Australian Public Assessment Report for ADCETRIS

Active ingredient: Brentuximab Vedotin

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

May 2024

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- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.

- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 3 of 30

List of abbreviations

Abbreviation	Meaning
A+AVD	Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
ACM	Advisory Committee on Medicines
ADC	Antibody drug conjugate
AE	Adverse Event
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ASCT	Autologous stem cell transplant
ASHL	Advanced stage Hodgkin lymphoma
ATA	Anti-therapeutic antibody
AUC	Area under the concentration vs time curve
AVD	Doxorubicin, vinblastine, and dacarbazine
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
cHL	Classical Hodgkin lymphoma
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CR	Complete Remission
DCO	Data cut-off date
DFS	Disease free survival
DLP	Data lock point
DLT	Dose-limiting toxicity
EFS	Event free survival
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET	fluorodeoxyglucose positron emission tomography
FFS	Failure-free survival
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
HL	Hodgkin lymphoma
HRQOL	Health related quality of life
IA	Interim analysis
ILD	Interstitial lung disease

Abbreviation	Meaning
IPFP	International Prognostic Factor Project
iPK	Intensive pharmacokinetics
IRF	Independent review facility
K-M	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
mPFS	Modified progression free survival
nATA	Neutralising anti-therapeutic antibody
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PD	Progressive disease
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PT	Preferred term
RACP	Royal Australasian College of Physicians
RATHL	Response Adapted Therapy in Advanced Hodgkin Lymphoma
SAE	Serious adverse event
SMQ	Standardised MedDRA Query
$t_{1/2z}$	Terminal disposition phase half-life
TAb	Total antibody
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 5 of 30

Product submission

Submission details

Types of submission:	New indication
Product name:	ADCETRIS
Active ingredient:	brentuximab vedotin
Decision:	Approved
Date of decision:	8 January 2024
Date of entry onto ARTG:	9 January 2024
ARTG numbers:	203372
▼ *Black Triangle Scheme*	No

Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd, Grosvenor Place Level 39 225 George Street, Sydney, NSW, 2000
Dose form:	Powder for injection
Strength:	50 mg
Container:	Vial
Pack size:	1
Approved therapeutic use for the current submission:	Hodgkin lymphoma Treatment of patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).
Route of administration:	Injection
Dosage:	The recommended dose in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]) is 1.2 mg/kg administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg. Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients with previously untreated HL receiving combination therapy.
Pregnancy category:	D
	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 6 of 30

medicines in pregnancy for specific cases. More information is available from [obstetric drug information services](#) in your state or territory.

Product background

This AusPAR describes the submission by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register ADCETRIS (brentuximab vedotin) 50 mg powder for injection, vial, for the following proposed extension of indications:[1]

> *Treatment of adult patients with previously untreated CD30+ advanced Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).*

The disease

Classical HL (cHL) is defined histopathologically by the presence of malignant Hodgkin-Reed-Sternberg (HRS) cells in a background of inflammatory cells. Classical HL occurs in patients in all age groups and presents a bimodal distribution with peaks at 15 to 35 years of age and greater than 60 years of age. Classical HL accounts for about 90-95% of cases of HL, with nodular lymphocyte predominant HL (NPHL) comprising the remaining 5-10%.[2]

The Ann Arbor staging classification for HL defines Stage I disease as involvement at a single site, Stage II disease as involvement of 2 or more lymph node regions on the same side of the diaphragm, Stage III disease as involvement of lymphoid tissue on both sides of the diaphragm, and Stage IV disease as the presence of HL in noncontiguous extralymphatic tissue. HL is further categorised by the absence or presence of one or more of the following systemic symptoms: fevers, night sweats, and weight loss exceeding 10% of the patient's baseline body weight. For the purposes of treatment planning, cHL is frequently divided into early-stage (Stage I/II) and advanced-stage (Stage III/IV) disease.

In Australia, the annual incidence of HL is estimated to be approximately 2.4 to 2.9/100,000. [3] The Australian Institute of Health and Welfare (AIHW) suggests that approximately 803 patients will be diagnosed with HL in Australia each year, with almost 100 of these being children and adolescents.[4]

Current treatment options

Advanced stage HL (ASHL) is typically managed by chemotherapy alone and includes Stage III/IV disease (European Organisation for Research and Treatment of Cancer [EORTC]). The Royal Australasian College of Physicians (RACP) position paper (2021) on the assessment and management of newly diagnosed cHL (ASHL) states that six, 28-day cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD x 6) achieves 5-year failure-free survival (FFS) rates of 61-85% and overall survival (OS) of 73-87% and remains a standard against which new therapies are compared[3].

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[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2017.

[3] Cochrane T, Campbell BA, Gangatharan SA. Assessment and management of newly diagnosed classical Hodgkin lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance. Internal Medicine Journal. 2021: 51; 2119-2128.

[4] Hodgkin Lymphoma (HL). Lymphoma Australia. www.lymphoma.org au, accessed 10 February 2023.

Maintaining dose intensity is important, and it is reported in the RACP position paper (2021) that ABVD does not require G-CSF as primary prophylaxis, even with Grade 4 neutropenia. Monitoring of respiratory symptoms is required with bleomycin, with omission of bleomycin advisable if new respiratory symptoms develop. Bleomycin must be used with caution in patients > 60 years, and the RACP position paper indicates that if bleomycin is used in this patient population it should be limited to 2 cycles. Some physicians are reported to add limited field consolidative radiotherapy to ABVD for bulky mediastinal involvement.

To improve frontline disease control in patients with advanced cHL, more aggressive multiagent chemotherapy regimens have been developed, such as standard-dose and escalated-dose versions of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). The RACP position paper (2021) reports that escalated BEACOPP for six 21-day cycles (eBEACOPP x 6) improves progression free survival (PFS) and OS relative to ABVD in patients aged < 60 years but comes with increased short and long-term toxicities. Treatment related mortality for BEACOPP can be unacceptably high in patients aged 60 years of age and older.

In addition, the RACP position paper (2021) advises caution for patients aged 40 to 59 years treated with eBEACOPP due to the increase in treatment-related mortality. Dose reductions may be required in patients being treated with BEACOPP due to toxicities and prophylactic medications are recommended. For reasons associated with toxicity of BEACOPP, the Sponsor states that ABVD remains the standard of care for advanced cHL in North America and throughout most of the world.

In advanced cHL, the results of fluorodeoxyglucose positron emission tomography (FDG-PET) after 2 cycles of treatment have been shown to predict long-term outcomes.[5] The recent RATHL (Response Adapted Therapy in Advanced Hodgkin Lymphoma) study evaluated whether results of early PET scanning could be used to modify treatment outcomes in patients with advanced cHL.[6] In this study, patients with a negative PET scan after 2 cycles of ABVD were randomised to continue with either 4 more cycles of ABVD or 4 cycles of AVD. Patients who had a Cycle 2 PET scan showing residual disease were treated with one of two intensive versions of the BEACOPP regimen.

The 3-year progression-free survival (PFS) for patients who were PET-negative at Cycle 2 was similar in both treatment arms (85.7% [95% CI: 82.1 to 88.6] for ABVD and 84.4% [95% CI: 80.7 to 87.5] for AVD), though patients randomised to drop bleomycin after 2 cycles experienced fewer grade 3 or 4 respiratory toxicities. The 3-year PFS for Cycle-2 PET-positive patients who went on to receive BEACOPP was 67.5% (95% CI: 59.7 to 74.2). The Sponsor comments that the results of the RATHL study are "intriguing; however, the role of interim PET imaging in the clinical management of cHL has not been fully defined." The RACP position paper (2021) recommends that "PET-adapted treatment is preferred for fit patients aged < 60 years" and describes PET-adapted strategies depending on whether interim PET is positive or negative.

Clinical rationale

The median age at diagnosis for patients with Hodgkin lymphoma is 39 years. The sponsor reports that, based on outcomes with current standard of care frontline treatments, 33% to 39% of patients with Stage III or IV HL are destined to die or have disease progression within 5 years of diagnosis. Treatment with salvage chemotherapy followed by high dose chemotherapy and autologous stem cell transplant (ASCT) is standard of care for patients with relapsed or refractory disease after frontline therapy.

Multiple large studies demonstrate that about half of patients undergoing ASCT can be cured. However, a significant percentage of patients with relapsed or refractory HL never make it to

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 8 of 30

ASCT because their disease does not respond adequately to salvage therapies or their clinical status, including age, precludes them from undergoing the procedure. Furthermore, the patients who achieve durable remissions are still subject to late ASCT-related complications including secondary malignancies, cataracts, cardiac dysfunction, osteoporosis/avascular necrosis, hypothyroidism, and infertility. Therefore, the sponsor considers that more effective frontline treatments with manageable toxicity profiles need to be developed in order to substantially improve outcomes in advance cHL.

Furthermore, the sponsor comments that approximately 20% of patients with HL are ≥ 60 years old at diagnosis, and these individuals represent a population of patients with an extreme unmet need. The RACP position paper (2021) states that in the context of HL, elderly is defined as > 60 years. Tolerance to ABVD is compromised in older patients, with increased toxicity of bleomycin in ABVD therapy (5-36%) and treatment-related mortality approaching 25%.

Population studies demonstrate that elderly patients with HL have significantly reduced disease-free and OS rates. A subgroup analysis of the North American Intergroup Trial E2496, that compared ABVD to Stanford V in patients with advanced cHL (including Stage II bulky disease), demonstrated 5-year FFS rates of 74% for patients < 60 years old versus 48% for patients ≥ 60 years old. The corresponding 5-year OS rates in each age group were 90% and 58%, respectively. Older patients experienced high rates of bleomycin-related toxicity (24%) and significantly greater treatment-related mortality (9% versus 0.3% for patients < 60 years old). The RACP position paper (2021) states that the "management of ASHL in older patients is challenging, with notable under representation in clinical trials".

There is an unmet need for effective therapies for cHL, particularly for patients aged > 60 years.

Regulatory status

Australian regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 20 December 2013. The following indications were approved at the time of submission of this extension of indications submission:

Hodgkin lymphoma

Treatment of adult patients with CD30+ HL at higher risk of relapse or progression following ASCT.

Treatment of adult patients with relapsed or refractory CD30+ HL:

1. *following autologous stem cell transplant (ASCT) or*
2. *following at least two 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 (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP). Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Cutaneous T cell lymphoma

Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 9 of 30

Foreign regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. Table 1 summarises these submissions and provides the indications where approved.

Table 1: International regulatory status at the time of product registration.

Region	Submission date	Status	Approved indications
EU - Centralised procedure	29 November 2018	6 February 2019	Hodgkin lymphoma ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)
	29 July 2022	17 November 2022	Same indication. Update of clinical content in the label with second interim analysis of OS.
	08 March 2023	12 October 2023	Hodgkin lymphoma ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)
USA	3 November 2017	20 March 2018	ADCETRIS is a CD30-directed antibody-drug conjugate indicated for treatment of adult patients with: Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine.
	29 August 2022	14 June 2023	Same indication. Update of clinical content in the label with second interim analysis of OS.

Region	Submission date	Status	Approved indications
Singapore	28 September 2018	16 January 2020	Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy ADCETRIS is indicated for the frontline treatment of adult patients with previously untreated CD30+ advanced cHL in combination with doxorubicin, vinblastine and dacarbazine (AVD)
Switzerland	26 March 2018	8 June 2018	Hodgkin lymphoma. ADCETRIS is indicated for the treatment of previously untreated adult patients with CD30-positive (+) Stage IV Hodgkin lymphoma (HL) in combination with chemotherapy with doxorubicin, vinblastine and dacarbazine (AVD) (see "Clinical efficacy"). ADCETRIS in combination with AVD has not been compared with BEACOPP-escalated chemotherapy, but with ABVD chemotherapy consisting of doxorubicin, bleomycin, vinblastine and dacarbazine.

Registration timeline

Table 2 captures the key steps and dates for this submission.

This submission was evaluated under the [standard prescription medicines registration process](#).

Table 2: Timeline for Submission PM-2022-04918-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2023
First round evaluation completed	22 June 2023
Sponsor provides responses on questions raised in first round evaluation	28 August 2023

Description	Date
Second round evaluation completed	29 September 2023
Sponsor's notification to the TGA of errors/omissions in evaluation reports	13 October 2023
Delegate's[5] Overall benefit-risk assessment and request for Advisory Committee advice	30 October 2023
Sponsor's pre-Advisory Committee response	10 November 2023
Advisory Committee meeting	30 November 2023 – 1 December 2023
Registration decision (Outcome)	8 January 2024
Administrative activities and registration in the ARTG completed	9 January 2024
Number of working days from submission dossier acceptance to registration decision*	239

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

Nonclinical

The sponsor has provided a 4-week repeat dose toxicity study in support of proposed changes to the Product Information (PI) in section *4.4 Paediatric Use* and section *4.6 Fertility, pregnancy and lactation*.

The non-clinical evaluator has evaluated the toxicity study and concluded that the proposed PI changes are supported by this study and therefore acceptable from a toxicological perspective.

Clinical

Summary of clinical studies

The clinical dossier consisted of the following studies:

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[5] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Pharmacology

Pharmacokinetics

ECHELON-1 (Study C25003)

The known pharmacokinetic properties of brentuximab vedotin are documented in the currently approved PI. The PK data submitted to support this extension of indications application come from the pivotal study ECHELON-1 (C25003), the single agent study C25005, and a population pharmacokinetics (popPK) analysis. A detailed description of ECHELON-1 can be found in the efficacy section of this overview. The PK parameters of antibody-drug conjugate (ADC), total antibody (TAb), monomethyl auristatin E (MMAE, the major metabolite of brentuximab vedotin), doxorubicin, vinblastine and dacarbazine were measured in ECHELON-1. A detailed description of PK methods and results can be found in the clinical evaluation report, p25-38.

In summary, the PK data from ECHELON-1 demonstrated the following (after IV brentuximab vedotin 1.2 mg/kg Q2W in combination with AVD):

- Median peak serum ADC and TAb concentrations occurred within 1 hour of the end of the infusion
- ADC and TAb elimination exhibited a multiexponential decline with a geometric mean $t_{1/2z}$ of 3.70 - 5.35 days
- Median peak MMAE concentrations occurred approximately 2 days after the end of infusion, then declined in a nearly log-linear manner
- Steady state for ADC and TAb was attained by cycle 3 and once achieved, the PK of ADC and TAb did not appear to change significantly with time
- Steady state for MMAE was attained by cycle 3; and MMAE exposure appeared to decrease with time by approximately 50%
- ADC accumulation was 1.27-fold, and TAb accumulation was 1.36-fold
- No marked differences were observed in the PK of doxorubicin, vinblastine, or dacarbazine following combined administration with brentuximab vedotin.

These PK data are consistent with the information in the currently approved PI.

Study C25005

The single agent study C25005, in which brentuximab vedotin was administered alone, has been previously evaluated by the TGA. It was a multicentre, open-label, 1:1, randomised, 2-arm study of brentuximab vedotin (1.8 mg/kg, IV Q3W) with and without concomitant rifampicin (Arm A and Arm B, respectively). Rifampicin is a cytochrome P450 (CYP) 3A4/5 inducer that could potentially enhance metabolism of free (unconjugated) MMAE. The sponsor has provided a comparison of the PK results of Arm A in study C25005 (brentuximab vedotin alone) with the A+AVD arm in ECHELON-1 in their module 2 summary of clinical pharmacology. After adjustment for the different doses used in the studies, C_{max} values for ADC, TAb, and MMAE were similar in the single agent and combination studies, and concentration-time profiles closely overlapped. The AUCs from the two studies are not directly comparable due to the difference in the time period used for their estimation.

The sponsor proposes to update section 4.5 (Interactions) of the PI with a statement that the PK characteristics of MMAE and ADC were similar for single agent brentuximab vedotin, and when used in combination with AVD. The proposed addition to the PI is acceptable.

Population pharmacokinetic data

A population pharmacokinetic (popPK) analysis was performed using data from patients in ECHELON-1. Two models were developed, one for ADC and one for MMAE. These models were based on existing popPK models previously evaluated by the TGA. The model for ADC included covariates of albumin, body surface area and sex. None of these covariates had a clinically meaningful impact on clearance or volume of distribution of ADC. In the MMAE model, body surface area, albumin and GFR were included as covariates and again, none had a clinically meaningful effect on clearance. Covariates of age, race (Asian vs non-Asian), antitherapeutic antibodies and neutralising antibodies, and International Prognostic Factor Project (IPFP) score on the pharmacokinetics of ADC and MMAE were not significant and therefore not retained in the model. The sponsor is not proposing dosing adjustment based on any of these factors, which is appropriate.

Pharmacodynamics

Pharmacodynamic (PD) results from the ECHELON-1 study and an exposure-response (E-R) analysis were included in the dossier. A detailed description of the PD and E-R methods and data can be found in the clinical evaluation report, p52-63.

In summary, the PD data from ECHELON-1 demonstrated that in terms of immunogenicity, 109 of 632 (17.2%) patients in the A+AVD arm were anti-therapeutic antibody (ATA)-positive at any post-baseline visit. Of these 109 ATA-positive patients, 12 (11.0%) were also neutralising anti-therapeutic antibody (nATA)-positive at any post-baseline visit. Among A+AVD-treated patients, no correlation was observed between either nATA status and response or nATA status and reports of TEAEs. This is consistent with the immunogenicity information in the current PI, therefore no changes are required.

The E-R analysis demonstrated a consistent treatment benefit across the range of ADC exposures with the proposed A+AVD treatment regimen in adult patients with advanced cHL. In terms of safety, ADC AUC/Time (but not MMAE AUC/time) was found to be a significant predictor of Grade ≥ 2 peripheral neuropathy. For both ADC and MMAE, the probability of a Grade ≥ 2 peripheral neuropathy event was higher during early treatment cycles compared to later cycles. MMAE AUC/Time (but not ADC AUC/time) was found to be a significant predictor of Grade ≥ 4 neutropenia. Both ADC and MMAE AUC/Time were found to be significant predictors of febrile neutropenia, and G-CSF was found to significantly reduce Grade ≥ 4 neutropenia and febrile neutropenia.

Dose Selection

Study SGN35-009

The dose of brentuximab vedotin selected for the ECHELON-1 study was based on the phase I dose escalation study SGN35-009. This was a multicentre study of brentuximab vedotin (A) with ABVD or AVD in the first line treatment of HL stage IIa-IV.

51 patients were enrolled and received at least one dose of brentuximab vedotin; 25 in the A+ABVD arm and 26 in the A+AVD arm. No dose-limiting toxicities (DLTs) were observed up to the proposed dose of 1.2mg/kg Q2W. Pulmonary toxicity of 44% (n=11 of 15), including 2 fatal pulmonary events, occurred with the combination of A+ABVD, however no pulmonary toxicity occurred with A+AVD. Almost all patients experienced at least one TEAE (95% in the A+ABVD;

100% in the A+AVD arm), most being treatment related. SAEs were reported notably more frequently in patients in the A+ABVD arm (n=14; 56%) than in the A+AVD arm (n=7; 27%).

At the end of treatment, 80% (n=41) of patients achieved CR, 92% in the A+AVD arm and 80% in the A+ABVD arm. The estimated progression-free survival rate was 91% for all patients at 12 months; 85% for patients in the A+ABVD arm and 95% for patients in the A+AVD arm.

The PI contains a statement in the contraindications section that the combination of bleomycin and brentuximab vedotin causes pulmonary toxicity. This contraindication is crucial given the high rate of pulmonary toxicity, and 2 fatal pulmonary events that occurred in the A+ABVD combination in this phase I study.

The dose of 1.2mg/kg brentuximab vedotin combined with AVD (and the omission of bleomycin from the combination regimen) is an appropriate dose for the pivotal study.

Efficacy

Pivotal Study: ECHELON-1 (C25003)

ECHELON-1 is the pivotal study supporting this extension of indications application. ECHELON-1 is a global multi-centre, open-label, randomised 2-arm phase III study comparing modified PFS (mPFS) in the brentuximab vedotin + chemotherapy (A+AVD) arm with the chemotherapy only (ABVD) arm. The trial was conducted at 218 sites in 21 countries, including Australia. The first patient was consented in November 2012, and the study is ongoing, with patients continuing to be followed up until 10 years after randomisation of the last patient. Clinical study reports from the first interim analysis, with a data cut-off date of 20 April 2017, and the second interim analysis, with data cut-off date of 1 June 2021 were evaluated by the TGA's clinical evaluator.

The pivotal ECHELON-1 study is summarised in Table 3:

Table 3: ECHELON-1 PICO Summary

Population	Treatment naïve patients with histologically confirmed stage III or IV cHL (n=1334) 1:1 randomisation stratified by international prognostic factor project (IPFP) risk factors (0-1 vs 2-3 vs 4-7) and region (Americas vs Asia vs Europe)
Intervention	A+AVD: brentuximab vedotin 1.2 mg/kg + doxorubicin (Adriamycin) 25 mg/m2, vinblastine 6 mg/m2, and dacarbazine 375 mg/m2 IV on days 1 and 15 of each 28 day cycle; up to 6 cycles n=664
Control	ABVD: doxorubicin (Adriamycin) 25 mg/m2, bleomycin 10 units/m2, vinblastine 6 mg/m2, and dacarbazine 375 mg/m2 IV on days 1 and 15 of each 28 day cycle; up to 6 cycles n=670 After the cycle 2 PET assessment, patients could be switched to an alternative regimen of the investigator's choice for the remainder of planned frontline therapy. Such switches were not considered to be mPFS events.
Outcomes	Primary endpoint: mPFS per independent review facility (IRF) (mPFS defined as time from randomisation to PD, death due to any cause, or receipt of subsequent anticancer therapy for patients not in CR after completion of first line treatment)

	Key secondary endpoint: OS Other secondary endpoints: CR, EFS, DFS, ORR, HRQOL PK of brentuximab vedotin, MMAE and TAb Immunogenicity Safety

Participants

1585 patients were screened, and 1334 were randomised, 664 to the brentuximab vedotin arm (A+AVD), and 670 to the control arm (ABVD). A total of 15 patients (2%) in the A+AVD arm and 9 patients (1%) in the ABVD arm switched to an alternative front-line medication. AEs were reported as the reason for switching to an alternative medication for 12 of the 15 patients (80%) in the A+AVD arm and for 1 of the 9 patients (11%) in the ABVD arm. Deauville score after the Cycle 2 PET assessment was reported as the reason for switching to an alternative for 1 of the 15 patients (7%) in the A+AVD arm and 4 of the 9 patients (44%) in the ABVD arm.

Baseline Demographics and Disease Characteristics

Baseline characteristics were well balanced between the two arms. 378 patients (57%) of the A+AVD arm and 398 (59%) of patients in the ABVD arm were male. The median age was 35 years in the A+AVD arm (range 18-82 years) and 37 years in the ABVD arm (range 18-83 years). The majority of patients were under the age of 45 years, with 60 patients (9%) in the A+AVD arm and 62 patients in the ABVD arm (9%) aged 65 years and over.
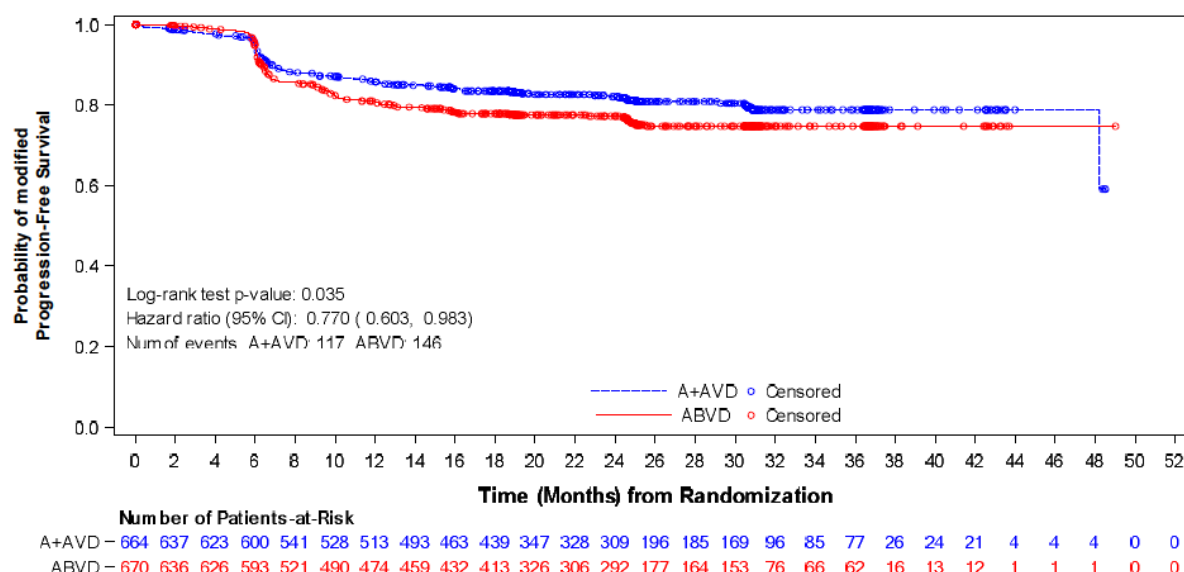
Nodular sclerosis cHL was the most common histological classification, occurring in 425 patients (64%) in the A+AVD arm and 386 patients (58%) in the ABVD arm. Stage IV disease was reported for 425 patients (64%) in the A+AVD arm and 421 patients (63%) in the ABVD arm, the remaining patients having stage III disease (except for 1 patient in the A+AVD arm who had stage II disease). 2 to 3 IPFP risk factors were reported for 354 patients (53%) in the A+AVD arm and 351 patients (52%) in the ABVD arm, and 4 to 7 IPFP risk factors were reported for 169 patients (25%) in the A+AVD arm and 178 patients (27%) in the ABVD arm.

In terms of concomitant medications, a higher use of myeloid growth factors was reported for patients in the A+AVD arm (n=536; 81%) compared to the ABVD arm (n=373; 57%), which the sponsor speculates as being concomitant medication or secondary prophylaxis for neutropenia.

Results: Primary Endpoint (mPFS per IRF)

At the 20 April 2017 data cut for the primary analysis, median mPFS was not reached in either arm. The stratified hazard ratio was 0.770 (95% CI: 0.603, 0.983, p=0.035), representing a statistically significant 23% reduction in the risk of an mPFS event in the treatment arm. At 2 years after randomisation, 82.1% (95% CI: 78.8, 85.0%) in the A+AVD arm versus 77.2% (95% CI: 73.7, 80.4%) in the ABVD arm were free from mPFS events. The K-M curve below (Figure 1) shows the sustained separation of the curves from approximately 6 months:

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 16 of 30

Figure 1: Kaplan-Meier curve: mPFS per IRF (ITT population), ECHELON-1, primary analysis

An ad-hoc analysis of standard PFS did not show a statistically significant difference: HR = 0.830 (95% CI: 0.642, 1.071); p=0.150. While not statistically significant, this result indicates a trend in favour of A+AVD.

Results: Sensitivity Analyses (mPFS)

A pre-specified sensitivity analysis of mPFS per investigator showed similar statistically significant results to the primary analysis of mPFS per IRF. Per investigator, the HR for mPFS was 0.724 (95% CI: 0.573, 0.914, p=0.006).

The EMA requested that mPFS events also include, (1) patients who discontinue treatment due to undocumented progressive disease, and (2) patients with events occurring after more than 1 missed visit. Results from sensitivity analyses based on the EMA definition of mPFS are consistent with those from the primary analysis: HR = 0.765 (95% CI: 0.603, 0.970, p=0.026) per IRF and HR = 0.725 (95% CI: 0.574; 0.914, p=0.006) per investigator.

A supplementary analysis of mPFS per IRF in the per protocol population showed similar results to the primary analysis in the ITT population: HR = 0.769 (95% CI: 0.600, 0.986, p=0.037).

Results: Subgroup Analyses (mPFS)

Subgroup analyses must be interpreted cautiously as ECHELON-1 was not powered for these analyses. Nevertheless, subgroup analyses are relevant to consideration of the proposed indication for this application. The following subgroups were pre-specified for subgroup analysis:

- Age
- Region
- Number of IPFP risk factors at baseline
- Cancer stage at baseline
- Baseline B symptoms
- Cycle 2 PET results
- Cycle 2 PET Deauville score
- Receipt of alternative frontline medication
- Extranodal sites at baseline

mPFS HR point estimates were below 1 for most subgroups, and although many confidence intervals included 1, the general trend favoured the A+AVD arm in most cases. Of particular relevance were the subgroup analyses by cancer stage and age.

Subgroup analysis: mPFS in Stage III vs Stage IV cHL

At baseline, 237 patients (36%) in the A+AVD arm and 246 patients (37%) in the ABVD arm had stage III disease. Stage IV disease was reported for 425 patients (64%) in the A+AVD arm and 421 patients (63%) in the ABVD arm.

For stage III disease, the unstratified HR for mPFS per IRF was 0.922 (95% CI: 0.599, 1.419), whereas for stage IV disease, the unstratified HR was 0.711 (95% CI: 0.529, 0.956). This suggests that the benefit derived from the A+AVD combination may be greater for patients with stage IV disease. The lack of statistical significance in stage III disease, and the very small benefit indicated by the HR of 0.922 suggests that there may be very little clinical benefit, if any, for stage III disease.

The following K-M curve (Figure 2) shows the difference in mPFS between stage III disease (blue treatment arm vs black control arm) and stage IV disease (red treatment arm vs green control arm).

Figure 2: K-M curve, mPFS per IRF, ITT population in patients with stage III or IV cHL, ECHELON-1
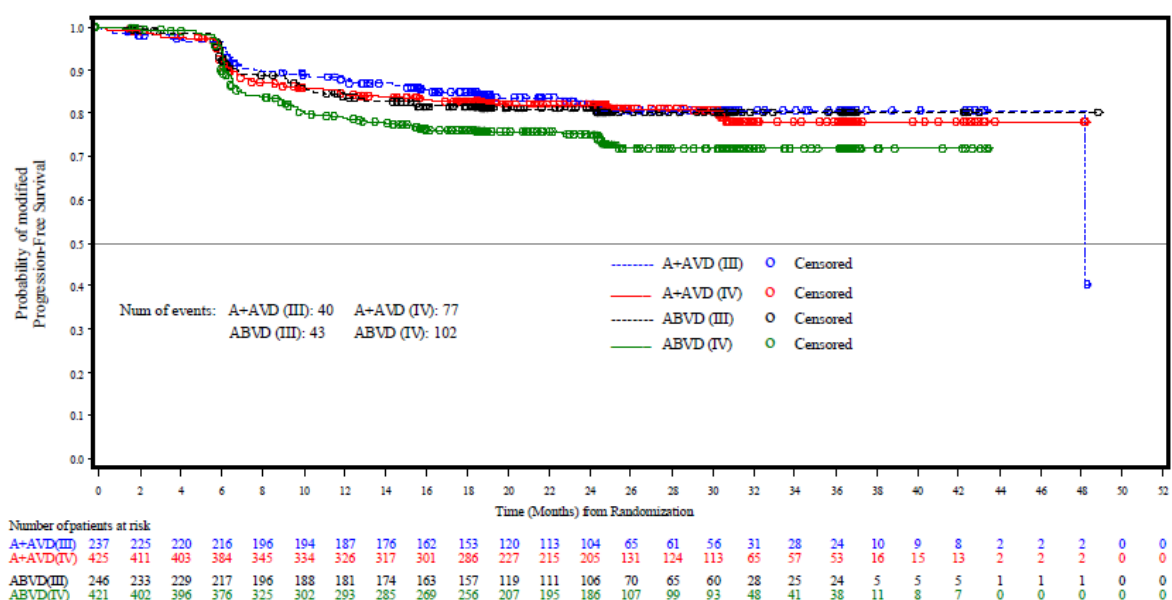
Subgroup analysis: Age <60 years vs age ≥ 60 years

580 patients (87%) in the A+AVD arm and 568 (85%) in the ABVD arm were aged < 60 years at baseline. There were 84 patients (13%) aged ≥ 60 years in the A+AVD arm, and 102 (15%) in the ABVD arm.

Results of the subgroup analyses based on age (< 60 vs ≥ 60 years) suggest that the mPFS benefit in the total ITT population for the A+AVD arm appears to be being driven primarily by patients aged < 60 years. For patients under 60 years of age, the unstratified HR was 0.733 (95% CI: 0.558, 0.963), demonstrating a statistically significant and clinically meaningful benefit in favour of A+AVD. For patients aged 60 and older, the unstratified HR was not significant, at 1.002 (95% CI: 0.583, 1.722), suggesting no difference between the treatment arms.

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 18 of 30

Results: Secondary Endpoint (OS)

The first interim analysis of OS was performed at the same time as the first mPFS analysis (data cut 20 April 2017). After a median follow-up of 27.8 months in the A+AVD arm and 27.4 months in the ABVD arm, 28 deaths had occurred in the A+AVD arm compared with 39 deaths in the ABVD arm (median OS not reached in either arm). An OS trend favouring A+AVD was observed (stratified HR=0.728 [95% CI: 0.448, 1.184, p=0.199), however, statistical significance was not reached.

At the second interim analysis of OS (data cut 1 June 2021), 39 deaths in the A+AVD arm had occurred, compared to 64 deaths in the ABVD arm. Median follow up was 73.3 months in the A+AVD arm and 72.4 months in the ABVD arm. Once again, median OS was not reached. The stratified OS HR was statistically significant at 0.59 (95% CI: 0.396, 0.879, p=0.009) based on a stratified log-rank test and the pre-specified boundary determined by the O'Brien-Fleming method with a Lan-DeMets alpha spending function. The K-M curve of OS at the second interim analysis is shown in Figure 3:

Figure 3: K-M curve of OS in ITT population at IA2, ECHELON-1
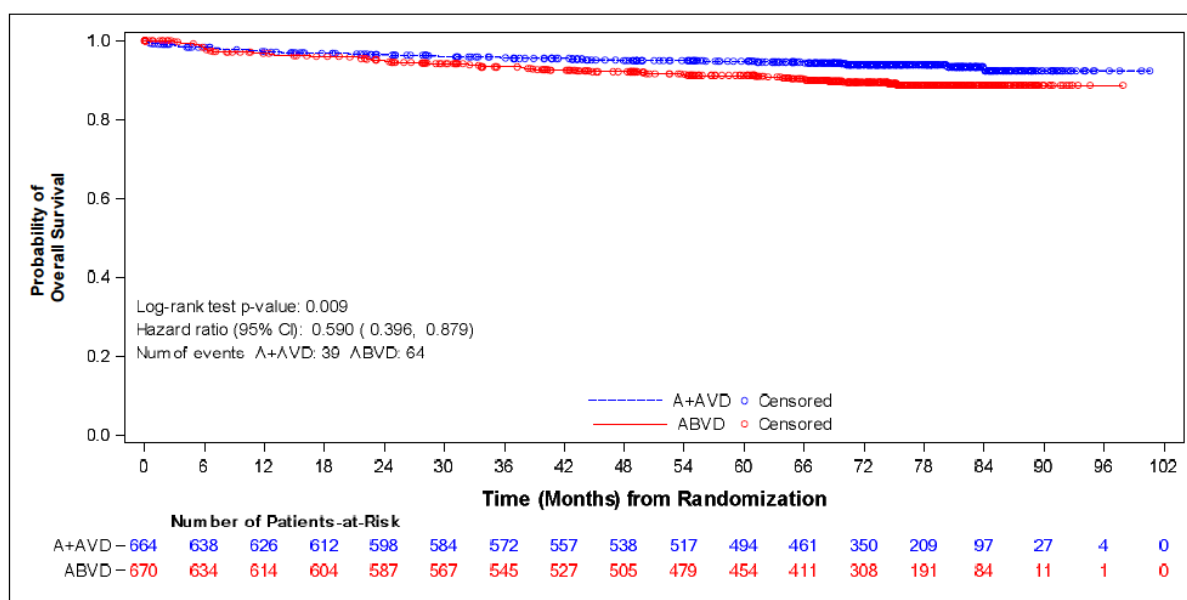
A multivariate analysis of OS, adjusting for treatment, stratification, and pre-specified prognostic factors also showed a statistically significant HR: 0.508 (95% CI: 0.324, 0.796, descriptive p=0.003).

OS subgroup analysis must again be interpreted cautiously, as the study was not powered for such analyses. Most HRs were below 1, and while some confidence intervals included 1, the overall trend favoured A+AVD for most subgroups. Subgroup analyses by disease stage and age are of note:

Subgroup analysis: OS in Stage III vs Stage IV cHL
In patients with stage III disease, the unstratified HR was 0.863 (95% CI: 0.452, 1.648), compared to 0.478 (95% CI: 0.286, 0.799) for patients with stage IV disease. This suggests that the OS benefit in the overall population may have been driven primarily by patients with stage IV disease.

OS in Age <60 years vs age ≥ 60 years
The OS HR for patients aged < 60 years was 0.509 (95% CI: 0.291, 0.89). For patients aged ≥ 60 years, the OS HR was 0.829 (95% CI: 0.469, 1.466). Once again, this suggests that the benefit of the A+AVD combination may have been limited to patients aged < 60 years.

The results for other secondary efficacy endpoints in the ITT population consistently showed a small numerical benefit in favour of the A+AVD arm compared with the ABVD arm.

Safety

The pivotal study, ECHELON-1, provides the key safety data for this submission. This includes safety data reported in the CSR for the primary analysis (DCO 20 April 2017) and updated post-treatment follow-up safety data from the second interim analysis (DCO 1 June 2021). The safety population included 662 patients in the A+AVD arm and 659 in the ABVD arm who received at least 1 dose of one of the study drugs. Relative dose intensity, duration of treatment, and maximum number of completed cycles of individual regimen components were all similar between the two treatment arms. Patients in both treatment arms received a median of 6 cycles of study treatment over a median of approximately 24 weeks.

TEAEs

Almost all patients experienced at least one TEAE. The most common TEAEs reported in ≥ 20% of patients in the A+AVD arm are shown in the table below (DCO 20 April 2017):

Table 4: TEAEs reported in ≥ 20% of patients in the A+AVD arm vs the ABVD arm, ECHELON-1

Preferred Term	A+AVD N=662 n (%)	ABVD N=659 n (%)
Patients with at least 1 TEAE	653 (99)	646 (98)
Neutropenia	382 (58)	295 (45)
Nausea	348 (53)	371 (56)
Constipation	279 (42)	241 (37)
Vomiting	216 (33)	183 (28)
Fatigue	211 (32)	211 (32)
Peripheral sensory neuropathy	189 (29)	111 (17)
Diarrhoea	181 (27)	121 (18)
Pyrexia	179 (27)	147 (22)
Neuropathy peripheral	174 (26)	85 (13)
Alopecia	173 (26)	146 (22)
Weight decreased	148 (22)	40 (6)
Abdominal pain	142 (21)	65 (10)
Anaemia	140 (21)	67 (10)
Stomatitis	138 (21)	104 (16)

TEAEs reported in ≥ 10% of patients in either treatment arm and in ≥ 10% more patients in the A+AVD arm than in the ABVD arm, respectively, were: neutropenia (58% vs 45%); peripheral sensory neuropathy (29% vs 17%); neuropathy peripheral (26% vs 13%); weight decreased (22% vs 6%); abdominal pain (21% vs 10%); anaemia (21% vs 10%); and febrile neutropenia (19% vs 8%).

TEAEs of Grade ≥ 3

In terms of severity, TEAEs of grade ≥3 were reported for 549 patients (83%) in the A+AVD arm and 434 patients (66%) in the ABVD arm (DCO 20 April 2017). Grade 3 or higher TEAEs reported in ≥ 5% of patients in either treatment arm (A+AVD vs ABVD, respectively) were: neutropenia (54% vs 39%); febrile neutropenia (19% vs 8%); neutrophil count decreased (13% vs 10%); anaemia (8% vs 4%); and peripheral sensory neuropathy (5% vs < 1%).

SAEs

At least 1 treatment-emergent SAE was reported for 284 patients (43%) in the A+AVD arm and 178 patients (27%) in the ABVD arm (DCO 20 April 2017). Treatment-emergent SAEs reported in ≥ 3% of patients in the A+AVD arm were febrile neutropenia (17%), pyrexia (7%), and neutropenia and pneumonia (3% each). Treatment-emergent SAEs reported in ≥ 3% of patients in the ABVD arm were febrile neutropenia (7%) and pyrexia (4%).

Deaths

In the updated safety data analysis (DCO 1 June 2021), death in the safety population was reported for 39 patients (6%) in the A+AVD arm and 64 patients (10%) in the ABVD arm. Deaths for 18 patients (3%) in the A+AVD arm and 28 patients (4%) in the ABVD arm were considered disease-related.

On-study death occurred in 9 patients (1%) in the A+AVD arm. 8 of these 9 deaths were considered treatment related by the investigator. The majority of on-study deaths were associated with neutropenia and its complications, including neutropenic sepsis and septic shock. 6 of the 9 on-study deaths reported in the A+AVD arm occurred in Cycle 1. 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 (2%) patients, and 7 of these were considered treatment related by the investigator. The majority of on-study deaths in the ABVD arm were associated with pulmonary toxicity. 10 of the 13 on-study deaths reported for patients in the ABVD arm occurred in cycles 5 and 6.

Deaths during post-treatment follow-up (30 days after the last dose of frontline therapy or later) were reported in 30 patients (5%) in the A+AVD arm and 51 patients (8%) in the ABVD arm.

TEAEs leading to discontinuations or dose modifications

TEAEs resulting in premature discontinuation of the study drug were reported more frequently for patients in the ABVD arm than in the A+AVD arm (105 patients [16%] vs 88 patients [13%] respectively). The most frequent TEAEs in the A+AVD arm leading to discontinuation were related to peripheral neuropathy or neutropenia.

TEAEs resulting in study drug modification were reported more frequently in patients in the A+AVD arm than in the ABVD arm (423 patients [64%] vs 293 patients [44%], respectively). In the A+AVD arm, the most frequent TEAEs leading to dose modification were related to neutropenia and neuropathy.

Adverse events of special interest

Febrile neutropenia

Febrile neutropenia was reported in 128 patients (19%) in the A+AVD arm and 52 (8%) patients in the ABVD arm. Age ≥ 60 years was identified as a risk factor for febrile neutropenia in patients with advanced cHL in both the A+AVD and ABVD arms, and for pulmonary-related toxicity in patients in the ABVD arm. Increased age was the only identified risk factor for febrile neutropenia among the potential risk factors examined. In the A+AVD arm, febrile neutropenia was reported in 97 patients (17%) aged < 60 years and 31 patients (37%) aged ≥ 60 years. In the ABVD arm, febrile neutropenia was reported in 35 patients (6%) aged < 60 years and 17 patients (17%) aged ≥ 60 years.

Across age groups, patients who received G-CSF prophylaxis experienced a lower rate of neutropenia than those who did not. Of all on-study deaths that occurred, none of the patients

had received G-CSF prophylaxis. The PI recommends primary prophylaxis with G-CSF, beginning with the first dose, for all patients receiving combination therapy. Detailed information, including the fact that advanced age is a risk factor for febrile neutropenia, is included in the warnings and precautions section of the PI.

Peripheral neuropathy

Treatment-emergent peripheral neuropathy (MedDRA SMQ) events were reported for 442 (67%) patients in the A+AVD arm and 286 (43%) patients in the ABVD arm, with most of the events being categorised as Grade 1 or 2 in severity. Peripheral neuropathy grade 3 events were reported for 69 patients (10%) in the A+AVD arm and 11 patients (2%) in the ABVD arm, and there was 1 grade 4 peripheral neuropathy event (in the A+AVD arm). Of patients with peripheral neuropathy TEAEs, premature study drug discontinuation was reported for 44 patients (10%) in the A+AVD arm and 11 patients (4%) in the ABVD arm. Peripheral neuropathy and associated dosing recommendations are adequately described in the PI.

Pulmonary toxicity

Treatment-emergent interstitial lung disease (MedDRA SMQ) events were reported more frequently in patients in the ABVD arm than in the A+AVD arm (44 patients [7%] vs 12 patients [2%], respectively). Grade 3 or 4 events were reported in 5 patients (< 1%) in the A+AVD arm and 18 patients (3%) in the ABVD arm. There were 3 patients (<1%) in the ABVD arm with grade 5 (fatal) interstitial lung disease events (1 each for pneumonitis, acute respiratory distress syndrome and pulmonary toxicity). There were no grade 5 interstitial lung disease events in the A+AVD arm. Pulmonary toxicity is known to be associated with bleomycin, which is likely the main contributor to these events in the ABVD combination. Pulmonary toxicity has also been associated with brentuximab vedotin and is included in the PI special warnings and precautions section. This is appropriate, given that interstitial lung disease TEAEs were reported in patients who received brentuximab but not bleomycin in the A+AVD arm, although at a much lower rate than in the ABVD arm.

Age ≥ 60 years was identified as a risk factor for pulmonary-related toxicity in patients who received ABVD, but not for A+AVD.

Infusion related reactions

At least 1 infusion related reaction was reported for 57 patients (9%) in the A+AVD arm and 100 patients (15%) in the ABVD arm. At least 1 grade 3 infusion related reaction was reported for 3 patients (<1%) in the A+AVD arm and 7 patients (1%) in the ABVD arm. No Grade 4 IRR was reported for either treatment arm. Information on infusion related reactions is included in the PI.

Second malignancies

In ECHELON-1, all new primary malignancies other than cHL diagnosed at any time before study closure were recorded as second malignancies. 23 patients (3%) in the A+AVD arm experienced a second malignancy compared to 32 patients (5%) in the ABVD arm.

Within the subgroup of patients aged <60 years, a second malignancy was reported for 14 patients (2%) in the A+AVD arm and 18 patients (3%) in the ABVD. Within the subgroup of patients aged ≥ 60 years, a second malignancy was reported for 9 patients (11%) in the A+AVD arm and 14 patients (14%) in the ABVD arm. The PI does not currently contain information about second malignancies, and the sponsor has been requested to add details of second malignancies to the adverse events section.

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 22 of 30

Pregnancy and Fertility

At least 1 pregnancy was reported for 49 female patients (17%) in the A+AVD arm, and 28 female patients (10%) in the ABVD arm. At least 1 pregnancy was reported for 33 partners (9%) of male patients in the A+AVD arm, and 33 partners (8%) of male patients in the ABVD arm. No stillbirths were reported for either female patients or partners of male patients across the 2 treatment arms. At least 1 live birth was reported for 42 patients (86%) of the 49 female patients in the A+AVD arm and for 19 patients (68%) of the 28 female patients in the ABVD arm for whom at least 1 pregnancy was reported. At least 1 live birth was reported for 31 partners (94%) of the 33 male patients in the A+AVD arm and 29 partners (88%) of the 33 male patients in the ABVD arm. More than 2 live births were reported for 1 female patient each across the 2 treatment arms.

Safety in patients aged ≥ 60 years

In response to the clinical evaluator's questions, the sponsor provided a summary of safety in patients ≥ 60 years compared to those <60 years of age (see clinical evaluation report p 154-165 for tables). The safety population included 1140 patients aged < 60 years (579 patients in the A+AVD arm and 561 patients in the ABVD arm) and 181 patients aged ≥ 60 years (83 patients in the A+AVD arm and 98 patients in the ABVD arm). The risks of treatment were consistently greater in the older patient population. Clinically relevant TEAEs such as haematological toxicity, grade ≥ 3 TEAEs, SAEs, and TEAEs leading to dose modification were reported in a higher proportion of patients aged ≥ 60 in the A+AVD arm compared to the ABVD arm.

Age was identified as a risk factor for febrile neutropenia and associated complications in both arms of ECHELON-1. Age was also a risk factor for pulmonary toxicity in the ABVD arm, but not the A+AVD arm.

Post-market data

As of the 18 August 2021 data-lock point for the currently approved Periodic Benefit-Risk Evaluation Report (PBRER), there are no new or unexpected safety signals for brentuximab vedotin. The cumulative estimated patient exposure to brentuximab vedotin was 97,652 patients.

Risk-benefit analysis

Delegate's considerations

Brentuximab vedotin is already registered on the ARTG for HL in patients at higher risk of progression following ASCT, and for patients with relapsed/refractory HL following ASCT or two prior therapies. The sponsor's current application seeks to extend these indications and bring brentuximab vedotin into first line treatment for all patients with advanced (stage III and IV) HL, in combination with AVD.

Pharmacology and Dose

The proposed dose of brentuximab vedotin for the new indication is 1.2 mg/kg Q2W in combination with AVD. This is different to the dose in the currently approved PI of 1.8 mg/kg Q3W for relapsed/refractory HL. The 1.2 mg/kg Q2W is adequately supported by the Phase I dose escalation study SGN35-009, as well as the sponsor's comparison of PK data from patients administered this dose in the pivotal ECHELON-1 study, with patients administered the

1.8mg/kg Q3W dose in the previously evaluated C25005 study. Appropriate information regarding the dose to be used for each indication has been added to the PI.

The additional PK, popPK and PD data submitted by the sponsor to support the proposed indication are in keeping with the known PK/PD profile of brentuximab vedotin, as documented in the currently approved PI. The sponsor has not proposed any changes to this information, however, given that the currently approved PI focuses on the 1.8 mg/kg Q3W dose regimen, the sponsor is requested to add information relevant to the 1.2 mg/kg Q2W dose regimen and the combination of brentuximab vedotin and AVD to the PI. It is noted that the EU SmPC includes such information under 'combination therapy.'

Indication

There are two key issues for this submission. Firstly, as discussed at length by the clinical evaluator, is the uncertainty of the risk-benefit balance in patients aged 60 years and older. The second is whether efficacy has been satisfactorily established for both stage III and IV disease. Both these issues arise from the results of subgroup analyses of the pivotal study ECHELON-1, and an analysis of safety in patients < 60 years compared with those ≥ 60 years. ECHELON-1 was not powered for such subgroup analyses, and this raises the question of whether the results of subgroup analyses carry sufficient weight to restrict the indication.

Efficacy

The ECHELON-1 study provides the key efficacy evidence supporting this submission. ECHELON-1 was a well-designed phase III study comparing A+AVD with ABVD in the first line treatment of stage III or IV cHL. Baseline and disease characteristics were reasonably well balanced between the treatment arms. The primary endpoint of modified PFS (mPFS) per IRF, rather than standard PFS, is appropriate for this relatively rare disease often treated with curative intent, where time to PFS or OS events may be long, and patient numbers limited. ABVD is an appropriate comparator, as stated in the 2021 RACP position paper. ECHELON-1 was an open label study in that investigators and patients were not blinded to treatment assignment. However, the IRF was blinded to treatment assignments, which reduces the risk of bias particularly in the assessment of the primary endpoint. Further, there was high concordance between IRF and investigator assessments of mPFS, which provides further reassurance.

ECHELON-1 met its primary endpoint; the stratified HR for mPFS per IRF was 0.770 (95% CI: 0.603, 0.983, p=0.035) at the primary analysis (DCO 20 April 2017). This represents a 23% reduction in the risk of an mPFS event for patients on the A+AVD combination, which is a statistically significant result in the overall population.

OS was not significant at the primary analysis, although a trend towards benefit was noted. At the second analysis of OS, a clear benefit was demonstrated with a statistically significant HR of 0.59 (95% CI: 0.396, 0.879, p=0.009). A 41% reduction in the risk of death represents a clinically meaningful survival benefit for patients.

While efficacy in the overall population appears to be established, subgroup analysis by disease stage and age raise concerns that this benefit may have been driven primarily by patients with stage IV disease, and younger patients aged < 60 years. ECHELON-1 was not powered for subgroup analyses, and therefore such analyses must be interpreted cautiously. Nevertheless, the results raise the possibility of a lack of efficacy in patients aged ≥ 60 years, and in those with stage III disease. This uncertainty must be taken into account in the risk-benefit assessment for these patient groups.

Efficacy in Stage III vs IV disease

Subgroup analysis of mPFS results by stage of disease demonstrated a statistically and clinically significant HR for stage IV disease (HR = 0.711 (95% CI: 0.529, 0.956)). However, results for stage III disease demonstrated a very small benefit, which did not reach statistical significance (HR = 0.922 (95% CI: 0.599, 1.419)). Subgroup analysis of OS reflected a similar pattern of greater benefit for patients with Stage IV disease (HR = 0.478 (95% CI: 0.286, 0.799)), and a smaller benefit that was not statistically significant in Stage III disease: HR = 0.863 (95% CI: 0.452, 1.648). This suggests that the benefit of the A+AVD combination may be substantially reduced in the Stage III population. The key question is whether results of these subgroup analyses, for which the study was not powered, and the proportion of patients with stage III disease was low, are sufficient to warrant restriction of the indication to stage IV disease.

Notably, the extension of indication to first line treatment of cHL was approved for both stage III and IV disease by the US FDA, and the CHMP has adopted a positive opinion on the indication for both disease stages (EU EMA approval for Stage III received 12 October 2023). Swissmedic however did not consider the data sufficient to approve for stage III disease, and in Canada, an application to extend to phase III was withdrawn after Health Canada requested additional data. The clinical evaluator suggests that the data is sufficient to support efficacy in Stage III and IV disease. The delegate is inclined to agree, however the ACM's opinion is requested.

Efficacy in patients aged <60 years vs ≥ 60 years

mPFS results in patients under 60 years of age were statistically significant and clinically meaningful (HR = 0.733 (95% CI: 0.558, 0.963), however there are concerns that efficacy is not sufficient in patients aged 60 years and older. The HR for older patients was not significant, and suggested no benefit in this age group: 1.002 (95% CI: 0.583, 1.722). OS results show a similar pattern of significant benefit for patients < 60 years (HR = 0.509 (95% CI: 0.291, 0.89)) compared to a substantially reduced benefit that does not reach statistical significance for patients aged ≥ 60 (HR = 0.829 (95% CI: 0.469, 1.466)). Nevertheless, the point estimate for the OS HR in older patients is in the same direction as for the overall population. This could be interpreted to mean that there may be a survival benefit, however statistical significance was not reached due to the small number of patients in this age group. Nevertheless, there is uncertainty regarding the efficacy of the A+AVD combination in older patients, which must be considered in the risk-benefit assessment.

Safety

The new safety data from the ECHELON-1 did not reveal any unexpected safety concerns. Almost all patients experienced at least one TEAE, with the most common AEs being those related to neutropenia, peripheral neuropathy, and gastrointestinal adverse effects. These events are well documented in the PI, and information on recommended dose delays and adjustments is clear.

Importantly, the A+AVD combination was inferior to the ABVD combination in several adverse event categories. There were substantially more grade ≥ 3 TEAEs in the A+AVD arm (83%) compared to the ABVD arm (66%). A similar pattern is reflected in SAEs, which were reported in 43% of the A+AVD arm vs 27% of the ABVD arm. There were also more TEAEs leading to study drug modification in the A+AVD arm (64%) compared to the ABVD arm (44%). Despite the increased rates of grade ≥ 3 TEAEs, SAEs and TEAEs leading to drug modification in the brentuximab vedotin arm, TEAEs leading to discontinuation of study drug were more frequent in the ABVD arm (16%) compared to the A+AVD arm (13%). This suggests that the AEs in the A+AVD arm were tolerable for most patients, and manageable with dose modifications. In addition, at the 1 June 2021 data cut, there were fewer deaths in the A+AVD arm (n=39; 6%)

compared to the ABVD arm (n=64, 10%), which provides a combined measure of efficacy and safety favouring A+AVD.

Adverse events of special interest occurring in ECHELON-1 were febrile neutropenia, peripheral neuropathy, pulmonary toxicity, infusion related reactions and second malignancy. The PI already contains important information about these risks, with the exception of second malignancy. In ECHELON-1, second malignancies occurred in a small proportion of patients in both arms, and while causality is difficult to ascertain, the occurrence of these malignancies is important given the relatively young median age of this patient population, and the long-expected survival for many patients. The sponsor is requested to add data on second malignancies to the PI.

Pulmonary toxicity is known to be associated with bleomycin, which was used in the control arm of ECHELON-1, and is also associated with brentuximab vedotin, as documented in the current PI. The use of brentuximab vedotin and bleomycin together is contraindicated in the PI. This is crucial information, given the fatal pulmonary toxicity observed when these drugs were used in combination in the dose escalation study SGN35-009.

Safety in Stage III vs Stage IV disease

Safety was not examined separately in stage III disease compared with stage IV disease. It would be expected in that the safety profile would be similar or slightly better in patients with earlier stage disease, due to higher levels of baseline function.

Safety in patients aged <60 years vs ≥ 60 years

ECHELON-1 was conducted in adult patients aged 18 years or older. A total of 83 patients in the A+AVD arm and 98 patients in the ABVD arm in the safety population were aged 60 years or older. In almost all categories of adverse events, patients aged ≥ 60 years experienced an inferior safety profile compared to patients aged <60 years. The clinical evaluator states "The safety profile for patients treated with A+AVD was notably inferior for patients aged ≥ 60 years compared with patients aged < 60 years. Furthermore, the safety profile of patients aged ≥ 60 years treated with A+AVD was generally inferior to patients in this age group treated with ABVD." Haematological toxicity was of particular concern for older patients, particularly febrile neutropenia and associated complications, for which age was a risk factor. While prophylaxis with G-CSF reduces the risks of neutropenia, it remains a serious TEAE.

The sponsor states that the A+AVD combination may provide an alternative for patients who cannot tolerate bleomycin. Indeed, rates of pulmonary toxicity in the A+AVD arm of ECHELON-1 were lower than in the ABVD arm in the ≥ 60 age group. Nevertheless, in other categories of adverse events, A+AVD displayed an inferior safety profile in older patients. This must be taken into consideration in the risk-benefit assessment.

Risk-benefit balance

In the overall patient population in ECHELON-1, a benefit in terms of mPFS and OS was clearly demonstrated. While the toxicities of the A+AVD arm are substantial, and in some cases greater than the ABVD arm, the risks are adequately described in the PI, and were largely tolerated by patients in the trial through dose modifications. It is considered that the benefit of A+AVD outweighs the risks in the overall patient population.

What is less clear, is the risk-benefit balance in patients with stage III disease, and in patients aged ≥ 60 years. For patients with stage III disease, subgroup analyses suggest that there may be no efficacy benefit in this patient population. The study was not powered for subgroup analyses,

and the proportion of patients with stage III disease was small, and therefore, the results of the subgroup analyses must be interpreted cautiously. While there is uncertainty in the efficacy benefit for stage III disease, the A+AVD combination provides an alternative to ABVD, which may be particularly beneficial for patients who cannot tolerate bleomycin. The safety profile in stage III disease appears to be comparable to stage IV disease, and it would be expected that patients with an earlier stage of disease may be able to better tolerate the treatment regimen. Whether the uncertainty of efficacy in the stage III population, in the absence of specific safety concerns, is sufficient to warrant restricting the indication is in question. The ACM's advice on the risk-benefit balance of A+AVD in patients with stage III cHL is requested.

For patients aged ≥ 60 years, subgroup analyses suggest that there may be no efficacy benefit in this patient population. Combined with the uncertainty of the efficacy benefit is the inferior safety profile of A+AVD in patients aged ≥ 60 years. Once again, efficacy concerns are based on subgroup analyses and therefore must be interpreted cautiously, but they do highlight uncertainty of the risk-benefit balance in older patients. Notably, no other international regulators appear to have restricted the indication according to age. Rather than restricting the indication, the sponsor proposes to add a warning to the PI regarding the safety profile in patients aged ≥ 60 years. Whether this is sufficient to mitigate the risks of A+AVD, and outweigh the uncertainty related to the efficacy benefit in the older patient population, is a key question for which ACM advice is sought.

Advisory Committee considerations

The [Advisory Committee on Medicines (ACM)](#), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. *Has the efficacy and safety of brentuximab vedotin in combination with AVD been satisfactorily established in the following patient groups?*

    a. *Stage III cHL*

    b. *Stage IV cHL*

    c. *cHL patients aged < 60 years*

    d. *cHL patients aged ≥ 60 years*

Overall, the ACM was of the view that efficacy and safety of brentuximab vedotin in combination with AVD has been satisfactorily established within the each of the listed patient groups.

The ACM noted that the pivotal study demonstrated both a mPFS and OS benefit for the whole study population. The ACM acknowledged that the study was not powered to show statistical significance for the subgroups, and neither disease stage nor age were stratification factors. However, the ACM noted superior benefit appears to be demonstrated within Stage IV cHL and cHL patients aged < 60 years. The ACM advised that restriction of the indication based on subgroup analysis was not warranted.

The ACM agreed the safety profile is well established and acknowledged that while the age > 60 years group appears to experience greater toxicity, this is also seen with other treatments (ABVD and BEACOPP).

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 27 of 30

2. *Please comment on your preferred wording of the indication.*

The ACM proposed that the indication be age agnostic. The ACM advised that there is a dual peak in HL occurring in adolescence / young adults and the elderly. Restricting the indication to adults allows access to 18-year-olds but not younger adolescents with the same disease and physiology.

The ACM advised that the word 'advanced' should be replaced with 'stage III and IV' for clarity, and alignment with the US.

3. *The committee is invited to comment on any other matters relevant to this application, such as the PI and CMI.*

The ACM agreed with the proposed changes as per the Delegate's overview.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Brentuximab Vedotin is indicated for patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

Outcome

The TGA decided to register ADCETRIS (brentuximab vedotin) for the following extension of indications:

Hodgkin lymphoma

Treatment of patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD)

As such, the full indications at this time were:

Hodgkin lymphoma

Treatment of patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

Treatment of adult patients with CD30+ HL at higher risk of relapse or progression following ASCT.

Treatment of adult patients with relapsed or refractory CD30+ HL:
1.following autologous stem cell transplant (ASCT) or
2. following at least two 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 (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).
Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Cutaneous T cell lymphoma
Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

The above extension of indications is inclusive of the previous approved indications.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for [Tradename] which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

The PI to be included with the AusPAR is the PI that was included with the approval letter. Note, this PI will not include the ARTG date.

AusPAR – ADCETRIS – brentuximab vedotin – Takeda Pharmaceuticals Australia Pty Ltd - PM-2022-04918-1-6
Date of Finalisation 7 May 2024

Page 29 of 30

Therapeutic Goods Administration