the current PBS listings for brentuximab vedotin in the relapsed/refractory setting, to allow for re-treatment following first line therapy and to change the restrictions from Authority Required to Authority Required (Streamlined).

- 3.8 The requested amendments to allow for re-treatment in the relapsed/refractory setting were inadequately justified given limited representation of use in this setting based on the key trial. No other evidence was presented in support of the requested amendment. The efficacy and safety of brentuximab vedotin as well as the cost-effectiveness of use in this circumstance is uncertain.
- 3.9 The evaluation considered the requested amendments to the current lifetime limits in the relapsed/refractory restrictions may not be appropriate. In November 2016, the PBAC noted that the impact of patients potentially accessing brentuximab vedotin more than once (before ASCT and then again after) was not considered in either of the two submissions for brentuximab vedotin that were considered at the same meeting (para 7.4, brentuximab vedotin – ASCT-naïve Public Summary Document (PSD), November 2016 PBAC meeting; para 7.4, brentuximab vedotin – post-ASCT PSD, November 2016 PBAC meeting). At that time, the PBAC noted that the product information allowed for a lifetime maximum of 16 treatment cycles and that both restrictions should be consistent with this. The Pre-Sub-Committee Response (PSCR) argued that first-line therapy for advanced Hodgkin lymphoma is administered with curative intent with only a small proportion of patients receiving later line treatment. In ECHELON-1, 20% of patients randomised to A+AVD received subsequent re-treatment after a median follow up of approximately 6 years with three patients (0.5%) re-treated with brentuximab vedotin. The PSCR stated there was no biological reason brentuximab vedotin would not be effective in the relapsed/refractory setting in patients who responded to A+AVD in first-line therapy. The ESC noted that only a very small number of patients were re-treated with brentuximab vedotin in ECHELON-1. The ESC noted that when recommending brentuximab vedotin combination therapy for the first-line treatment of peripheral T-cell lymphoma in March 2021 the PBAC allowed re-treatment for patients who had responded to first-line brentuximab vedotin (paragraph 7.14, brentuximab vedotin PSD, March 2021 PBAC Meeting). The ESC acknowledged the limited evidence base for re-treatment but considered it would likely be appropriate in this context. The ESC noted a lifetime maximum of 16 treatment cycles in the product information for relapsed or refractory Hodgkin lymphoma and considered that this remained appropriate to accommodate use across both settings.
- 3.10 The submission claimed that the proposed change to Authority Required (Streamlined) is consistent with the existing PBS listing for pembrolizumab for the same indication. The initial pembrolizumab restriction was an Authority Required (telephone/online/in writing) listing (pembrolizumab PSD, August 2017 PBAC meeting). In July 2022, the PBAC considered a Category 3 submission requesting the addition of the 400 mg every 6 weeks pembrolizumab dosing regimen for multiple PBS listings including relapsed/refractory Hodgkin lymphoma (pembrolizumab PSD, July 2022 PBAC meeting). As part of this consideration, the relapsed/refractory Hodgkin lymphoma listing was amended to an Authority Required (Streamlined) listing.

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

4 Population and disease

- 4.1 Hodgkin lymphoma is a type of fast-growing (aggressive) blood cancer that affects a type of white blood cell called B-cell lymphocytes, which are part of the immune system. The disease is defined by the presence of unusually large, malignant (cancerous), Hodgkin-Reed-Sternberg cells, which help differentiate Hodgkin lymphoma from non-Hodgkin lymphoma. Classical Hodgkin lymphoma is typically characterised by the expression of CD30 surface markers on these cancer cells. The disease has a bimodal age distribution with peaks at 15 to 35 years of age and greater than 60 years of age. Classical Hodgkin lymphoma accounts for the majority of cases of Hodgkin lymphoma, with nodular lymphocyte predominant Hodgkin lymphoma comprising the minority of cases.
- 4.2 Disease staging is carried out according to the modified Ann Arbor classification that is based on the number and location of affected lymph nodes as well as whether the disease has spread to the bone marrow or other organs. The disease is further categorised by the presence or absence of B-type symptoms such as fevers, night sweats and weight loss exceeding 10% of the patient's baseline body weight. Advanced stage Hodgkin lymphoma includes stage III or IV disease (Ann Arbor classification) and stage IIB disease with bulk or extranodal disease (German Hodgkin Study Group classification).
- 4.3 The submission positioned A+AVD as a first-line treatment option for patients with previously untreated CD30 positive advanced (Ann Arbor stage III or IV) Hodgkin lymphoma. The ESC noted the submission's proposed clinical algorithm assumed people receiving A+AVD will not get interim positron emission tomography after 2 cycles of chemotherapy (iPET2). The ESC considered that iPET2 would likely continue with A+AVD despite the fact that it was not used in the ECHELON-1 trial.
- 4.4 More recently published international guidelines recommend a narrower place in therapy than proposed in the submission; for treatment of stage III or IV disease in patients aged 60 years or younger who are fit (i.e. do not have poor performance or substantial co-morbidities) (The National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2024 Hodgkin Lymphoma). The NCCN guidelines also note that use of A+AVD is contraindicated in those with neuropathy.
- 4.5 The submission presented a current treatment algorithm for relapsed/refractory disease. Patients who fail first line therapy are treated with second line (salvage) chemotherapy followed by high dose chemotherapy and ASCT unless they are not suitable. Based on current PBS listings, patients who have undergone ASCT and are relapsed/refractory are eligible for brentuximab vedotin or pembrolizumab. Patients who have not undergone ASCT, and are unsuitable for ASCT or unsuitable for treatment with multi-agent chemotherapy, and have relapsed/refractory disease after 2 prior treatments are also eligible for brentuximab vedotin or pembrolizumab.

The submission noted that consolidation treatment with brentuximab vedotin may be considered in patients at high risk of relapse or progression after ASCT. Brentuximab vedotin is TGA-approved but not PBS-listed for consolidation therapy after ASCT.

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

5 Comparator

- 5.1 The submission nominated PET-adapted ABVD as the main comparator. The main arguments provided in support of the nominated main comparator were that ABVD is the most commonly used first-line treatment for advanced classical Hodgkin lymphoma in Australia and that PET-adapted strategies are recommended in Australian guidelines as they provide similar efficacy to non-PET-adapted strategies but with an improved safety profile.
- 5.2 The submission presented analyses of initial treatment regimens used in Australia based on the Lymphoma and Related Diseases Registry (LaRDR) and Australian Lymphoma Alliance (ALA) datasets (Nguyen 2023, Wellard 2023 unpublished analysis, Goh 2023). Based on the results, the submission claimed that the most commonly used treatment regimen was ABVD. However, the submission acknowledged that the analyses only captured regimens used in the first treatment cycles and therefore would not capture the use of PET-adapted regimens or modifications to regimens in subsequent treatment cycles.
- 5.3 While treatment guidelines recommend the use of PET-adapted regimens, the level of utilisation in the Australian setting is unclear due to limitations with data capture in the identified studies. The authors of the Nguyen 2023 study noted that the uptake of PET-adapted regimens appeared relatively low (data not presented) but suggested that it could be due to limited follow-up in more recently enrolled patients. The ESC agreed with the submission and the PSCR that PET-adapted ABVD is the standard of care for ABVD treatment in Australia.
- 5.4 The submission claimed that while A+AVD is not a PET-adapted regimen, it is expected to substitute for PET-adapted ABVD. It is unclear whether A+AVD is more likely to substitute for PET-adapted ABVD or non-PET-adapted ABVD given treatment guidelines recommend the use of PET-adapted regimens over non-PET-adapted regimens. Therefore, both regimens may be relevant comparators.
- 5.5 The submission nominated PET-adapted escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (eBEACOPP) as a supplementary comparator. The submission claimed that eBEACOPP is an alternative to ABVD but used less commonly in Australia as it is a more intensive regimen, and it is not recommended in patients aged above 60 years. The ESC advised that eBEACOPP was standard of care for a specific subgroup of patients with Hodgkin lymphoma (used for at least the first 2 cycles for fit patients < 45 years).

- 5.6 The use of brentuximab vedotin in the first line setting may displace the use of brentuximab vedotin and/or immunotherapies (e.g. pembrolizumab) in later line settings, which was captured in the trial, and was considered in the economic analysis but not the financial estimates.

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 comments

- 6.2 The PBAC noted and welcomed the input from an individual (1) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments from an individual who would like to access the medicine to treat their own health condition described the impact of Hodgkin lymphoma on their quality of life and noted a willingness to access any treatment options that would improve outcomes. The comments from the Leukaemia Foundation highlighted the impact of Hodgkin lymphoma on patients and that additional options are needed for patients to increase clinical choice given the diverse Hodgkin lymphoma population.

Clinical trials

- 6.3 The submission was based on a head-to-head trial comparing A+AVD with ABVD (as a proxy for PET-adapted ABVD) for the treatment of adult patients with previously untreated advanced stage (Ann Arbor stage III or IV) classical Hodgkin lymphoma (ECHELON-1).
- 6.4 No head-to-head trials were identified comparing A+AVD with PET-adapted ABVD or eBEACOPP. The submission provided data from the following trials as supportive evidence for the nominated comparators:
- A trial of PET-adapted ABVD in adult patients with newly diagnosed advanced (Ann Arbor stage IIB, III, IV or stage IIA with adverse features) classical Hodgkin lymphoma (RATHL). The trial included randomised use of ABVD or AVD for 4 cycles in patients with negative PET findings after 2 cycles of ABVD. Patients with positive PET findings received a BEACOPP-based regimen (eBEACOPP or BEACOPP-14).
 - A head-to-head trial comparing PET-adapted eBEACOPP with non-PET-adapted eBEACOPP in patients aged 16-60 years who had newly diagnosed advanced (Ann Arbor stage IIB, III or IV) classical Hodgkin lymphoma (AHL2011).

An overview of the HD18 trial of PET-adapted eBEACOPP was also included during the evaluation for completeness as it forms part of the main body of evidence informing published guidelines.

6.5 The submission claimed that naïve comparisons of treatment efficacy using the A+AVD arm from ECHELON-1 with PET-adapted regimens in the RATHL and AHL2011 trials were not possible due to differences in trial design and patient populations. A naïve comparison, as opposed to a Bucher indirect comparison, is still possible despite the observed differences. However, the comparisons may not be informative given major differences in both study design, populations and outcomes.

6.6 Details of the key trial presented in the submission are in Table 2 below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trials of brentuximab vedotin		
ECHELON-1 (NCT01712490)	Clinical Study Report C25003. A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma.	Clinical Study Report, August 2017
	Clinical Study Report Addendum 1. Study C25003 (ECHELON-1). A randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin lymphoma.	Clinical Study Report Addendum 1, May 2022
	Connors et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma.	N Engl J Med (2018), 378, 331-344
	Straus et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial.	Lancet Haematol (2021), 8, e410-e421
	Ansell et al. Overall survival with brentuximab vedotin in Stage III or IV Hodgkin's lymphoma.	N Engl J Med (2022), 387, 310-320

Source: Table 2.2-1, p62 of the submission

6.7 The key features of the ECHELON-1 trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
A+AVD versus ABVD						
ECHELON-1	1,334	Phase III, MC, OL, RCT. Primary analysis period (median 24 months follow-up) and up to 10 years follow-up	High	Adult patients with previously untreated stage III or IV classical Hodgkin lymphoma	mPFS, OS, complete remission, overall response	mPFS, OS, adverse events, EQ-5D-3L, use of subsequent treatments

Source: Section 2.4, pp69-85 of the submission

Abbreviations: MC, multi-centre; mPFS, modified progression-free survival; OL, open label; OS, overall survival; RCT, randomised controlled trial

6.8 ECHELON-1 is an ongoing trial with continuing follow-up of the remaining study participants until the accrual of 112 deaths or 10 years from the randomisation date of the last patient, whichever occurs first. Results in the submission are based on the primary outcome analysis and first interim overall survival analysis (20 April 2017 data cut, median follow-up 24 months) and second interim overall survival analysis (1 June 2021 data cut, median follow-up 73 months).

6.9 The open-label trial design has the potential to introduce bias as knowledge of treatment assignment may affect disease management decisions and assessment of

outcomes that are not centrally assessed. The risk of bias was minimised for results that were independently reviewed during the primary analysis period (April 2017 data cut). The independent review facility was disbanded after this period, therefore there is potential risk of bias for outcomes that were investigator-assessed only during the post-treatment follow-up period.

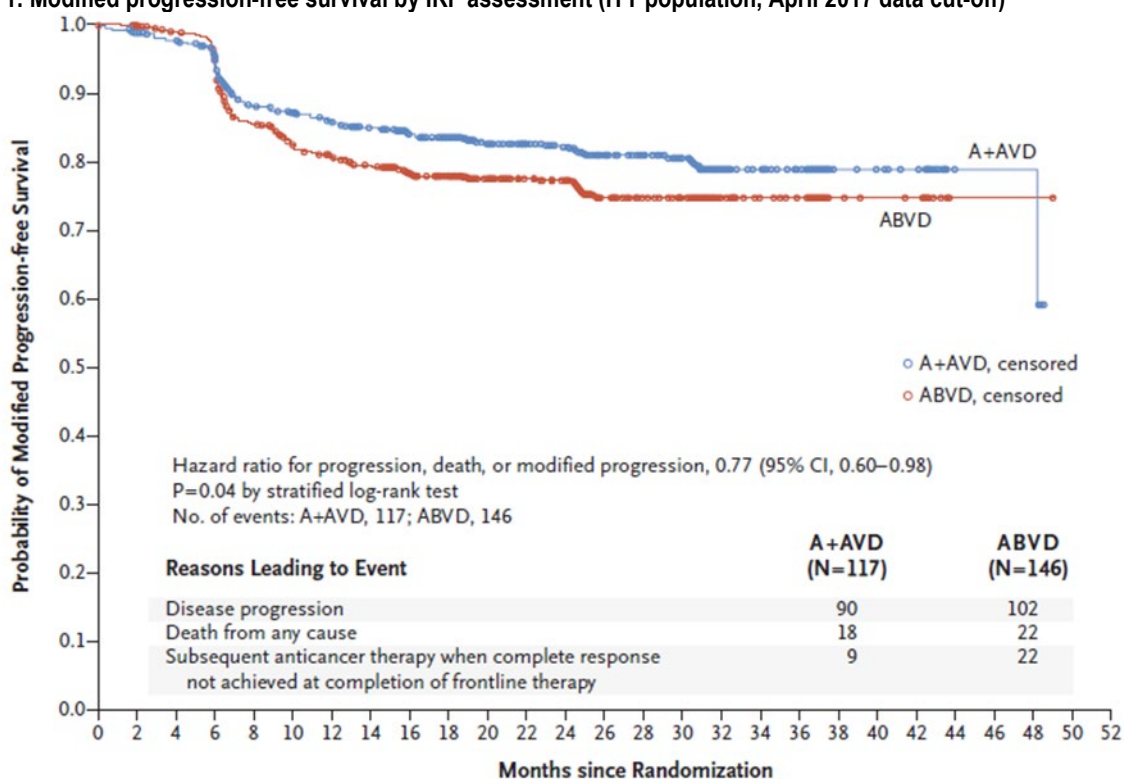
- 6.10 During the trial, an *ad hoc* safety review was initiated at the sponsor's request for the independent data monitoring committee (IDMC) to review adverse event data in both arms of the trial. Due to increased risk of neutropenia and febrile neutropenia, the IDMC recommended that all newly enrolled patients randomised to receive A+AVD be given primary prophylactic granulocyte colony-stimulating factor (G-CSF). The IDMC members also observed a trend in serious and sometimes fatal pulmonary complications in the ABVD arm, particularly notable among elderly patients. The IDMC suggested that the trial investigators consider age and age-related co-morbidities when enrolling patients, as elderly patients may not have been fit for multi-agent chemotherapy regimens such as A+AVD or ABVD. These changes were included in revised guidelines for study conduct after approximately 70% of study participants were enrolled.
- 6.11 The treatment regimen for ABVD in the trial may not be representative of recommended regimens for patients aged above 60 years or those who are unfit for multi-agent chemotherapy. Published guidelines do not recommend the use of bleomycin in older patients and if used, should be administered for no more than 2 cycles of treatment. Available data indicated that the total number of bleomycin-containing treatment cycles was lower in the Australian setting (median 2 cycles; Goh 2023) compared to the trial (median 6 cycles). The ESC agreed with the evaluation that this may affect the applicability of efficacy and safety data from the trial to the Australian setting.

Comparative effectiveness

A+AVD versus ABVD

- 6.12 The primary outcome in the ECHELON-1 trial was modified progression-free survival which, in addition to progressive disease and death, included receipt of subsequent anti-cancer therapy in patients not in complete response after completion of frontline therapy, defined as Deauville scores ≥ 3 as per the independent review facility.
- 6.13 Figure 1 presents the Kaplan-Meier plot for independently reviewed modified progression-free survival (ITT population, April 2017 data cut-off).

Figure 1: Modified progression-free survival by IRF assessment (ITT population, April 2017 data cut-off)



No. at Risk

A+AVD	664	637	623	600	541	528	513	493	463	439	347	328	309	196	185	169	96	85	77	26	24	21	4	4	4	0	0
ABVD	670	636	626	593	521	490	474	459	432	413	326	306	292	177	164	153	76	66	62	16	13	12	1	1	1	0	0

Source: Figure 1A, Connors 2018 publication

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; IRF, independent review facility

6.14 Table 4 is a summary of modified progression-free survival by independent review facility assessment (April 2017 data cut) and by investigator assessment (June 2021 data cut). Data from the June 2021 cut were used in the economic model of the submission.

Table 4: Summary of modified progression-free survival results

	IRF assessment, April 2017 cut-off		Investigator assessment, June 2021 cut-off	
	A+AVD N=664	ABVD N=670	A+AVD N=664	ABVD N=670
Median follow-up, months (95% CI)	24.9 (24.6, 25.0)	24.9 (24.6, 25.1)	73.3 (72.5, 74.1)	71.6 (70.4, 72.9)
Events, n (%)	117 (18)	146 (22)	135 (20)	183 (27)
- Disease progression	90 (14)	102 (15)	80 (12)	111 (17)
- Death	18 (3)	22 (3)	16 (2)	28 (4)
- Subsequent treatment after noncomplete response ^a	9 (1)	22 (3)	39 (6)	44 (7)
Censored, n (%)	547 (82.4) ^b	524 (78.2) ^b	529 (79.7) ^b	487 (72.7) ^b
Median mPFS, months (95% CI)	NE (31.2, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates, % (95% CI)				
- 6 months	95.5 (93.5, 96.8)	94.9 (92.9, 96.4)	95.5 (93.6, 96.9)	93.5 (91.3, 95.1)
- 1 year	86.3 (83.3, 88.7)	80.7 (77.3, 83.6)	83.4 (80.3, 86.0)	77.0 (73.5, 80.0)
- 2 years	82.1 (78.7, 85.0)	77.2 (73.7, 80.4)	81.1 (77.9, 84.0)	74.4 (70.9, 77.6)
- 3 years	78.8 (74.7, 82.3)	74.7 (70.8, 78.2)	80.1 (76.8, 83.0)	73.1 (69.4, 76.3)
- 4 years	-	-	79.1 (75.7, 82.1)	72.5 (68.9, 75.8)
- 5 years	-	-	78.8 (75.4, 81.7)	71.8 (68.1, 75.1)
- 6 years	-	-	78.8 (75.4, 81.7)	70.9 (67.1, 74.3)
- 7 years	-	-	78.8 (75.4, 81.7)	70.9 (67.1, 74.3)
Hazard ratio (95% CI)	0.770 (0.603, 0.982)		0.708 (0.566, 0.884) ^c	

Source: Tables 2.5-1 and 2.5-2, pp85-87 of the submission; Table 11.g, p108 of the ECHELON-1 clinical study report and Table 3.n, p51 of the ECHELON-1 clinical study report addendum 1

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; IRF, independent review facility; mPFS, modified progression-free survival; NE, not estimable

Bolded results were statistically significant

^a Noncomplete response was defined as a Deauville score of ≤3 at the end-of-treatment PET scan

^b The primary reason for censoring was no documented mPFS event at the time of analysis

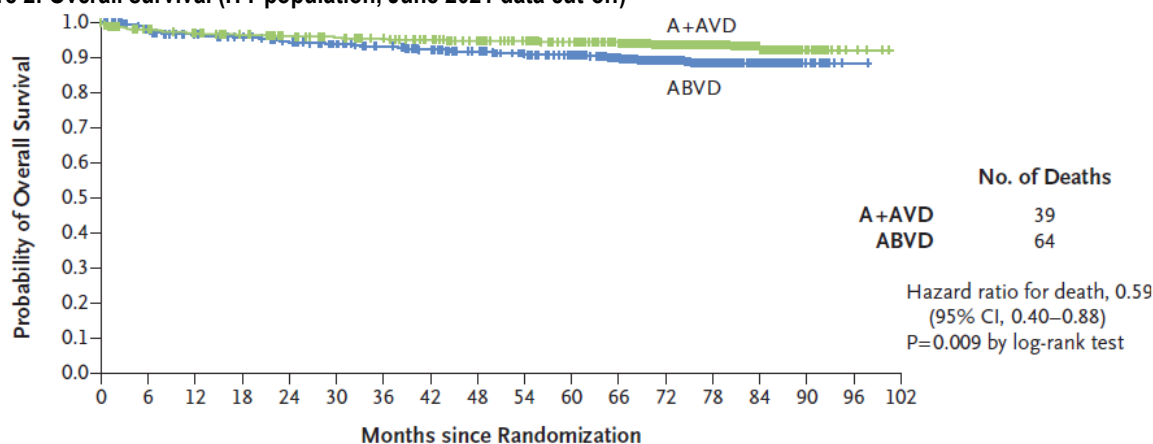
^c The 95% CI was descriptive and unadjusted for multiplicity

- 6.15 Median modified progression-free survival was not reached in either treatment arm. For the primary analysis period, modified progression-free survival was statistically significantly improved in the A+AVD group compared to the ABVD group. Results based on the June 2021 data cut favoured A+AVD, with greater numerical benefit compared to results from the primary analysis period. Results from the later data cut may be subject to bias as the data were not independently reviewed. The PSCR noted that at the earlier data cut-off there was a high concordance (91%) between modified progression-free survival as assessed by a blinded independent review facility and an unblinded investigator. The PSCR argued that this suggested that there was minimal bias for the later results based only on modified progression-free survival by an unblinded investigator.
- 6.16 The trial included pre-specified subgroup analyses for modified progression-free survival. Almost all subgroups demonstrated a consistent trend, with results favouring patients in the A+AVD arm compared to the ABVD arm (HR <1). However, there were subgroups where the hazard ratio was ≥1 including patients aged ≥60 years, patients aged ≥65 years and patients with no extranodal sites. There was also a numerically greater benefit for patients with stage IV disease treated with A+AVD (28.9% relative risk reduction) compared to patients with stage III disease (7.8% relative risk

reduction). The magnitude of benefit of A+AVD in patients aged ≥ 60 years and patients with stage III disease is uncertain, however, the analyses were not powered to detect statistically significant differences. No interaction testing was performed.

- 6.17 Exploratory analyses of progression-free survival using standard definitions (i.e. time to disease progression or death) were presented in the submission. The ESC noted that independently assessed results from the primary analysis period showed a trend in favour of A+AVD, however the results did not achieve statistical significance (HR 0.83; 95% CI: 0.64, 1.07). The trial report stated that the results should be interpreted with caution as protocol-directed study conduct related to the primary endpoint had the potential to impact the determination of progression-free survival events.
- 6.18 The ESC considered that the use of modified progression-free survival was clinically robust in this context as if a patient had not achieved a complete response they would be given further treatment (i.e. they would not wait for disease progression after first-line treatment). As such, the ESC considered the use of modified progression-free survival was more likely to reflect what would occur clinically than the analyses of progression-free survival using standard definitions.
- 6.19 Figure 2 presents the Kaplan-Meier plot of overall survival, a key secondary outcome in the trial (ITT population, June 2021 data cut).

Figure 2: Overall survival (ITT population, June 2021 data cut-off)



No. at Risk

A+AVD	664	638	626	612	598	584	572	557	538	517	494	461	350	209	97	27	4	0
ABVD	670	634	614	604	587	567	545	527	505	479	454	411	308	191	84	11	1	0

Source: Figure 1, Ansell 2022 publication

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval

- 6.20 Table 5 is a summary of overall survival from the primary analysis period (April 2017 data cut) and second interim analysis for overall survival (June 2021 data cut). Data from the June 2021 cut-off were used in the economic model of the submission.

Table 5: Summary of overall survival results

	April 2017 cut-off		June 2021 cut-off	
	A+AVD N=664	ABVD N=670	A+AVD N=664	ABVD N=670
Median follow-up, months (95% CI)	28.0 (26.4, 28.3)	27.5 (25.9, 28.1)	73.3 (72.6, 74.1)	72.4 (71.1, 73.6)
Deaths, n (%)	28 (4)	39 (6)	39 (6)	64 (10)
Censored, n (%)	636 (96)	631 (94)	420 (63)	468 (70)
Alive, n (%)	580 (87)	560 (84)	415 (63)	372 (56)
Median OS, months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates, % (95% CI)				
- 6 months	98.3 (97.0, 99.1)	98.1 (96.8, 98.9)	98.3 (97.0, 99.1)	98.1 (96.8, 98.9)
- 1 year	97.4 (95.8, 98.4)	96.9 (95.2, 98.0)	97.2 (95.7, 98.3)	96.7 (95.1, 97.9)
- 2 years	96.6 (94.8, 97.7)	94.9 (92.9, 96.4)	96.5 (94.7, 97.6)	94.7 (92.6, 96.2)
- 3 years	94.4 (91.4, 96.4)	92.9 (90.1, 95.0)	95.6 (93.7, 97.0)	93.3 (91.1, 95.0)
- 4 years	-	-	94.9 (92.9, 96.4)	92.1 (89.7, 94.0)
- 5 years	-	-	94.8 (92.7, 96.2)	91.2 (88.6, 93.2)
- 6 years	-	-	93.9 (91.6, 95.5)	89.4 (86.6, 91.7)
- 7 years	-	-	93.3 (90.7, 95.2)	88.7 (85.6, 91.1)
Hazard ratio (95% CI)	0.72 (0.44, 1.17)		0.59 (0.40, 0.88)	

Source: Table 2.5-3, p99 of the submission; Table 11.q, p130 of the ECHELON-1 clinical study report

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CI, confidence interval; NE, not estimable; OS, overall survival

- 6.21 Median overall survival was not reached for either treatment arm. Results from the primary analysis indicated improved overall survival in the A+AVD group compared the ABVD group, however the results did not achieve statistical significance. However, the second interim analysis using the later data cut showed statistically significantly improved overall survival for A+AVD compared to ABVD.
- 6.22 Pre-specified subgroup analyses were conducted based on data from the second interim analysis of overall survival. Results from most subgroups showed consistent treatment benefits in favour of A+AVD compared to ABVD except for patients with no extranodal site involvement (HR>1). Analyses according to disease stage and age indicated that survival benefit in the overall population may have been driven primarily by patients with stage IV disease and those aged <60 years. However, there was a notable imbalance in the number of patients aged <60 years (1,148 (86%)) compared to those aged ≥60 years (186 (14%)) in the trial.
- 6.23 Both modified progression-free survival and overall survival data were subject to relatively high levels of censoring as most patients had yet to experience an event, with potential confounding due to the use of subsequent treatments (20.4% in A+AVD arm and 23.8% in ABVD arm at the June 2021 cut-off). While modified progression-free survival captured the use of subsequent treatments, this was only in patients with incomplete response at the end of first line treatment (less than 3% of patients at approximately 6 months in the primary analysis). The proportion of patients with disease progression who received subsequent treatments was not reported and could not be determined from modified progression-free survival as it was a composite endpoint.

- 6.24 The submission presented results from other secondary outcomes that were independently assessed including complete remission and overall response (rates and duration), PET negativity after Cycle 2, noncomplete responders who received irradiation, duration of response, disease-free survival and event-free survival. The results consistently showed a small numerical benefit in favour of the A+AVD arm compared with the ABVD arm.
- 6.25 The submission also presented patient-reported outcomes based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC QLQ-C30) and health utility values captured via the EQ-5D-3L instrument (see pp100-107 of the submission). Results from both instruments indicated worsening trends in both arms during the frontline treatment period that was worse for the A+AVD group compared to the ABVD group. Both arms improved during the post-treatment follow-up period (up to 36 months after the end of treatment) with no appreciable differences between arms. The trial report noted the observed differences were not clinically meaningful as they were below published minimal clinically important differences (MCID) of 10 for EORTC QLQ-C30 subscales (range 0-100) and 0.07 for EQ-5D-3L utility values using the UK value set.
- 6.26 The trial also captured the impact of lung toxicity using the Functional Assessment of Chronic Illness Therapy (FACIT-Dyspnea 10) and neurotoxicity using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity subscale (FACT/GOG-Ntx subscale) during the frontline treatment period. A trend was observed for worsening dyspnoea and functional limitation for patients on A+AVD compared to ABVD, however, the trial report noted there is no established MCID for the FACIT-Dyspnea 10 subscale and assumed no clinically important differences between arms based on a 0.5 standard deviation of baseline scores. Mean neurotoxicity scores were worse in the A+AVD arm compared to the ABVD arm during treatment. The trial investigators considered the differences to be clinically meaningful and reflective of the higher proportion of patients in the A+AVD arm experiencing peripheral neuropathy.
- 6.27 All patient-reported outcomes were also analysed according to whether patients had experienced a modified progression-free survival event within each treatment arm. The trial report noted no clinically meaningful differences associated with a modified progression-free survival event.
- 6.28 In terms of health resource utilisation, a higher proportion of patients in the A+AVD arm were hospitalised (38%) compared to those in the ABVD arm (29%). The median duration of hospitalisation was 9 days (range 1-772 days) in the A+AVD arm and 8 days (range 1-668 days) in the ABVD arm. The hospitalisation rate was also higher in the A+AVD arm (0.15 per patient-year) compared to the ABVD arm (0.11 per patient-year). The main reason for hospitalisation was adverse events (A+AVD 71%; ABVD 63%).

A+AVD versus PET-adapted regimens and non-PET-adapted eBEACOPP

- 6.29 The submission presented a comprehensive overview of the RATHL and AHL2011 trials of PET-adapted ABVD and eBEACOPP, respectively. An overview of the HD18 trial of PET-adapted eBEACOPP was included during the evaluation for completeness as it contributes to the main body of evidence informing published guidelines.
- 6.30 Overall, the current body of evidence suggests that PET-adapted regimens have similar efficacy compared to non-PET-adapted regimens as well as improved short-term safety in patients who de-escalate treatment following a negative interim PET scan. However, longer term outcomes are uncertain due to limited follow-up (median follow-up 5-6 years) which does not allow for complete identification of late complications such as secondary malignancies.
- 6.31 The study designs of the RATHL, AHL2011 and HD18 trials were complex, with different points of randomisation and escalation/de-escalation of investigated treatment regimens which limited comparability between these trials and the key trial, ECHELON-1. The RATHL, AHL2011 and HD18 trials also assessed progression-free survival using standard definitions while the ECHELON-1 trial assessed modified progression-free survival.
- 6.32 Despite these limitations, the submission claimed the ABVD arm of the ECHELON-1 trial is a reasonable proxy for the efficacy of PET-adapted ABVD given the results from the RATHL trial were supportive of similar efficacy between PET-adapted ABVD and non-PET-adapted ABVD. The submission acknowledged however, that PET-adapted ABVD is likely to be less toxic than non-PET-adapted ABVD given the ability to reduce the number of bleomycin-containing treatment cycles. The ESC noted that the RATHL trial only provided a randomised comparison of ABVD and AVD in patients with PET-negative findings after 2 cycles of ABVD. The trial was not designed to compare ABVD and BEACOPP-based regimens in PET-positive patients. Therefore, the ESC agreed with the evaluation that the overall comparative efficacy and safety of PET-adapted ABVD (with options to escalate/de-escalate treatment) compared to non-PET-adapted ABVD remains uncertain.
- 6.33 No data comparing A+AVD and non-PET-adapted eBEACOPP were presented in the submission. There are no head-to-head trials of A+AVD and eBEACOPP, however, a Cochrane systematic review of eBEACOPP versus ABVD as first-line treatment for early unfavourable and advanced stage Hodgkin lymphoma was identified during the evaluation (Skoetz 2017).
- 6.34 The Skoetz 2017 review included five randomised controlled trials that included either eBEACOPP or ABVD as the primary treatment regimen (EORTC 20012, GHSG HD9, GHSG HD 14, GSM-HD 2008 and HD 2000). Meta-analysed results suggested statistically significant improvements in overall survival (HR 0.74; 95% CI: 0.57, 0.97) and progression-free survival (HR 0.54; 95% CI: 0.45, 0.64) in patients treated with eBEACOPP compared to ABVD. However, there was also increased incidence of acute toxicity (e.g. haematological, respiratory, gastrointestinal) with eBEACOPP and

potential for increased risk of long-term side effects such as secondary malignancies and infertility although there was insufficient data to determine if there was a difference compared to ABVD.

Comparative harms

6.35 Table 6 summarises the safety outcomes in the key trial during the primary analysis period (April 2017 data cut). The ECHELON-1 trial was open-label, which may bias the reporting of adverse events. Adverse event data were based on patient incidence only, which does not capture the occurrence of multiple events of the same type in individual patients.

Table 6: Summary of key adverse events in the ECHELON-1 trial (safety population, April 2017 data cut)

Patients, n (%)	A+AVD N=662	ABVD N=659
Any adverse event	653 (99)	646 (98)
Grade 3 or higher adverse event	549 (83)	434 (66)
Serious adverse event	284 (43)	178 (27)
Adverse events resulting in study drug discontinuation	88 (13)	105 (16)
Adverse event resulting in dose modification	423 (64)	293 (44)
- Dose held	44 (7)	32 (5)
- Dose interrupted	22 (3)	33 (5)
- Dose reduced	191 (29)	65 (10)
- Dose delayed	318 (48)	217 (33)
On-study deaths	9 (1)	13 (2)
Deaths due to study treatment-related adverse events	8 (1)	7 (1)
Adverse events of special interest		
Neutropenia	454 (69)	361 (55)
Febrile neutropenia	128 (19)	52 (8)
Peripheral neuropathy	442 (67)	286 (43)
Pulmonary toxicity	12 (2)	44 (7)
Infusion-related reactions	57 (9)	100 (15)

Source: Table 12.f, p234 of the ECHELON-1 clinical study report

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine

6.36 Almost all patients in both treatment arms experienced an adverse event. Treatment-emergent adverse events reported in $\geq 10\%$ of patients in either treatment arm and in $\geq 10\%$ more patients in the A+AVD arm compared to the ABVD arm were neutropenia, peripheral neuropathy, weight decreased, abdominal pain, anaemia and febrile neutropenia. Adverse events leading to premature discontinuation of study drug were reported more frequently for patients in the ABVD arm compared to the A+AVD arm. However, more patients in the A+AVD arm experienced adverse events resulting in dose modifications compared to ABVD, most commonly due to neutropenia and neuropathy.

6.37 More patients in the A+AVD arm experienced a serious adverse event compared to those in the ABVD arm. The most frequently reported serious adverse events in the A+AVD arm were febrile neutropenia, pyrexia, neutropenia, pneumonia, abdominal

pain, sepsis, constipation, diarrhoea, pulmonary embolism, vomiting and dehydration. In the ABVD arm, the most frequently reported serious adverse events were febrile neutropenia, pyrexia, pneumonia and pneumonitis.

- 6.38 On-study death occurred in 9 patients in the A+AVD arm (8 were treatment related). The majority of on-study deaths were associated with neutropenia and its complications, including neutropenic sepsis and septic shock. Most of the deaths (6 of 9) occurred in the first cycle of treatment. None of the A+AVD patients who died on-study had received G-CSF primary prophylaxis. In the ABVD arm, on-study death occurred in 13 patients and 7 of these were considered treatment related. The majority of on-study deaths were associated with pulmonary toxicity. Most of the deaths (10 of 13) occurred in the fifth and sixth cycles of treatment.
- 6.39 In the updated safety analysis (June 2021 cut-off), there were 39 deaths (6%) in the A+AVD arm and 64 deaths (10%) in the ABVD arm. These totals included additional deaths during the follow-up period reported in 30 patients in the A+AVD arm and 51 patients in the ABVD arm. The primary cause of deaths was Hodgkin lymphoma or its complications. A detailed breakdown of causes of death during the follow-up period was not available.
- 6.40 The submission claimed the safety profile of A+AVD in the trial may be worse than in clinical practice due to differences in the use of G-CSF primary prophylaxis. Subgroup analyses indicated lower incidence of febrile neutropenia, neutropenia, infections and infestations and deaths in both treatment arms with use of G-CSF by day 5 of the first treatment cycle. However, the proportion of patients with these adverse events (including serious adverse events) remained higher in the A+AVD arm compared to the ABVD arm regardless of G-CSF use.
- 6.41 The trial included a comprehensive review of peripheral neuropathy. The most frequently reported peripheral neuropathy events were peripheral sensory neuropathy, peripheral neuropathy, paraesthesia and peripheral motor neuropathy. A higher proportion of patients in the A+AVD arm had peripheral neuropathy events of Grade 3 or higher severity (9%) compared to those in the ABVD group (2%). At the last follow-up (June 2021 data cut), more patients in the A+AVD group (19%) had ongoing peripheral neuropathy compared to the ABVD group (9%). Most events were of Grade 2 or less severity. The assessment of ongoing Grade 3 or higher peripheral neuropathy was limited to a small number of patients, of which the majority were lost to follow-up, had withdrawn from the study or had died at the latest data cut (11 of 16 patients in the A+AVD arm and 4 in the ABVD arm).
- 6.42 Pulmonary toxicity is known to be associated with bleomycin, which is the likely contributor to the increased incidence of these events in the ABVD arm compared to the A+AVD arm. Serious pulmonary toxicity events were reported for 5 A+AVD patients (<1%) and 21 ABVD patients (3%), including 3 ABVD patients with a fatal event. No fatal events related to pulmonary toxicity were reported for the A+AVD arm.

- Pulmonary toxicity was not systematically assessed after the completion of frontline treatment.
- 6.43 The incidence of secondary malignancies was a long-term safety outcome in the trial. A secondary malignancy (solid tumours and haematological malignancies) was reported for 23 A+AVD patients (3%) and 32 ABVD patients (5%) based on the updated safety analysis (June 2021 data cut). The incidence of secondary malignancies was higher among patients aged ≥ 60 years, with 9 patients in the A+AVD arm (11%) and 14 patients in the ABVD arm (14%).
- 6.44 Fertility was not formally assessed in the trial; however, similar numbers of pregnancies were reported in each treatment group based on the June 2021 cut-off. There were 114 pregnancies in 82 patients or partners in the A+AVD group (12%) and 81 pregnancies in 61 patients or partners in the ABVD group (9%).
- 6.45 The submission also presented a naïve (indirect) comparison of safety outcomes between the A+AVD arm of the ECHELON-1 trial and the PET-adapted eBEACOPP arm of the AHL2011 trial. The analyses compared the incidence of adverse events in both trials using the safety populations as well as the subgroup aged < 60 years from the ECHELON-1 trial. The submission claimed that the results support a claim of superior safety for A+AVD compared to PET-adapted eBEACOPP based on statistically significantly fewer patients experiencing haematological adverse events of grade 3 or higher. However, the naïve comparison also showed higher incidences of serious adverse events in the A+AVD arm compared to the PET-adapted eBEACOPP arm. Overall, the naïve (indirect) comparison was non-informative given the lack of a common reference arm and limited comparability between the trials.
- 6.46 The submission presented data on potential safety concerns based on the Periodic Benefit-Risk Evaluation Report (PBRER) for the period from 19 August 2022 to 18 February 2023. Important identified risks included progressive multifocal leukoencephalopathy, pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin, peripheral neuropathy, myelosuppression, infections, infusion-related reactions, hyperglycaemia, Steven-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN), tumour lysis syndrome and anti-drug antibodies. Important potential risks were severe hepatotoxicity, pulmonary toxicity, gastrointestinal complications, reproductive toxicity and thymus depletion (paediatrics). Missing information included long term safety. No new safety signals were identified during the reporting period.
- 6.47 There are limited long-term safety data particularly for late secondary complications such as secondary malignancies as these tend to occur 10 to 20 years post treatment, beyond the planned follow-up for the ECHELON-1 trial.

Benefits/harms

- 6.48 On the basis of direct evidence presented in the submission, after a median duration of follow-up of 2 years (April 2017 cut off), for every 100 patients treated with A+AVD compared to ABVD:
- Approximately 4 fewer patients would experience a modified progression-free survival event at 3 years (disease progression, death or subsequent treatment after incomplete response at the end of frontline treatment).
 - No apparent difference in deaths.
 - Approximately 16 additional patients would experience a serious adverse event that is life-threatening or required hospitalisation.
 - Approximately 14 additional patients would experience neutropenia.
 - Approximately 11 additional patients would experience febrile neutropenia.
 - Approximately 24 additional patients would experience peripheral neuropathy.
 - Approximately 5 fewer patients would experience pulmonary toxicity.
- 6.49 On the basis of direct evidence presented in the submission, after a median duration of follow-up of 6.1 years (June 2021 cut off), for every 100 patients treated with A+AVD compared to ABVD:
- Approximately 8 fewer patients would experience a modified progression-free survival event at 7 years (disease progression, death or subsequent treatment after incomplete response at the end of frontline treatment).
 - Approximately 5 fewer patients would have died at 7 years.
- 6.50 Comprehensive safety data were not available for the June 2021 cut off.

Clinical claim

- 6.51 The submission did not make a clinical claim for A+AVD versus non-PET-adapted ABVD. The clinical evidence was supportive of superior efficacy and inferior safety for A+AVD versus non-PET-adapted ABVD.
- 6.52 The submission described A+AVD as superior in terms of efficacy and inferior in terms of safety compared to PET-adapted ABVD. The comparative efficacy and safety of these regimens is uncertain given the lack of comparative data. The PSCR noted that the RATHL trial was presented as evidence of similar efficacy between PET-adapted and non-PET adapted ABVD and argued that the (non-PET-adapted) ABVD arm from the ECHELON-1 trial may be a reasonable proxy for the efficacy of PET-adapted ABVD. The ESC agreed with the PSCR that the RATHL trial provided evidence of similar efficacy between a PET-adapted and non-PET-adapted regimen. However, the ESC noted the RATHL trial was not designed to determine the overall efficacy and safety of PET-adapted ABVD (with options to escalate/de-escalate treatment) compared to

non-PET-adapted ABVD (see paragraph 6.32). The ESC advised that the clinical claim was potentially reasonable but uncertain.

- 6.53 The submission did not make a clinical claim for A+AVD versus non-PET-adapted eBEACOPP. The comparative efficacy and safety of these regimens is uncertain given the lack of comparative data. The submission described A+AVD as superior in terms of safety compared to PET-adapted eBEACOPP. The ESC agreed with the evaluation that the claim may not be reasonable given the lack of comparative data between A+AVD and PET-adapted eBEACOPP. No clinical claim was made in regard to comparative efficacy. The ESC considered that eBEACOPP (both non-PET adapted and PET-adapted) was unlikely to be replaced by A+AVD in clinical practice.
- 6.54 The magnitude of long-term survival benefit associated with A+AVD versus ABVD is uncertain given the relatively long expected overall survival in a trial population with a median age of 36 years and relatively high survival rates (89-93% at 7 years). The ESC agreed with the PSCR that patients with advanced Hodgkin lymphoma are treated frontline with curative intent which makes it difficult to show an overall survival advantage in clinical trials for new treatments. The ESC noted that survival endpoints in the trial were subject to high levels of censoring as most patients had yet to experience an event, with potential confounding due to subsequent treatments. There are also limited data for late complications such as secondary malignancies as these tend to occur 10 to 20 years post treatment. The ESC acknowledged the PSCR argument that ECHELON-1 was not powered or of sufficient duration to detect a difference in late secondary complications but noted that with high cure rates a key goal is also the prevention of such events.
- 6.55 The PBAC considered that the claim of superior effectiveness compared to PET-adapted ABVD was highly uncertain but likely reasonable.
- 6.56 The PBAC considered that the claim of inferior safety compared to PET-adapted ABVD was reasonable.

Economic analysis

- 6.57 The submission presented a cost-utility analysis of A+AVD compared to PET-adapted ABVD in patients with previously untreated CD30+ stage III or IV Hodgkin lymphoma. The economic evaluation was based on data from the ECHELON-1 trial of A+AVD versus ABVD as well as other modelled variables. The submission assumed that ABVD was a reasonable proxy for PET-adapted ABVD as all inputs were based on the ABVD arm of the trial except for drug costs. During the evaluation, ABVD was considered as the comparator in a revised base case and the analysis using PET-adapted ABVD treatment costs was presented in a sensitivity analysis.

Table 7: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Treatments	A+AVD versus ABVD
Outcomes	Life years and quality-adjusted life years
Time horizon	65 years in the model base case versus a maximum of 8.1 years (97 months) in ECHELON-1
Cycle length	1 week
Methods used to generate results	Partitioned survival analysis
Health states	Progression-free survival, post-progression survival and dead
Health state distribution	<p>The proportions of patients who were progression-free, post-progression and dead were informed by modelled overall survival (OS) and modified progression-free survival (mPFS) curves.</p> <p>Kaplan-Meier estimates for OS and mPFS were derived from ECHELON-1 and were used directly in the model up to extrapolation points of between 6.5-6.8 years. Mixture cure models (weighted curves based on statistically cured and uncured fractions) were used to extrapolate OS and mPFS until the end of the model. During the extrapolated period, the model used an additional adjustment that attributed the risk of death based on the overall survival curve to patients who were progression-free.</p> <p>Background mortality was informed by age- and gender-specific general population mortality estimates from the Australian Life Tables 2019-2021, adjusted for excess mortality due to long-term treatment-related complications using a published standardised mortality ratio of 2.87 (Nunez-Garcia 2023). The adjusted mortality estimate was used to generate the mixture cure model parameters for overall survival and as a survival cap in the model.</p>
Adverse events	Modelled using trial-based incidence of adverse events in ECHELON-1.
Utilities	A+AVD on-treatment progression-free: 0.7525, ABVD on-treatment progression-free: 0.8056; off-treatment progression-free: 0.8429 and post-progression: 0.8037. Based on a regression model using individual patient EQ-5D-3L data in ECHELON-1 (converted to utilities using an Australian value set). An age-adjusted utility cap was implemented using Australian general population utility estimates (Clemens 2014).
Costs	First line drug costs were based on trial-based circumstances of use of A+AVD and ABVD and assuming all patients treated with ABVD received supportive treatments. Subsequent anti-cancer treatment costs were based on the recorded use of multiple treatment modalities (chemotherapy, stem cell transplant, immunotherapy and radiation) in the ECHELON-1 trial. Chemotherapy administration costs were based on the MBS item fee. The costs of monitoring and follow-up in progression-free and post-progression patients were based on expert advice and relevant MBS item fees. Adverse event costs were based on the modelled incidence of adverse events and hospitalisation costs using relevant AR-DRGs (Round 25 NHCDC Cost Weights 2020-2021 Public Sector report).
Discounting	5% per year applied to costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1-1, p180 of the submission

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AR-DRG, Australian Refined Diagnosis Related Groups; NHCDC, National Hospital Cost Data Collection

6.58 The economic model utilised a partitioned survival analysis with three mutually exclusive health states of progression-free, post-progression and dead. The selected model structure relies on a fundamental structural assumption that the survival endpoints (progression-free survival and overall survival) are independent. This has implications for extrapolations beyond the trial period as the extrapolations are dependent on within-trial trends of mortality and disease status that may not be reflective of future trends (e.g. late complications, competing risks of mortality). The lack of an explicit link between clinical endpoints also limits the degree to which the

clinical plausibility of extrapolations can be validated and limited the ability to quantify any uncertainties through sensitivity analyses.

- 6.59 The model structure also limited the ability to appropriately incorporate costs and consequences associated with the utilisation of subsequent anti-cancer treatments. The attribution of costs required assumptions that lacked face validity (see Table 8 below) and there was no transparency in regard to likely changes in disease trajectory that would have impacts on both survival and quality of life.
- 6.60 Overall, the evaluation considered the use of the partitioned survival analysis was inadequately justified given multiple structural limitations. Published economic evaluations identified in the submission were based on Markov state transition and microsimulation models that incorporated additional health states which captured changes in disease status (relapse/remission) and risk of mortality after subsequent therapies. The PSCR argued that the simplest approach to capture the benefits of A+AVD versus ABVD based on the goals of treatment and the available data from ECHELON-1 was a partitioned survival analysis. The ESC advised that a Markov model structure would provide a more flexible and transparent approach to modelling longer term outcomes. The PBAC noted the pre-PBAC response highlighted that the impact of subsequent treatments in the relapsed/refractory setting was not captured in the ECHELON-1 trial and hence assumptions around this would need to be sourced from other trials and/or published literature which the response argued would increase the complexity of the model and uncertainty.
- 6.61 The modelled proportion of patients who were post-progression was based on modified progression-free survival in the key trial, which incorporated events of disease progression, death and the initiation of subsequent anti-cancer treatment in patients with incomplete response at the end of frontline chemotherapy. The ESC agreed with the evaluation that this mix of events introduced added uncertainty in determining the validity of costs and consequences attributed to patients in the post-progression health state in the model.
- 6.62 Key drivers of the economic model are summarised in Table 8.

Table 8: Key drivers of the model

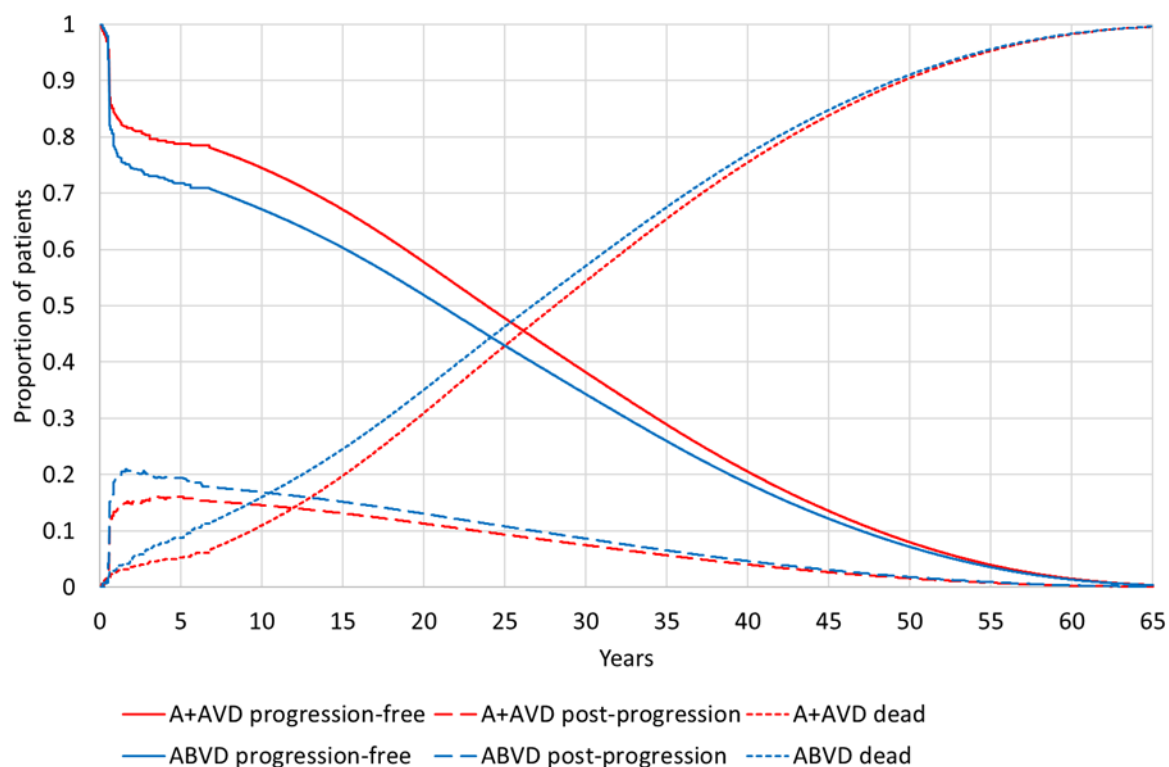
Description	Method/Value	Impact
Model structure	The partitioned survival analysis structure limited the ability to determine the validity of extrapolated survival benefits, which was a key driver of modelled outcomes. Any likely differences in mortality due to disease status could not be quantified as modelled overall survival and modified progression-free survival are assumed to be independent. The model was also unable to capture the impact of subsequent treatments on patient outcomes, with associated changes to mortality risk and quality of life.	Unclear
Time horizon	The ESC considered the 65-year time horizon may be reasonable given the potential for cure with initial and subsequent treatments and the bimodal age distribution evident in this disease area. However, the ESC considered the model was unable to adequately capture the impact of subsequent treatments that are likely to alter disease trajectories.	High, favours A+AVD

Description	Method/Value	Impact
Extrapolation	The validity of extrapolated survival outcomes based on mixture cure models could not be determined given the underlying assumptions appear clinically implausible (e.g. patients are cured/uncured at time of diagnosis before any treatment is administered). Additionally, model outputs such as statistical cure fractions and predicted estimates in uncured patients only serve as mathematical functions to achieve goodness of fit to observed data. The validity of extrapolated survival benefits is discussed further under Figure 3 below.	Unclear
Health state utilities	Health state utility values in the model were based on EQ-5D-3L data from the ECHELON-1 trial. The utility values were highly uncertain and difficult to validate due to poor documentation regarding the transformation of EQ-5D-3L data from the trial, choice of regression model and selected covariates. Modelled improvements in quality of life were also reliant on the assumption that, over time, surviving patients would have the same quality of life as the general population. This appeared optimistic given the potential for long term disease- and treatment-related complications.	High, favours A+AVD
Subsequent treatment costs	<p>Based on circumstances of use in the ECHELON-1 trial. The estimated cost of subsequent treatments was highly uncertain due to the following reasons:</p> <ul style="list-style-type: none"> • The assumption that patients treated with nivolumab (not PBS-listed for relapsed or refractory Hodgkin lymphoma) would otherwise receive pembrolizumab may not be reasonable given relatively low use of pembrolizumab (<3%) compared to nivolumab (13%) among those who received subsequent treatments. • The weighted cost was agnostic to lines of therapy, and effectively distributed the full cost of all treatments in a single model cycle irrespective of time on treatment or treatment modality. In this instance, the cost of subsequent treatment is likely overestimated given the relatively high cost of pembrolizumab based on the maximum length of treatment (\$277,494 over 35 x 21-day cycles). • Due to limitations with the partitioned survival analysis, additional assumptions were required to estimate the incidence of newly progressed disease as a proxy for the proportion of patients initiating subsequent treatments. Effectively, the approach assumed that all deaths are occurring in patients with progressed disease only. The approach lacks face validity but may be necessary given the model is unable to track the occurrence of events and/or patient transitions at any given time. • The PBS listing of pembrolizumab for relapsed/refractory disease is subject to a special pricing arrangement. Costs of pembrolizumab in the model were based on published prices. • The submission did not provide rationale for the use of the proposed effective price of brentuximab vedotin for first line treatment instead of the effective prices of brentuximab vedotin for its relapsed/refractory disease listings. <p>Overall, the difference in subsequent treatment costs between arms was mainly driven by differences in the use of brentuximab vedotin, pembrolizumab and allogeneic stem cell transplants. The degree to which these treatments are displaced by the use of A+AVD in the first-line setting is uncertain.</p>	High, favours A+AVD

Source: constructed during the evaluation based on Section 3, pp174-243 and the brentuximab vedotin economic model of the submission
Abbreviation: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine

6.63 Figure 3 presents the model traces for A+AVD and ABVD.

Figure 3: Model traces for A+AVD and ABVD



Source: Figures 3.7-1 and 3.7-2, pp236-237 of the submission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine

- 6.64 The model traces show a modelled survival benefit for A+AVD compared to ABVD that persists throughout the 65-year model duration. A difference in mortality is observed from around 6 months, corresponding to the end of the initial treatment period in the key trial. There is an increasing difference in mortality after this timepoint, peaking at around 6.3 years (5.2%) and then slowly converging over time.
- 6.65 The traces also show a difference in progression-free survival in favour of A+AVD compared to ABVD. The progression-free survival curves separate from around 6 months, with a peak difference at 6.8 years (7.7%), after which the curves slowly converge over time.
- 6.66 The post-progression traces show a modelled benefit in favour of A+AVD, with fewer patients experiencing a progression event compared to ABVD. However, the predicted estimates show an unexpected pattern during the extrapolated period (from 6.5-6.8 years) where this group of patients experienced lower rates of mortality than patients who were progression-free. This appears clinically implausible and may be a consequence of an error in the generation of mixture cure models for progression-free survival that required a crude adjustment to incorporate the risk of death from the overall survival curve to all patients who are progression-free. The PSCR argued that there was no error in the generation of the mixture cure models for progression free survival as background mortality was subsequently applied to the progression-

free health states in both treatment arms of the model. The ESC advised that the multi-step approach used in the submission could be justified on a statistical basis. However, the ESC considered the approach used introduced greater uncertainty compared to one in which background mortality was incorporated during the model fitting stage.

- 6.67 The submission claimed the model traces correspond to observed Kaplan-Meier estimates for modified progression-free survival and overall survival up to the point of extrapolation (6.5–6.8 years). The modelled estimates were consistent with key trial data using the most recent data cut. However, modified progression-free survival in the model was assessed by investigators, which is at greater risk of bias compared to independently reviewed outcomes. This potentially overestimates the magnitude of benefit with A+AVD compared to ABVD. As outlined in paragraph 6.15, the PSCR argued that there was minimal bias for the later results based only on modified progression-free survival by an unblinded investigator.
- 6.68 The submission claimed that the plateaus at the tail-end of the Kaplan-Meier curves for modified progression-free survival and overall survival were indicative of high cure rates. There is known potential for cure with frontline chemotherapy treatment. However, the likely proportion who achieve cure based on the trial data is uncertain given the high degree of censoring with potential for confounding due to the use of subsequent therapies in a significant proportion of patients.
- 6.69 The validity of modelled cure rates was not discussed in the submission. During the evaluation, the probabilities of death in each arm were compared with background mortality in the model to determine the effective cure rates and cure timepoint applied in the model based on modelled overall survival. Beyond the extrapolation point (approximately 6.8 years), the risk of death in the A+AVD arm was equal to background mortality while the risk of death in the ABVD arm remained marginally elevated although the difference was negligible (<0.01% difference). Effectively, this assumes that all surviving patients at 6.8 years (93% A+AVD, 88% ABVD) had achieved cure. The ESC considered the clinical plausibility of these cure rates is uncertain as it includes patients who are post-progression (15% A+AVD, 17% ABVD) in addition to those who are progression-free (78% A+AVD, 71% ABVD). This suggests that all surviving patients who have experienced a post-progression event also achieve cure (potentially due to subsequent therapies), or that the overall survival data may not be sufficiently mature to provide a robust estimate of cure.
- 6.70 The submission presented a comparison of modelled outcomes with published estimates from studies that reported survival in patients with advanced classical Hodgkin lymphoma. It was difficult to compare modelled modified progression-free survival estimates with published estimates as the studies used a more standard definition of progression-free survival (i.e. disease progression or death only). There were also concerns with the applicability of data from the external sources due to differences in population and disease characteristics. Additionally, survival outcomes in the model were extrapolated over a 65-year horizon that exceeded follow-up times

in all the identified studies, most of which had median follow-up times of up to 10 years. Overall, the external validity of extrapolated outcomes in the model was uncertain.

- 6.71 The submission presented results of the stepped economic evaluation based on modelled PET-adapted ABVD costs in the comparator arm as the base case. Estimates in some of the steps could not be reproduced during the evaluation due to poor documentation in the submission.
- 6.72 The following errors were identified during the evaluation and corrected in the revised base case:
- The submission used an estimated AEMP of \$14.67 instead of \$73.34 for 2 x 10 mg vials per administration of the vinblastine component of A+AVD and ABVD regimens (and the AVD regimen as part of PET-adapted ABVD in sensitivity analyses).
 - There were no administration costs for the first 2 cycles of treatment in the ABVD arm.
 - The attribution of progression-free utility values in both treatment arms included a switch that resulted in occasional attribution of the off-treatment progression-free utility value despite the value being higher than the age-adjusted utility value for the general population.
- 6.73 The following errors were also corrected for in the sensitivity analyses conducted during the evaluation:
- Changes to the time horizon affected the calculation of quality-adjusted life years (QALYs) but not costs (remained based on the base case time horizon).
 - For PET-adapted ABVD, on-treatment progression-free utility values were only applied for 2 treatment cycles (i.e. 8 weeks) rather than 6 treatment cycles as per treatment costs in the submission.
- 6.74 During the evaluation, a stepped analysis was conducted with ABVD as the comparator in the revised base case (see Table 9 below).

Table 9: Results of the stepped economic evaluation

Step and component	A+AVD	ABVD	Increment
Step 1a: time horizon of 8.1 years (maximum trial follow-up), include costs of drug acquisition, supportive therapies and treatment administration			
Costs	\$█	\$█	\$█
Life years gained	7.68	7.45	0.23
Incremental cost per life year gained			\$¹
Step 1b: add costs of subsequent therapies			
Costs	\$█	\$█	\$█
Life years gained	7.68	7.45	0.23
Incremental cost per life year gained			\$²
Step 1c: add costs of monitoring and follow-up			
Costs	\$█	\$█	\$█
Life years gained	7.68	7.45	0.23
Incremental cost per life year gained			\$²
Step 1d: add costs of adverse events			
Costs	\$█	\$█	\$█
Life years gained	7.68	7.45	0.23
Incremental cost per life year gained			\$²
Step 2: extrapolate to 65 years			
Costs	\$█	\$█	\$█
Life years gained	28.80	27.32	1.48
Incremental cost per life year gained			\$³
Step 3: add utilities			
Costs	\$█	\$█	\$█
QALYs	23.84	22.61	1.23
Incremental cost per QALY gained			\$⁴
Step 4: discounting 5% to costs and outcomes			
Costs	\$█	\$█	\$█
QALYs	11.66	11.14	0.52
Incremental cost per QALY gained (revised base case)			\$⁵

Source: constructed during the evaluation using the brentuximab vedotin economic model of the submission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; QALY, quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$95,000 to < \$115,000

³ \$5,000 to < \$15,000

⁴ \$15,000 to < \$25,000

⁵ \$45,000 to < \$55,000

6.75 Based on the economic model, treatment with A+AVD was associated with an incremental cost per QALY gained of \$45,000 to < \$55,000 compared to ABVD. The PSCR provided a revised economic model that corrected for the errors identified by the evaluation (see paragraph 6.72) and produced the same incremental cost-effectiveness ratio (ICER) as the revised base case.

6.76 The inclusion of costs of subsequent therapies and extrapolation of survival benefits to 65 years had the largest impacts on the economic analysis. In the model, 73% of incremental QALYs were accrued in the extrapolated period beyond 8.1 years. The incremental cost reduced by 3% during the extrapolated period due to higher post-progression monitoring and follow-up costs in the comparator arm of the model.

6.77 For every patient treated with A+AVD versus ABVD and followed up for 65 years, the economic model (without discounting) estimated that there would be:

- Additional treatment costs (drug acquisition, supportive therapies, administration) of \$1 and additional adverse event management costs of \$1,559.
- Reduced costs of subsequent therapies of \$1 and reduced monitoring and follow-up costs of \$3,198.
- An additional 1.48 years of life lived and an additional 1.23 quality-adjusted life years.
- No difference in long-term treatment- or disease-related complications.

6.78 The submission presented results of sensitivity analyses based on PET-adapted ABVD as the comparator arm in the base case. During the evaluation, sensitivity analyses were conducted with ABVD as the comparator in the revised base case (summarised in Table 10). The analyses include corrections to multiple errors identified in the submission’s model (see paragraphs 6.72 and 6.73 above).

Table 10: Sensitivity analyses

Analysis	Incremental cost	Incremental QALY	ICER	% change
Revised base case	\$1	0.52	\$1 ¹	-
Submission’s base case (PET-adapted ABVD ^a as the comparator without corrections for errors)	\$1	0.50	\$1 ¹	+1%
Discount rate (base case 5% costs and outcomes)				
0%	\$1	1.23	\$1 ²	-1%
3.5%	\$1	0.65	\$1 ³	-1%
Time horizon (base case 65 years)				
8.1 years	\$1	0.14	\$1 ⁴	+1%
10 years	\$1	0.19	\$1 ⁵	+1%
15 years	\$1	0.31	\$1 ⁶	+1%
20 years	\$1	0.39	\$1 ⁷	+1%
30 years	\$1	0.48	\$1 ¹	+1%
50 years	\$1	0.52	\$1 ¹	<1%
Overall survival extrapolation (base case exponential dependent MCM, statistical cure fraction 97% A+AVD, 92% ABVD)				
Gompertz dependent MCM, statistical cure fraction 97% A+AVD, 19% ABVD	\$1	0.75	\$1 ⁸	-1%
Generalised gamma independent MCM, statistical cure fraction 90% A+AVD, 82% ABVD	\$1	0.43	\$1 ¹	+1%
Health state utilities (base case progression-free on-treatment A+AVD 0.7525, ABVD 0.8056; progression-free off-treatment 0.8429; and post-progression 0.8037)				
Different off-treatment utilities between arms (A+AVD 0.8429, ABVD 0.8665)	\$1	0.40	\$1 ⁷	+1%
Based on alternative regression model with time since randomisation as a covariate: progression-free on-treatment (A+AVD 0.7356, ABVD 0.7887), progression-free off-treatment (A+AVD 0.8121, ABVD 0.8358) and post-progression (0.7729)	\$1	0.28	\$1 ⁶	+1%

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Analysis	Incremental cost	Incremental QALY	ICER	% change
First line drug costs (base case A+AVD for 5.6 cycles and ABVD for 5.7 cycles)				
A+AVD for 5.6 cycles and PET-adapted ABVD for 6 cycles ^a	\$ ¹	0.52	\$ ¹	+ ¹ %
A+AVD for 6 cycles and PET-adapted ABVD for 6 cycles ^a	\$ ¹	0.52	\$ ¹	+ ¹ %
Subsequent treatment costs (base case weighted cost \$² in A+AVD arm and \$³ in ABVD arm)^b				
Pembrolizumab costs halved assuming patients are treated for half the maximum duration	\$ ⁴	0.52	\$ ⁵	+ ⁶ %
Assume the treatment duration for pembrolizumab is the same as brentuximab vedotin (6.81 cycles)	\$ ⁴	0.52	\$ ⁷	+ ⁸ %
Brentuximab vedotin based on the effective price for ASCT-naïve relapsed/refractory patients (AEMP \$ ²)	\$ ⁴	0.52	\$ ³	- ³ %
Brentuximab vedotin based on the effective price for relapsed/refractory post-ASCT patients (AEMP \$ ²)	\$ ⁴	0.52	\$ ³	- ³ %
No subsequent treatment costs	\$ ⁴	0.52	\$ ⁷	+ ⁸ %

Source: constructed during the evaluation using the brentuximab vedotin economic model of the submission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AEMP, approved ex-manufacturer price; ASCT, autologous stem cell transplant; PET, positron emission tomography; MCM, mixture cure model

^a 2 cycles of ABVD followed by 4 cycles of AVD in 91.3% of patients and 4 cycles of eBEACOPP in 8.7% of patients

^b Based on costs of chemotherapy, stem cell transplant, pembrolizumab (published PBS price for relapsed/refractory disease), brentuximab vedotin (proposed effective AEMP \$² for first line treatment) and radiotherapy

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$15,000 to < \$25,000

³ \$35,000 to < \$45,000

⁴ \$155,000 to < \$255,000

⁵ \$115,000 to < \$135,000

⁶ \$75,000 to < \$95,000

⁷ \$55,000 to < \$75,000

⁸ \$25,000 to < \$35,000

6.79 The model was most sensitive to time horizon, health state utilities, the discount rate and subsequent treatment costs. Due to the partitioned survival design, changes to subsequent treatments only affected modelled costs without affecting the modelled survival endpoints or quality of life. There were additional uncertainties associated with the implementation of subsequent treatment costs that could not be quantified as the model structure is unable to track the occurrence of events and/or patient status at any given time.

6.80 The ESC advised that the use of a partitioned survival analysis was not justified and that a simple Markov model would provide a more flexible and transparent approach. The ESC considered a revised Markov model should consider inclusion of additional health states for relapse and subsequent treatments so that the impacts of assumptions around long term modelled outcomes may be appropriately tested and validated. In addition, the ESC considered that further information and justification for the approach used in estimating utility values was required.

Drug cost/patient/course

Table 11: Drug cost per patient for A+AVD, ABVD and PET-adapted ABVD

	A+AVD			ABVD			PET-adapted ABVD ^a	
	Trial	Economic model	Financial estimates	Trial	Economic model	Financial estimates ^b	Economic model	Financial estimates
Mean cycles of treatment	5.6	5.6	5.6	5.7	5.7	-	6.0	6.0
Dose intensity	94-99% ^c	100%	100%	94-99% ^c	100%	-	100%	100%
Cost/patient/course ^d	-	\$■	\$■	-	\$■	-	\$■	\$■ ^e

Source: constructed during the evaluation using the economic model and financial estimates in the submission

Abbreviations: A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone

^a 2 cycles of ABVD followed by 4 cycles of AVD in 91.3% of patients and 4 cycles of eBEACOPP in 8.7% of patients

^b Cost offsets were estimated in the submission assuming A+AVD would only substitute for use of PET-adapted ABVD

^c Reported relative dose intensities were lower for brentuximab vedotin (mean 94.0%) and bleomycin (mean 93.5%) compared to other components in the A+AVD and ABVD regimens of the trial (approximately 97-99%)

^d Based on 51%/49% public/private hospital split for dispensing fees and mark-ups

^e The difference in cost compared to the economic model was due to an error in the calculation of prednisolone scripts (included as part of the eBEACOPP regimen) in the financial estimates that was not corrected during the evaluation

Note: The submission did not include costs for the dacarbazine component of A+AVD and ABVD, or the costs of the procarbazine component of eBEACOPP as these drugs are not PBS-listed

Estimated PBS usage & financial implications

6.81 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts of listing brentuximab vedotin on the PBS/RPBS, for the first-line treatment of advanced (stage III or IV) classical Hodgkin lymphoma.

6.82 The sources of data used to derive the financial estimates are presented in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Evaluation comments	DUSC comments
Australian population	Yr 1: 27,562,195 Yr 2: 27,970,435 Yr 3: 28,372,315 Yr 4: 28,765,734 Yr 5: 29,157,085 Yr 6: 29,545,877 ABS population 3222.0, Series B.	This was reasonable. The proposed restriction does not limit treatment to adults.	DUSC considered this to be reasonable for an age agnostic listing however noted the evidence primarily supports use in the 18-60 year old population.

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Parameter	Value applied and source	Evaluation comments	DUSC comments
Incidence of Hodgkin lymphoma	2.64 per 100,000. The annual incidence of Hodgkin lymphoma (crude rate) from 1982 to 2018 published by the AIHW was extrapolated using a logarithmic function. The submission's estimate was the average incidence over the 2024 to 2029 period.	The submission did not adequately justify the selection of the logarithmic function for extrapolation given that the linear trendline appeared to have a better visual fit. Based on a linear extrapolation, the average incidence was 3.08 per 100,000. Based on AIHW projections for 2024 to 2029, the annual average incidence was 2.9 cases per 100,000.	DUSC agreed with the evaluation that the incidence is likely to be underestimated however considered the linear extrapolation of 3.08 per 100,000 to be unlikely as the data appears to be plateauing. DUSC considered that as the AIHW data appears to plateau at 3 per 100,000 it would be an appropriate input to use. DUSC noted that there is the potential for a small prevalent patient pool which remains untreated however considered the impact of this on the financials to be minimal.
Proportion of Hodgkin lymphoma that is classical Hodgkin lymphoma	94.2%; based on the average of values reported by Cochrane et al. (2021; 90 to 95%), Eichenauer et al. (2018; 95%) and Cancer Council NSW (2023; 95%).	The primary data sources for the estimates included in the Eichenauer et al. and the Cancer Council NSW publications were not reported.	DUSC considered this to be reasonable if not slightly underestimated.
Proportion with stage III or IV disease	47.99%; based on the characteristics of patients included in the Lymphoma and Related Diseases Registry (Wellard et al., 2023). The submission's estimate was derived by dividing the number of patients with stage III and stage IV disease by the total number of patients in the registry sample ([106 + 180]/596).	The proportion appeared to be underestimated, as the total number of patients in the registry sample included 28 patients with missing data for disease stage. Excluding patients with missing disease stage data resulted in a higher proportion (286/568 = 50.35%). The representativeness of the registry sample to the Australian population was unclear.	DUSC agreed with the evaluation that this proportion is underestimated as the calculation included those patients with missing disease stage data in the denominator. DUSC also noted that the Lymphoma and Related Diseases Registry is a voluntary register and is likely biased.
Proportion with an ECOG ≤2	88.7%; based on the characteristics of patients included in the Lymphoma and Related Diseases Registry (Wellard et al., 2023). Among 238 patients with stage III-IV disease, the ECOG was reported to be ≥2 in 11.3% of patients. The submission assumed that the complement (88.7%) would be eligible for treatment.	The proposed restriction does not include criteria relating to patient fitness. The submission incorrectly assumed that the complement of ECOG ≥2 was ECOG ≤2 (rather than <2). The representativeness of the registry sample to the Australian population was unclear.	DUSC agreed with the evaluation that the proposed restriction does not include criteria relating to patient fitness. DUSC considered this to be an underestimate and noted the proportion in the ECHELON trial was 100%.

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Parameter	Value applied and source	Evaluation comments	DUSC comments
Uptake of A+AVD	█% in Year 1 increasing to █% in Year 6. Assumption	Treatment uptake rates were considered uncertain.	DUSC considered the uptake rates to be underestimated as brentuximab offers a better side effect profile than bleomycin. DUSC considered a range increasing by █% per year from █% and remaining steady at █% would be more appropriate.
Number of cycles (A+AVD)	5.6 cycles; based on the reported mean number of treatment cycles in the ECHELON-1 trial (5.5 cycles for brentuximab vedotin and 5.6 cycles for doxorubicin, vinblastine and dacarbazine), assuming the highest number of cycles among the individual treatments.	The assumed compliance for treatment with A+AVD differed from the assumed compliance for PET-adapted ABVD (patients were assumed to complete all planned treatment cycles). This assumption was not adequately justified.	DUSC agreed with the evaluation that there would likely be 100% compliance.
Number of cycles (PET-adapted ABVD)	ABVD: 2 cycles; AVD/eBEACOPP: 4 cycles. The submission assumed that all patients treated with A+AVD would otherwise have received treatment with PET-adapted ABVD (2 cycles of ABVD followed by 4 cycles of either AVD or eBEACOPP).	The assumption that all patients treated with A+AVD would otherwise have received treatment with PET-adapted ABVD was not adequately justified.	DUSC agreed with the submission that everyone who is diagnosed at stage III or IV would be treated.
Proportion of patients receiving de-escalated therapy with AVD	91.3%; based on the proportion of patients in the ECHELON-1 trial with a Deauville score of 1 to 3 (86.1%) or no available Deauville score (5.2%).	It is unclear whether the Deauville score alone would form the basis for treatment decisions in Australian clinical practice. The assumption that patients with no Deauville score would receive de-escalated treatment was considered uncertain.	DUSC considered this was reasonable.
Dose intensity for A+AVD and PET-adapted ABVD	100%; assumption.	The assumption of 100% dose intensity for all components in each regimen was inconsistent with trial data. The assumption of 100% dose intensity for A+AVD and PET-adapted ABVD may overestimate the cost to the PBS/RPBS, given the higher cost of A+AVD compared to PET-adapted ABVD.	DUSC agreed with the evaluation.

Source: Section 4, pp248-272 of the submission.

Abbreviations: A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AIHW, Australian Institute of Health and Welfare; AVD, doxorubicin, vinblastine, and dacarbazine; ECOG, Eastern Cooperative Oncology Group; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; PET, positron emission tomography.

6.83 The estimated utilisation and financial impacts of listing brentuximab vedotin on the PBS/RPBS are summarised in Table 13.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Cost to the PBS/RPBS (less copayments)						
Cost to PBS/RPBS for increased use of A+AVD	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²
Cost offsets for substituted use of PET-adapted ABVD ^a	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²
Net cost to the PBS/RPBS	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²
Cost to the MBS						
Costs associated with additional chemotherapy administrations ^a	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²
Net financial implications						
Net cost to PBS/RPBS/MBS	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²	\$ ²

Source: Table 4.2-1, p264; Table 4.2-2, p264 of the submission; Section 4 utilisation and cost model Excel workbook.

^a The number of substituted PET-adapted ABVD patients in Years 1 to 6 was corrected during the evaluation to match the number of patients electing treatment with A+AVD.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

- 6.84 The estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, a total cost of \$40 million to < \$50 million over the first 6 years of listing. The net cost to PBS/RPBS/MBS was \$40 million to < \$50 million over the first 6 years of listing.
- 6.85 Sensitivity analyses assuming all patients treated with A+AVD would otherwise receive non-PET-adapted ABVD had relatively modest impacts on the financial estimates, with a net cost to the PBS/RPBS/MBS of approximately \$40 million to < \$50 million over the first 6 years of listing.
- 6.86 The submission’s estimates only considered the impact of listing brentuximab vedotin on first-line therapy utilisation. Use of A+AVD as first-line treatment may have flow-on impacts to the utilisation and costs associated with later-line therapies that were captured in the trial and considered in the economic evaluation. There may be implications for existing risk-sharing arrangements for brentuximab vedotin listings in relapsed/refractory disease.
- 6.87 DUSC considers the estimates presented in the submission to be underestimated. The main issues are:
- The eligible population was underestimated with inputs for incidence rate, proportion at stage III/IV and ECOG ≤2 underestimated.
 - The treated population was underestimated with a lower than expected uptake rate. DUSC considered that A+AVD will result in a change in standard therapy due to the favourable toxicity profile of brentuximab vedotin when compared to bleomycin. The PBAC noted treatment guidelines recommend the use of PET-adapted regimens over non-PET-adapted regimens.

- Cost offsets were overestimated. DUSC considered that the 100% uptake and compliance in the comparators is inappropriate and overestimates cost offsets. DUSC noted that cost offsets will be reduced with a greater uptake of A+AVD which will result in a greater overall cost. DUSC also noted that the potential cost offsets for a reduction in pulmonary adverse events have not been provided.

6.88 The pre-PBAC response provided revised financial estimates in which the incidence of Hodgkin lymphoma was revised to 3 per 100,000, the proportion with stage III/IV disease was increased to 50.35%, the ECOG requirement was removed and uptake rates were increased in accordance with DUSC advice (Yr 1: |%, Yr 2: |%, Yr 3: |%, Yr 4: |%, Yr 5: |%, Yr 6: |%).

Quality Use of Medicines

- 6.89 No quality use of medicines issues were raised in the submission, and no activities to support the quality use of medicines were proposed.
- 6.90 DUSC considered that brentuximab vedotin would be a familiar medicine with the relevant health practitioners however agreed with the evaluation that A+AVD requires dacarbazine which may lead to equity of access issues and increased private costs to patients or state governments.
- 6.91 DUSC noted that there was a high risk of febrile neutropenia, neutropenia and deaths in the trial and considered that the recognition of the requirement for granulocyte-colony stimulating factors in this treatment protocol should be conveyed to health practitioners.
- 6.92 DUSC considered that there would be a large degree of wastage in patients over 100 kg given that brentuximab vedotin is only supplied in 50mg vials without any excess product limiting vial sharing.

Financial Management – Risk Sharing Arrangements

- 6.93 No risk-sharing arrangements were proposed. A risk-sharing arrangement may be required given the use of A+AVD as first-line treatment may affect the utilisation of brentuximab vedotin in the relapsed/refractory setting, which is currently subject to risk-sharing arrangements.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend brentuximab vedotin, in combination with doxorubicin, vinblastine and dacarbazine (A+AVD), for the first line treatment of advanced classical Hodgkin lymphoma. The PBAC considered the availability of alternative treatment options reduced the clinical need for A+AVD. The PBAC advised that the claim of superior effectiveness compared to PET-adapted doxorubicin, bleomycin, vincristine and dacarbazine (ABVD) was highly uncertain due to the indirect evidence presented and the high level of censoring in the key trial evidence, but considered it was likely

- reasonable. In addition, the PBAC considered the economic model structure used in the submission resulted in an incremental cost effectiveness ratio (ICER) that was highly uncertain and advised that the cost-effectiveness of A+AVD was unable to be reliably assessed.
- 7.2 The PBAC considered the primary reason for this outcome was due to the economic evaluation provided.
- 7.3 The PBAC noted the consumer comments received which highlighted the impact of Hodgkin lymphoma on patients' quality of life and that additional treatment options would be welcomed to increase clinician choice when selecting therapies for their patients. The PBAC considered that the current availability of alternative treatment options in this condition reduced the clinical need for A+AVD.
- 7.4 In terms of the proposed restriction, the PBAC considered it was appropriate for it to be silent on age. The PBAC agreed with the ESC that the criterion regarding ECOG status was not required in the restriction (see paragraph 3.5). The PBAC noted that a very small number of patients were re-treated with brentuximab vedotin in ECHELON-1. The PBAC also recalled that when recommending brentuximab vedotin combination therapy for the first-line treatment of peripheral T-cell lymphoma in March 2021 the Committee had allowed re-treatment for patients who had responded to first-line brentuximab vedotin (paragraph 7.14, brentuximab vedotin PSD, March 2021 PBAC Meeting). The PBAC agreed with the ESC that re-treatment would likely be appropriate in this context and considered a lifetime maximum of 16 treatment cycles remained fitting to accommodate use across both settings (see paragraph 3.9).
- 7.5 The PBAC noted the submissions claim that while A+AVD is not a PET-adapted regimen, it is expected to substitute for PET-adapted ABVD. The PBAC considered the clinical place of A+AVD was uncertain given treatment guidelines recommend the use of PET-adapted regimens over non-PET-adapted regimens. The PBAC agreed with the ESC that interim positron emission tomography after 2 cycles of chemotherapy (iPET2) would likely continue with A+AVD despite the fact it was not used in the ECHELON-1 trial.
- 7.6 Acknowledging the uncertainty regarding the clinical place of A+AVD, the PBAC accepted the nomination of PET-adapted ABVD as the main comparator, noting that it is the standard of care for ABVD treatment in Australia.
- 7.7 The PBAC noted the key trial evidence (ECHELON-1) was a head-to-head trial comparing A+AVD with non-PET-adapted ABVD in patients with previously untreated advanced Hodgkin lymphoma. The primary outcome in the ECHELON-1 trial was modified progression-free survival which, in addition to progressive disease and death, included receipt of subsequent anti-cancer therapy in patients not in complete response after completion of frontline therapy. The PBAC noted that a statistically significant benefit in modified progression-free survival was reported in the A+AVD group compared to the ABVD group for the primary analysis period (HR 0.770; 95% CI: 0.603, 0.982). The PBAC considered the results from the later data cut may be subject

to bias as the data were not independently reviewed. The PBAC noted that exploratory analyses of progression-free survival using standard definitions showed a trend in favour of A+AVD, however the results did not achieve statistical significance (HR 0.83; 95% CI: 0.64, 10.7). The PBAC agreed with the ESC that the use of modified progression-free survival was more likely to reflect what would occur clinically in this context than the analyses of progression-free survival using standard definitions (see paragraph 6.18). The PBAC noted that results from the June 2021 data cut showed statistically improved overall survival for A+AVD compared to ABVD (HR 0.59; 95% CI: 0.40, 0.88). However, the PBAC noted both modified progression-free survival and overall survival data were subject to relatively high levels of censoring as most patients had yet to experience an event, with potential confounding due to the use of subsequent treatments (20.4% in A+AVD arm and 23.8% in ABVD arm at the June 2021 cut-off)(see paragraph 6.23).

- 7.8 The PBAC noted there are no data directly comparing A+AVD versus PET-adapted regimens. In addition, the PBAC considered a lack of a common reference and limited comparability between trials of PET-adapted regimens and ECHELON-1 precluded any useful indirect comparisons. The RATHL trial was presented as evidence of similar efficacy between PET-adapted and non-PET adapted ABVD with the Pre-Sub-Committee Response (PSCR) arguing that the (non-PET-adapted) ABVD arm from the ECHELON-1 trial was a reasonable proxy for the efficacy of PET-adapted ABVD. The PBAC agreed with the PSCR that the RATHL trial provided evidence of similar efficacy between PET-adapted and non-PET-adapted regimens. However, the PBAC agreed with the ESC that the RATHL trial was not designed to determine the overall efficacy and safety of PET-adapted ABVD (with options to escalate/de-escalate treatment) compared to non-PET-adapted ABVD (see paragraph 6.32). As such, the PBAC considered the use of the ABVD arm from the ECHELON-1 trial as a proxy for the efficacy of PET-adapted ABVD was uncertain.
- 7.9 Overall, the PBAC considered that the claim of superior effectiveness compared to PET-adapted ABVD was highly uncertain due to the indirect evidence presented and the high level of censoring in the key trial evidence, but likely reasonable.
- 7.10 The PBAC considered that the claim of inferior safety compared to PET-adapted ABVD was reasonable.
- 7.11 The submission presented a cost-utility analysis of A+AVD compared to PET-adapted ABVD based on the ECHELON-1 trial of A+AVD versus non-PET-adapted ABVD. As outlined in paragraph 7.8, the PBAC considered the use of the ABVD arm from the ECHELON-1 trial as a proxy for the efficacy of PET-adapted ABVD was uncertain. The method used to generate the economic model results was a partitioned survival analysis over a 65-year time horizon. The PBAC considered that the 65-year time horizon may be reasonable given the potential for cure with initial and subsequent treatments and the bimodal age distribution evident for this condition. However, the PBAC considered the use of a partitioned survival analysis was inadequately justified given multiple structural limitations associated with the approach, which had

implications on the validity of extrapolated outcomes and the ability to appropriately model the impact of subsequent anti-cancer treatments; and limited the ability to quantify any uncertainties through sensitivity analyses (see paragraphs 6.58 and 6.59). The PBAC did not accept the PSCR argument that the simplest approach to capture the benefits of A+AVD versus ABVD based on the goals of treatment and the available data from ECHELON-1 was a partitioned survival analysis. The PBAC noted the pre-PBAC argument that the use of a Markov model structure would increase complexity and uncertainty as assumptions regarding the impact of subsequent treatments in the relapsed/refractory setting would need to be sourced from other trials and/or published literature. The PBAC noted that the impact of subsequent treatments in the relapsed/refractory setting was a key driver of the economic model with the level of impact considered high and to favour A+AVD (see Table 8). Furthermore, the PBAC considered that there were additional uncertainties associated with the implementation of subsequent treatment costs that could not be quantified. Overall, the PBAC considered the economic model structure resulted in an ICER that was highly uncertain and advised that the cost-effectiveness of A+AVD was unable to be reliably assessed. The PBAC agreed with the ESC that a simple Markov model would provide a more flexible and transparent approach to assess the cost-effectiveness of A+AVD.

- 7.12 The PBAC noted that DUSC considered the estimates presented in the submission to be underestimated (see paragraph 6.87). The PBAC noted that consistent with the advice from DUSC the pre-PBAC response provided revised financial estimates with changes to inputs for incidence rate, proportion at stage III/IV and ECOG requirements (see paragraph 6.88). The PBAC considered these revised inputs appropriate. The PBAC noted that, consistent with DUSC advice, the revised estimates provided in the pre-PBAC response included increased uptake rates. The PBAC acknowledged DUSC advice that the uptake rate may increase due to the favourable toxicity profile of brentuximab vedotin when compared to bleomycin. However, the PBAC noted treatment guidelines recommend the use of PET-adapted regimens over non-PET-adapted regimens and considered that this may impact uptake rates.
- 7.13 The PBAC considered a resubmission for A+AVD should address the following issues:
- Provide a revised economic analysis using a Markov model structure and addresses the points raised by ESC in paragraph 6.80.
 - Provide updated financial estimates utilising the pre-PBAC response inputs for incidence rate, proportion at stage III/IV and ECOG requirements.
- 7.14 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.