14 September 2023
EMA/CHMP/440104/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ADCETRIS

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0107

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

A+AVD	brentuximab vedotin (ADCETRIS®), doxorubicin (Adriamycin®), vinblastine, and dacarbazine
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
auto-HSCT	autologous hematopoietic stem cell transplantation
AVD	doxorubicin (Adriamycin), vinblastine, and dacarbazine
BSA	body surface area
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CR	complete remission
CT	computed tomography
CTCL	cutaneous T-cell lymphoma
DFS	disease-free survival
DOCR	duration of complete remission
DOR	duration of response
ECHELON-1	clinical study C25003 of brentuximab vedotin (SGN-35)
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
FDA	(United States) Food and Drug Administration
GFR	glomerular filtration rate
HL	Hodgkin lymphoma
IDMC	independent data monitoring committee
IPFP	International Prognostic Factors Project
IRF	independent (radiologic) review facility
ITT	intent-to-treat
MMAE	monomethyl auristatin E
mPFS	modified progression-free survival
NE	not estimable
NOS	not otherwise specified
ORR	overall response rate

OS	overall survival
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetic
PN	peripheral neuropathy
PR	partial remission
PTFU	posttreatment follow-up
Q2W	once every 2 weeks
QLQ-C30	(EORTC) Quality of Life Questionnaire – Core 30
QoL	quality of life
sALCL	systemic anaplastic large-cell lymphoma
sCD30	soluble CD30
SGN-35	brentuximab vedotin, ADCETRIS
SPD	sum of the product of the (tumor) diameters
USPI	United States product insert

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 8 March 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to include treatment of adult patients with previously untreated CD30+ advanced (including Stage III) Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine and dacarbazine (AVD), for ADCETRIS, based on the second interim analysis of OS data from ECHELON-1 study (C25003); this is a randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical HL. As a consequence, sections 4.1 and 5.1 of the SmPC are updated.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information relating to orphan designation

ADCETRIS, was designated as an orphan medicinal product EU/3/08/596 on 15 Jan 2009. ADCETRIS was designated as an orphan medicinal product in the following indication:

Treatment of Hodgkin's lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Adcetris as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: http://www.ema.europa.eu/en/medicines/human/EPAR/Adcetris

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0013/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0013/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0013/2021.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol assistance from the CHMP on 16 February 2012 and 23 October 2014. The protocol assistance pertained to clinical aspects of the ECHELON-1 study (C25003). With regard to Hodgkin Lymphoma patients with Ann Arbor stage III (the intended target population with the current extension of indication), it was advised to restrict the indication to patients with stage III/IV disease as included in the ECHELON-1 study. As it was not presumed that the study results could also be extrapolated to stage II patients, the term 'advanced' (instead of specific Ann Arbor stages) was not recommended.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	8 March 2023
Start of procedure:	25 March 2023
CHMP Rapporteur Assessment Report	17 May 2023
PRAC Rapporteur Assessment Report	26 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	14 August 2023
PRAC Rapporteur Assessment Report	18 August 2023
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur Assessment Report	7 September 2023
Opinion	14 September 2023

2. Scientific discussion

2.1. Introduction

Problem statement

Hodgkin Lymphoma (formerly called Hodgkin's disease) is a lymphatic neoplasm, accounting for approximately 10 percent of all lymphomas. HL is histologically characterized by malignant Hodgkin and Reed Sternberg (HRS) cells that are surrounded by non-malignant inflammatory cells. HL is divided in two major subtypes: classical (cHL) and nodular lymphocyte predominant (NLPHL), based on immunohistological features and microscopic appearance of the malignant cells. The cHL subtype expresses CD30, and accounts for 95% of all HL. There are 4 histopathologic subtypes of cHL in the World Health Organization classification: nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted.

Disease or condition

With the current extension of indication, the first line indication in HL is proposed to be extended to advanced HL instead of Stage IV HL patients as follows:

> *Hodgkin lymphoma*
>
> *ADCETRIS is indicated for adult patients with previously untreated CD30+* ***advanced*** *~~Stage IV~~ Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) (see sections 4.2 and 5.1).*
>
> *ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT) (see section 5.1).*
>
> *ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):*
>
> 1. *following ASCT, or*
> 2. *following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

Epidemiology and risk factors, screening tools/prevention

The incidence in Europe is ~ 2.4 cases per 100.000 persons. Young adults aged 20–40 years are most often affected; a second incidence peak is seen in individuals aged 55 and older. HL demonstrates a bimodal age distribution with the first peak occurring at about 20-30 years of age and a second peak in patients >65 years of age. In the European Union (EU), GLOBOCAN estimates that 20,410 new HL cases were diagnosed and 5,887 HL-related deaths occurred in 2012 (across all ages), with a 5-year prevalence of 67,782 cases in adults.

Clinical presentation, diagnosis and stage/prognosis

Clinical symptoms are present in 2/3 of patients, and could include the presence of B symptoms (fever, night sweats, unexplained weight loss >10% in 6 months), fatigue, pruritus and alcohol-induced pain.

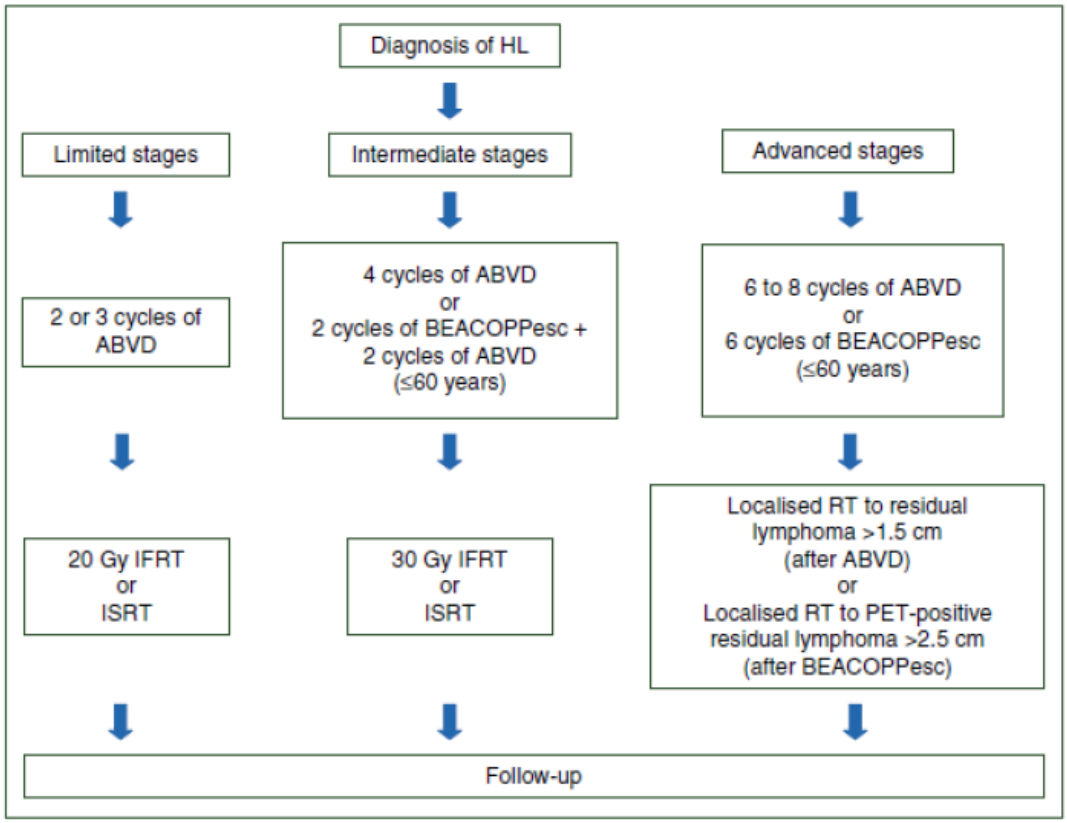
Staging is according to the Ann Arbor criteria, which are based on localisation, the extent of nodal and extranodal involvement and the presence of the classical B symptoms. For the purposes of treatment planning, cHL is frequently divided into early-stage (Stage I/II) and advanced-stage (Stage III/IV) disease. In the absence of unfavourable features, the prognosis for early-stage disease is excellent. Thus, the frontline treatment approach for these individuals is focused on minimizing toxicity of therapy while maintaining high cure rates.

In addition to clinical staging, other clinical features can predict outcomes in these patients. The international prognostic score is a tool that assesses 7 potentially unfavourable clinical features in HL at diagnosis: serum albumin <4 g/dL, haemoglobin <10.5 g/dL, male gender, age >45 years, Stage IV disease, white blood cell count ≥15,000/µL, and absolute lymphocyte count <600/µL and/or <8% of the total white blood cell count. When applied retrospectively to patients who were treated with current standard-of-care combination chemotherapy regimens, the 5-year OS for patients with lower scores (0-3) was 93% ±1% and those with higher (≥4) scores was 78% ±4%.

HL prognosis is worse in patients who present with advanced disease and 30-40% relapse within 5 years after initial treatment or have immediate treatment failure. Five-year survival for patients with Stage III cHL is approximately 80%, whereas the 5-year survival rate for patients with Stage IV cHL is approximately 65%. 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 ASCT because their disease does not respond adequately to salvage therapies or their clinical status, including age, precludes them from undergoing the procedure.

Management

After diagnosis of HL, chemotherapy and radiotherapy regimens are recommended, depending on the stage of the disease. According to the ESMO Clinical Practice guidelines (Eichenauer et al, 2018), the following therapeutic algorithm can be used (Figure 1).



HL, Hodgkin's lymphoma; RT, radiotherapy; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPPesc, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone escalated dose regimen; ISRT, involved-site radiotherapy; PET, positron emission tomography; NLPHL, nodular lymphocyte-predominant Hodgkin's lymphoma; IFRT, involved-field RT.

Figure 1. Therapeutic algorithm for newly diagnosed Hodgkin Lymphoma (ESMO Clinical Practice guideline)

Patients with early-stage disease are typically treated with 2 to 4 cycles of ABVD, with or without focal radiotherapy to sites of disease. This approach results in 3- to 5-year progression-free and OS rates exceeding 90% and 95%, respectively, in patients with favourable disease, and 85% and 90%, respectively, in patients with unfavourable disease.

Patients diagnosed with Stage III/IV cHL are usually treated with 6 to 8 cycles of ABVD, with some physicians adding limited field consolidative radiotherapy for bulky mediastinal involvement. In multiple studies of Stage III/IV patients treated with ABVD, the 5-year failure free survival rates ranged from 61% to 67% and 5-year OS rates ranged from 73% to 85%. In patients ≤ 60 years who are eligible for a more intensive treatment, escalated-dose versions of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) could also be considered. Several trials randomly comparing ABVD and BEACOPP escalated have shown a superior tumour control with BEACOPP escalated, and a meta-analysis including 9993 patients also indicted a significantly better OS. However, given the relevant acute toxicity, appropriate surveillance and supportive care must be available. Moreover, the BEACOPP regimen should not be given in patients >60 years, as an increased treatment-related mortality has been observed in this age group. In 2018, brentuximab vedotin + AVD was approved as alternative treatment option for patients with Stage IV HL. This was based on the ECHELON-1 trial, for which updated OS analyses have currently been submitted in support of an extension of indication to advanced HL.

For most patients with refractory or relapsed HL after frontline therapy, the treatment of choice consists of high-dose chemotherapy followed by ASCT. The use of brentuximab vedotin represents an option in patients relapsing after ASCT or at increased risk of relapse after ASCT.

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, to make substantial improvements to the outcomes in advanced cHL, more effective frontline treatments with manageable toxicity profiles need to be developed.

2.1.1. About the product

Adcetris (brentuximab vedotin; SGN35) is a CD30-directed antibody-drug conjugate (ADC), that consists of the chimeric anti-human CD30 monoclonal antibody (cAC10) conjugated to the small molecule cytotoxic anti-tubulin agent MMAE by a protease-cleavable linker. CD30 is a member of the tumour-necrosis factor receptor superfamily. Mechanistically, the antibody targeted chemotherapeutic brentuximab vedotin acts by binding to the cell surface marker CD30, expressed on cells of several types of malignancy, including HL. After binding to CD30 positive cells, brentuximab vedotin is internalized, and MMAE is released from the conjugate through proteolytic degradation of the drug linker. Released MMAE binds to the tubulin and leads to G2/M cell cycle arrest and cell death. CD30 expression on normal cells is rare, i.e. less than 1% of lymphoid cells, being activated, but not resting lymphocytes (T, B and NK cells) and weakly on activated monocytes. CD30 is not present on cells from solid organs.

Pharmacological classification (ATC-code): L01XC12. The first marketing authorization for brentuximab vedotin in the EU was granted in October 2012 and is currently indicated for:

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) (see sections 4.2 and 5.1).

ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. *following ASCT, or*
2. *following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.*

Systemic anaplastic large cell lymphoma

ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL.

Cutaneous T-cell lymphoma

ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice

The applicant received Protocol assistance from the CHMP on 16 February 2012 and on 23 October 2014 for the pivotal trial of the current application, ECHELON-1. The Protocol assistance pertained to clinical aspects of the dossier. It was advised to exclude patients with pre-existing neuropathy (as has been done by the MAH); and to restrict the indication to the patients with stage III/IV disease as included in the pivotal study (use similar definition, and not 'advanced'), which advice was not followed. The comparator arm ABVD, number of cycles of study treatments, and the primary endpoint modified PFS (mPFS) were agreed. As the trial is open label, any HRQL measure was by the CHMP considered prone to bias, and only of limited value. The proposed increase in sample size with 200 patients was endorsed, considering the provided extrinsic data that point to a longer than previously projected mPFS.

Previous review of the pivotal trial

The pivotal clinical trial ECHELON-1 for the current extension of indication (EoI) application has been reviewed as pivotal trial for the EoI to the treatment of previously untreated CD30+ Stage IV HL as well (II/0055). In this previous EoI, the MAH initially applied for an indication in advanced HL (which is the same as the current proposed target population), as the trial included HL patients with Ann Arbor Stage III and Stage IV. During the 2018 review of the data from the 2017 primary analysis of ECHELON-1, the MAH changed the applied indication to Stage IV cHL, based on interim overall survival (OS) results for patients with Stage III cHL. This 2017 interim OS analysis yielded a hazard ratio in excess of 1 (HR=1.216, 95% CI 0.563 to 2.630).

Results of a second interim analysis (IA2) of OS data (data cut-off 01 June 2021) were reviewed as part of a variation to update SmPC section 4.8 and 5.1 with long-term follow-up data from ECHELON-1 (II/0103). In this procedure, it was concluded that the updated data confirm the benefit of treatment and the safety profile of the A+AVD regimen as was noted at the time of approval of brentuximab vedotin for the treatment of previously untreated CD30+ Stage IV Hodgkin lymphoma (HL).

Based on the same data, the MAH is now seeking an extension of indication in advanced HL, i.e. including Stage III HL patients. This since updated OS results of the second interim analysis in 2021 showed a HR point estimate below 1 in patients with Stage III HL

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The most recent ERA included the current three indications in calculations for environmental exposure. As long as the extension of indication variation does not increase the potential population treated beyond these indications, there is no need for a revised ERA.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

C25003 Phase 3	Open-label, randomized, 2-arm, A+AVD vs ABVD	Efficacy, quality of life, and safety	Advanced classical HL (treatment-naïve)	1.2 mg/kg IV q2wk 6 cycles	modified PFS per IRF	1240/ 1334 (d)	≥18	Nov 2012–	US, Canada, Europe, Asia

2.3.2. Pharmacokinetics

No new pharmacokinetic or pharmacodynamic data have been submitted.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No new dose response studies have been submitted. There are no changes proposed in the current recommended dose for previously untreated patients, i.e. 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 in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]).

2.4.2. Main study(ies)

The pivotal clinical trial ECHELON-1 for the current extension of indication (EoI) application has been reviewed as pivotal trial for the EoI to previously untreated CD30+ Stage IV HL as well (II/0055; please also refer to section 5.1.3). Results of a second interim analysis of OS data were reviewed as part of a variation to update SmPC section 4.8 and 5.1 with long-term follow-up data from ECHELON-1 (II/0103). The study design as well as results for the primary analysis (2017), first OS interim analysis (2017 IA1) and second OS interim analysis (2021 IA2) are for convenience repeated below. In addition, a descriptive analysis of OS is included, which was presented by the MAH in response to a request for supplementary information.

In this variation the applied indication changed to advanced HL and hence the focus of the data shifted from Stage IV patients to the ITT population with advanced Stage III or IV disease.

ECHELON-1 (C25003)

This study is a randomized, open-label, Phase 3 trial to compare the modified progression-free survival (mPFS) obtained with brentuximab vedotin + AVD (Adcetris plus doxorubicin [Adriamycin], vinblastine and dacarbazine, abbreviated A+ AVD) versus that obtained with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) in frontline treatment of adult patients with CD30+ advanced Hodgkin Lymphoma (HL) in combination with chemotherapy.

Methods

Study participants

Patients in this study were to be treatment-naïve, with Ann Arbor Stage III or IV histologically-confirmed classical HL. Other key inclusion and exclusion criteria are described below.

Other key inclusion criteria

- Male or female patients 18 years or older.
- ECOG performance status ≤2.
- Bidimensional measurable disease as documented by radiographic technique (spiral CT scan preferred) per the International Working Group Revised Criteria for Response Assessment for Malignant Lymphoma.
- Clinical laboratory values as specified within 7 days before the first dose of study drug:
    - Absolute neutrophil count (ANC) ≥1,500/μL unless due to known HL marrow involvement.
    - Platelet count ≥75,000/μL unless due to known HL marrow involvement.
    - Total bilirubin must be <1.5×the upper limit of normal (ULN) unless the elevation was known to be due to Gilbert syndrome.
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was required to be <3 ULN. AST and ALT could be elevated up to 5 times the ULN if their elevation could be reasonably ascribed to the presence of HL in liver.
    - Serum creatinine must be <2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance >40 mL/minute.
    - Haemoglobin (Hgb) was required to be ≥8 g/dL.

Key exclusion criteria

- Nodular lymphocyte predominant HL.
- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially have interfered with the completion of treatment according to this protocol.
- Known cerebral or meningeal disease (HL or any other aetiology), including signs or symptoms of progressive multifocal leukoencephalopathy (PML).

- Symptomatic neurologic disease compromising normal activities of daily living or requiring medications.
- Any sensory or motor peripheral neuropathy (PN).
- Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first study drug dose.
- Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy (e.g., immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first study drug dose.
- Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin or any component of ABVD.
- Known human immunodeficiency virus (HIV) positive, hepatitis B surface antigen positive, or known or suspected active hepatitis C infection.
- Diagnosed or treated for another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type were not excluded if they had undergone complete resection.
- Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:
    - A left ventricular ejection fraction <50%
    - Myocardial infarction within 2 years of randomization
    - New York Heart Association (NYHA) Class III or IV heart failure, and
    - Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

Treatments

Patients in this study were randomized 1:1 to receive up to 6 cycles of either A+AVD or ABVD by IV infusion on Days 1 and 15 of each 28-day cycle.

A+AVD: doxorubicin (Adriamycin) 25 mg/m2, vinblastine 6 mg/m2, dacarbazine 375 mg/m2, and brentuximab vedotin (Adcetris) 1.2 mg/kg. Brentuximab vedotin was administered by IV infusion over approximately 30 minutes within approximately 1 hour after completion of AVD therapy.

No routine premedication was required for patients who received A+AVD. However, the use of prophylactic growth factor support was recommended for patients in this treatment arm, according to institutional guidelines beginning with Cycle 1.

ABVD: doxorubicin (Adriamycin) 25 mg/m2, bleomycin 10 units/m2, vinblastine 6 mg/m2, and dacarbazine 375 mg/m2.

Dose modifications

The dose modifications recommended for brentuximab vedotin in response to treatment-related toxicity are presented in Table 1.

Table 1. Study C25003: Recommended Dose Modifications for Brentuximab Vedotin

Toxicity	Grade 2 or Lower		Grade 3 or Higher	
Nonhematologic (excluding neuropathy)	Continued at same doses.		A+AVD was held until toxicity resolved to Grade 2 or lower or returned to baseline. (a)	
Hematologic	Continued at same doses.		For neutropenia, managed with growth factors (G-CSF or GM-CSF) per institutional guidelines. For thrombocytopenia, consider platelet transfusion and/or proceed according to institutional guidelines. For anemia, manage per institutional guidelines.	
Peripheral neuropathy	**Grade 1** Continued at same dose.	**Grade 2** Reduced the dose to 0.9 mg/kg and resumed treatment; if already at 0.9 mg/kg, continued at the same dose.	**Grade 3** Withheld brentuximab vedotin until toxicity was ≤Grade 2, dose reduced to 0.9 mg/kg. If already at 0.9 mg/kg, consulted with sponsor. (AVD could be continued or held concurrently at physician's discretion.)	**Grade 4** Discontinued brentuximab vedotin.

Source: Protocol C25003 Amendment 7 Table 6-1.
A+AVD=brentuximab vedotin +doxorubicin, vinblastine, and dacarbazine, G-CSF=granulocyte-colony stimulating factor, GM-CSF=granulocyte macrophage colony stimulating factor.
(a) Patients who developed clinically insignificant Grade 3 or Grade 4 electrolyte laboratory abnormalities could continue study treatment without interruption.

Co-medication

The following medications and procedures were allowed during the study:

- Radiotherapy: Patients in PR upon completion of frontline chemotherapy with PET results indicative of PET-positive disease could have received radiotherapy.
- The use of topical, inhalational and ophthalmic steroids was permitted.
- Patients were allowed to receive concomitant hormonal therapy provided they had been on a stable dosage for at least 1 month before enrolment.
- The use of platelet and/or red blood cell supportive growth factors or transfusions was allowed when applicable.
- The use of colony stimulating factors (CSFs) for neutropenia was permitted during therapy for patients in both treatment arms according to institutional practice. After enrolment of approximately 70% of study participants the use of prophylactic CSFs for neutropenia was recommended for patients in the A+AVD treatment arm starting with the first treatment cycle 1. This recommendation that was communicated to investigators through a DIL dated 10 April 2015.

A switch to a physician's choice of alternative therapy for the remainder of frontline therapy was permitted at the investigator's discretion after the Cycle 2 CT scan and PET assessment (including those with a Deauville score of 5). A switch to alternative frontline medication (AFM) for other reasons (such as adverse event) was also permitted at the investigator's discretion.

Objectives

The primary objective of the study was to compare the mPFS per IRF assessment obtained with A+AVD to that obtained with ABVD for the frontline treatment of advanced HL.

The key secondary objective was to determine if A+AVD improved OS vs that obtained with ABVD.

Outcomes/endpoints

Primary efficacy endpoint

Modified (m)PFS per IRF assessment using the criteria defined in the Revised Response Criteria for Malignant Lymphoma. *

> mPFS is defined as the time from the date of randomization to the date of the first of (1) documentation of PD; (2) death due to any cause; (3) for patients who failed to achieve a CR per IRF, receipt of subsequent anticancer therapy for HL after completion of frontline therapy. The mPFS event date for these patients was the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a Deauville score of ≥3.

Secondary efficacy endpoints

- Overall survival (OS) was the key secondary endpoint, defined as the time from the date of randomization to the date of death.
- Rate of CR as best overall response achieved at the end of randomized regimen (A+AVD or ABVD) per IRF assessment using the Revised Response Criteria for Malignant Lymphoma.
- Event-free survival (EFS) defined as the time from randomization until any cause of treatment failure: disease progression, premature discontinuation of randomized treatment for any reason, or death due to any cause, whichever occurred first.
- Disease-free survival (DFS) was defined as the time from CR to disease progression or to death from lymphoma or acute toxicity from treatment. Analyses of DFS were performed on the subset of the ITT population who achieved a CR.
- Objective Response Rate (ORR)
- Duration of response (DOR) per IRF assessment. For patients with confirmed response, the duration of response (DOR) is defined as the time between first documentation of objective response (PR or CR) and disease progression.
- Duration of complete response (DOCR) per IRF assessment - In patients with confirmed CR is defined as the time between the first documentation of CR and disease progression.
- Rate of patients not in CR that received irradiation
- CR rate per IRF assessment at the end of frontline therapy.
- The rate of Cycle 2 PET negativity.
- Patient-reported outcomes (PRO) per European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30.
- The presence of antitherapeutic antibodies (ATA) to brentuximab vedotin.

Exploratory efficacy endpoints

- PRO per FACIT-Dyspnea 10 (lung-specific PRO).
- PRO per Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group- Neurotoxicity (FACT/GOG-Ntx) subscale questionnaire (ITT)
- Patient-reported health utility values per EuroQoL (EQ)-5D-3L.

- Utilization of medical resources.
- Percent of patients alive without HL at 3 and 5 years.
- Percent of patients switching therapy after Cycle 2 and before EOT.

* Of note: a sensitivity analysis of PFS by investigator was prespecified as exploratory endpoint.

Sample size

The study is powered on the following assumption: a 2-year mPFS of 81% for patients in the A+AVD treatment group versus 73% for patients in the ABVD treatment group (HR = 0.67, assuming an emergent plateau in the PFS event rate after 2 years). A total of 260 mPFS events will provide 90% power to detect a hazard ratio of 0.67 at a 1-sided significance level of 0.025 using a log-rank test. Approximately 1240 patients will be randomized to achieve (with 95% probability) 260 mPFS events in about 60 months assuming 36 months of accrual, a 5% annual dropout rate, and 24 months of mPFS follow-up after last patient in.

The original sample size was lower (1040 patients), and increased to 1240 patients in protocol amendment 7 in March 2015. The 200 patient increase in sample size was accepted at follow up scientific advice in 2014. During the original design of ECHELON-1, assumptions regarding the expected number of progression events for the control arm were made on the basis of FFS estimates from an intergroup cooperative study comparing ABVD with Stanford V in 404 patients with locally extensive HL. However, aggregate data for 299 patients and a 167-patient dataset for patients with advanced HL from the British Columbia Cancer Agency (BCCA) provided the sponsor with an opportunity to revise projected estimates of the expected mPFS rate for the patient population in ECHELON-1. The statistical modelling with the aggregate data and the 167-patient dataset suggested that an increased sample size of 1240 randomized patients provided a higher than 90% projected probability of accruing 260 mPFS events by 2 years after randomization of the last patient. The revised statistical modelling for ECHELON-1 using the data from the BCCA suggested that approximately 90% of mPFS events occurred within 2 years of the initial diagnosis with an emergent plateau in the PFS event rate after approximately 2 years. A similar trend of few late progression events was noted in published results from other well controlled studies in patients with advanced HL.

Randomisation

Patients were randomized 1:1 to receive either A+AVD or ABVD, with stratification by the number of International Prognostic Factor Project (IPFP) risk factors (0-1 vs 2-3 vs 4-7), and region (Americas vs Asia vs Europe).

Blinding (masking)

This was an open-label study; investigators and patients were not blinded to the individual treatment assignments. However, the sponsor’s study team, investigators, and patients were blinded to aggregate efficacy data throughout the study according to a prespecified blinding procedure. The independent review facility (IRF) was blinded to study treatment assignments.

Statistical methods

Analysis sets

The primary population for efficacy analysis was the intent to treat (ITT) population, which included all randomized patients. The Per-Protocol (PP) population included all randomized patients who do not have a major protocol violation, and will be analysed according to the actual treatment received. The PP population was used as supportive analysis for the primary endpoint.

The response-evaluable population was defined as the subset of the ITT population with diagnosis as confirmed by an independent pathology review facility, with measurable disease at baseline, who receive at least 1 dose of study drug, and have at least 1 post-baseline response assessment. The response-evaluable population was used for the analyses of CR rate, overall response rate, and duration of response.

Analysis methods

Primary hypothesis to be tested:

> The primary null hypothesis is that there is no difference in modified progression-free survival (mPFS) between the 2 treatments of A+AVD and ABVD. The alternative hypothesis is that A+AVD improves mPFS.

Key secondary hypothesis to be tested:

The null hypothesis is that there is no difference in overall survival (OS) between the 2 treatments of A+AVD and ABVD. The alternative hypothesis is that A+AVD improves OS.

Modified PFS was to be tested at a 1-sided significance level of 0.025. The key secondary endpoint was to be tested at 1-sided, 0.025 level only when the test of the primary endpoint (mPFS) is statistically significant.

Interim analysis

Two interim analyses were planned:

- The first formal interim analysis to be performed was a futility analysis. The CR rate at the end of frontline therapy will be analysed when the first approximately 348 patients have completed the regimen to which they were randomized or have discontinued treatment prior to completion. An independent data monitoring committee (IMDC) reviewed safety and efficacy data at the interim analysis.

- The second formal interim analysis for OS was to be performed at the time of the final mPFS analysis. Overall type-I error for OS will be controlled using the O'Brien-Fleming method with a Lan-DeMets alpha spending function, with final OS analysis scheduled for when 112 deaths have occurred (Table 2).

Table 2. Study C25003: Analysis Points

Analysis	Purpose	Trigger	Endpoints Analyzed	Data Cutoff Date
Interim Analysis 1 (IA1)	Futility	355 patients completed [a] or discontinued randomization regimen	CR	2015
Primary Analysis of Primary Endpoint	Superiority	260 mPFS events	mPFS final analysis [b, c] OS interim analysis 1 [c]	2017
Interim Analysis 2 (IA2)	Superiority	103 OS events	OS interim analysis 2 [c] PFS per investigator (exploratory)	2021
Final Analysis of OS	Descriptive	112 OS events or 10 years after last patient randomized (13 January 2026)	OS final analysis [d] PFS per investigator (exploratory)	Not yet triggered; 111 events accrued [e]

Source: ECHELON-1 SAP Amendment 1.

CR, complete remission; IA, interim analysis; mPFS, modified progression-free survival; OS, overall survival.

a Completed randomization regimen with ≤2 missed doses

b Powered analysis

c Type I error control applied

d The final analysis of OS will be descriptive because OS achieved statistical significance at IA2.

e As of 22 February 2023

Primary efficacy endpoint analysis

Final analysis of mPFS was planned to be performed when 260 mPFS events have been observed, which was estimated to occur by 24 months after the last patient is randomized.

Stratified log-rank testing was to be used to compare mPFS between the 2 treatment arms as the primary analysis. The stratification factors included region and number of IPFP risk factors at baseline. The hazard ratios along with the 95% confidence interval (CI; 2-sided) were estimated using the stratified Cox model with treatment as the explanatory variable. The Kaplan-Meier (K-M) survival curves and survival probability at 2 and 3 years along with the 2-sided 95% CIs were provided for each treatment group. In addition, a stratified Cox regression model was used to further evaluate the treatment effects on mPFS after adjusting for some prognostic factors.

Sensitivity analyses were performed for mPFS to evaluate the robustness of treatment effects.

Key secondary endpoint analysis

There were 2 formal analyses planned for OS, an OS interim analysis at the time of the final mPFS analysis, and the OS final analysis when 112 deaths have occurred. OS analysis was based on the ITT population. Overall type I error was controlled using the O'Brien-Fleming method with a Lan-DeMets alpha spending function. Stratified log-rank testing was used to compare OS between the 2 treatment arms. The stratification factors were similar to the primary endpoint analysis.

The hazard ratios along with the 95% CIs (2-sided) were estimated using a stratified Cox regression model. The Kaplan-Meier method was used to estimate the distribution of the OS endpoint for each treatment.

Missing data handling

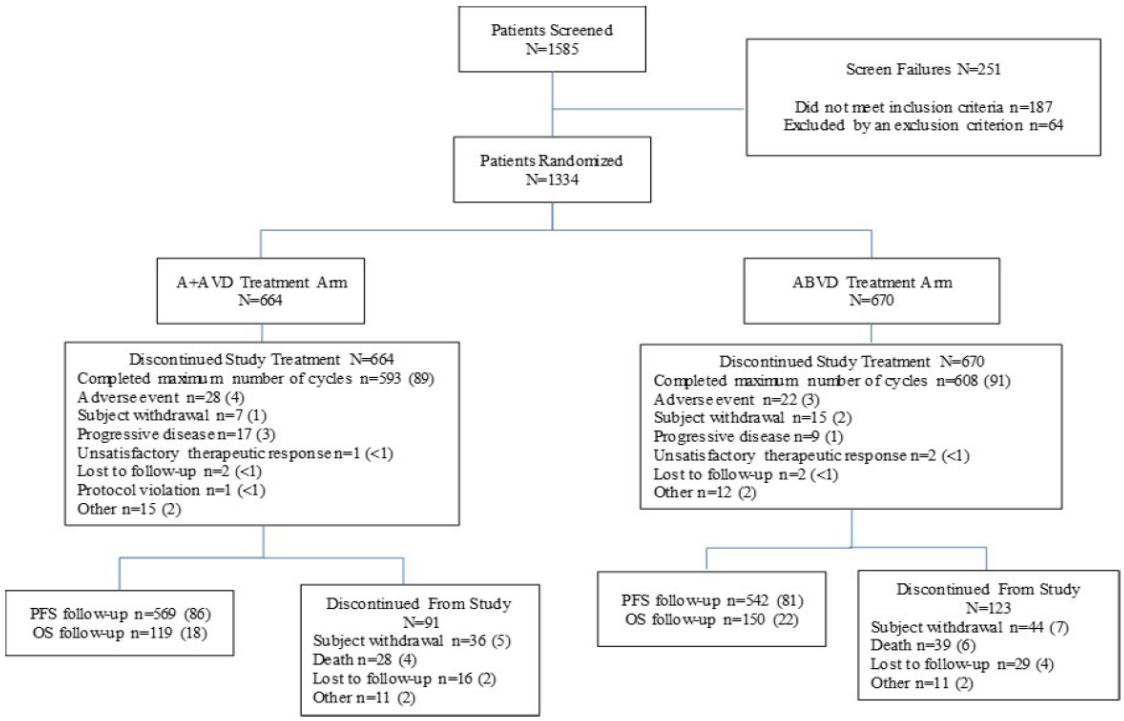
In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For Quality of Life Data, missing elements may be substituted with the average of non-missing items per published methods of analysis.

Results

Participant flow

The planned sample size was 1240 patients, and a total of 1334 patients were actually included in the ITT population and randomized to receive A+ AVD (n=664) or ABVD (n=670). The study was conducted in 218 investigative sites located in 21 countries across 4 regions: Asia Pacific, Europe, Latin America and North America.

As of the previous presented 20 April 2017 data cut-off, a total of 91 A+AVD patients (13%) and 123 ABVD patients (17%) discontinued from the study; for 28 A+AVD patients (4%) and 39 ABVD patients (6%), the reason for study discontinuation was death (Figure 2). The completed maximum number of cycles per protocol was approximately 90% in both arms. This remained similar with the second interim analysis (IA2) in 2021, as all patients had discontinued study treatment at the 2017 primary analysis.



Source: Table 15.1.1.1.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, OS=overall survival, PFS=progression-free survival.

Figure 2 Study C25003: Subject Disposition as of 20 April 2017 Data Cut-off

As of the 01 June 2021 IA2 data cut-off, 103 deaths were reported for the ITT population. On-study death was reported for 9 A+AVD patients (1%) and 13 ABVD patients (2%; Table 3). Death during post-treatment follow-up (PTFU) was reported for 30 A+AVD patients (5%) and 51 ABVD patients (8%). OS follow-up is ongoing for 9% of patients in the A+AVD arm and 11% in the ABVD arm.

Table 3. Study C25003: Overall Disposition (ITT Population), 2021 IA2 data ut-off

Number of patients (%)	A+AVD N=664	ABVD N=670
ITT population [a]	664 (100)	670 (100)
Safety population [b]	662 (100)	659 (98)
Patients Completing Study Treatment Per Protocol *	628 (95)	634 (95)
Completed frontline therapy **	608 (92)	622 (93)
Randomized regimen only	594 (89)	613 (91)
Randomized regimen with AFM	14 (2)	9 (1)
Experienced PD or died before completion of frontline therapy	20 (3)	12 (2)
Primary Reason Off Study Treatment		
Total	664 (100)	670 (100)
Adverse event	28 (4)	22 (3)
Completed maximum number of cycles per protocol	593 (89)	607 (91)
Lost to follow-up	2 (<1)	2 (<1)
Progressive disease	17 (3) (g)	10 (1)
Protocol violation	1 (<1)	0
Unsatisfactory therapeutic response	1 (<1)	2 (<1)
Withdrawal by patient	7 (1)	15 (2)
Other	15 (2)	12 (2)
Patients who have participated in PFS follow-up	572 (86)	544 (81)
Patients who have participated in OS follow-up	155 (23)	189 (28)
Patients currently in PFS follow-up	335 (50)	277 (41)
Patients currently in OS follow-up	59 (9)	73 (11)
Death	39 (6)	64 (10)
On-study death [c]	9 (1)	13 (2)
Death during PTFU [d]	30 (5)	51 (8)
Reason For End of (Discontinuation From) Study		
Total	270 (41)	320 (48)
Lost to follow-up	81 (12)	95 (14)
Withdrawal by patient	131 (20)	143 (21)
Death	39 (6)	64 (10)
Other	19 (3)	18 (3)

Source: T15.1.1.1.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; AFM: alternate frontline medication; HL: Hodgkin lymphoma; ITT: intent-to-treat; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PTFU: posttreatment follow-up. All percentages are based on the number of patients in the ITT population.

* Patients were considered to have completed study treatment per protocol if they completed frontline treatment or experience PD per investigator or died before completion of frontline treatment.

** Completion of frontline treatment was defined as: upon receipt of planned study drug regimen with no more than 2 missed doses of A+AVD or ABVD, or upon conclusion of 1 alternative anticancer regimen for HL subsequent to A+AVD or ABVD discontinuation.

[a] ITT population was defined as patients who were randomized to treatment.

[b] Safety population was defined as all enrolled patients who received at least 1 dose of study medication.

[c] On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.

Recruitment

First patient enrolled: 9 November 2012

Last patient assessed for primary analysis: 20 April 2017 (primary analysis, first OS interim analysis)

Clinical database lock: 12 June 2017

Second OS interim analysis: 01 June 2021

The study is ongoing with patients continuing to be followed during post-treatment follow-up until 10 years from the randomization date of the last patient.

Conduct of the study

Study protocol amendments

The original protocol was dated 29 March 2012, and subsequently amended 9 times. Key changes are described below:

Protocol amendment 1 (12 May 2012 , no patients enrolled under this amendment)

- Changed the mPFS event date for patients who receive subsequent anticancer chemotherapy in absence of disease progression. The mPFS event will be recorded as occurring on the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a Deauville score of ≥3.
- Specified that Deauville scoring must be performed for the EOT PET scan and any unscheduled PET scan to support objective determination of mPFS.

Protocol amendment 3 (13 Jul 2012 , no patients enrolled)

- Changed the scheduled timing of the Cycle 2 PET/CT scan to Day 25 (± 1 day).

Protocol amendment 4 (3 Aug 2012 , 615 patients enrolled)

- Allow sites' determination of PET positivity to guide additional radiotherapy for noncomplete responders at the conclusion of frontline therapy, and allow radiation to be given for patients with PET-positive residual masses of any size instead of only those with masses of 2.5 cm or larger.
- Clarify that, unless otherwise specified, only those SAEs that occur during long term follow-up that are considered related to study drug (instead of 'frontline therapy') will be reported.

Protocol amendment 5 (6 Feb 2014 , 1 patient enrolled)

- Add acute pancreatitis and hepatotoxicity to the discussion of potential risks associated with brentuximab vedotin.

Protocol amendment 6 (27 May 2014, 536 patients enrolled)

- Remove the exclusion criterion pertaining to pulmonary diffusion capacity.

Protocol amendment 7 (2 Mar 2015, 182 patients enrolled)

- Increase the sample size by 200 patients to a total of approximately 1240 patients, and increase the anticipated enrollment period.
- Increase enrollment to 620 patients per arm, and increase the estimated number of sites to 250 globally.
- Align the timing of interim OS analysis with final mPFS analysis
- Revise timing of final OS analysis.

Protocol amendment 9 (24 Sep 2021, enrolment complete/ no patients enrolled)

- *Added a second interim analysis of OS with alpha spending after 103 deaths were reported.*

Changes in the SAP

A revised statistical analysis plan (SAP) was submitted in conjunction with protocol amendment 7. The revised SAP described the rationale for the increase in the planned number of randomized patients and the revised assumptions pertaining to the analysis of the primary endpoint, mPFS.

Changes in analyses

A number of additional subgroup analyses not described in the SAP were added to the prespecified analyses in June 2016, approximately 1 year before clinical database lock, without knowledge of the treatment effect in efficacy data. These included mPFS per IRF and mPFS per investigator by age dichotomized around 45 and 65 years, ECOG performance status score 0 vs 1 vs 2, and gender (male vs female).

Protocol compliance

The major protocol deviations identified in the study as of the primary analysis data cut-off 20 April 2017 fell into 2 categories:

- Patients who were enrolled in the study even though they did not satisfy eligibility criteria (n=4 in A+ AVD arm vs. n=12 in ABVD arm).
- Patients who received incorrect treatment or dose of the study drug(s) n=9 in A+AVD arm vs. n=2 in ABVD arm).

No deviations were identified relating to patients receiving excluded medication or not being discontinued from the study despite study withdrawal criteria being met.

Baseline data

Patient demographics were generally balanced between the two treatment arms (Table 4). In the ITT population, a slightly higher proportion of patients was male (~58% in both arms), most patients were white (~83%) and not Hispanic or Latino (86%). The median age was ~36 years.

Table 4 Study 25003: Demographics (ITT population)

	A+AVD N=664	ABVD N=670
Sex n (%)		
Male	378 (57)	398 (59)
Female	286 (43)	272 (41)
Ethnicity n (%)		
Hispanic or Latino	51 (8)	55 (8)
Not Hispanic or Latino	571 (86)	577 (86)
Not reported	42 (6)	38 (6)
Race n (%)		
White	560 (84)	554 (83)
Asian	56 (8)	57 (9)
Korean	23 (3)	22 (3)
Japanese	10 (2)	12 (2)
Asian Indian	8 (1)	9 (1)
Chinese	9 (1)	7 (1)
Other	4 (<1)	4 (<1)
Not reported	2 (<1)	3 (<1)
Black or African American	20 (3)	25 (4)
Other	18 (3)	17 (3)
Not reported	10 (2)	17 (3)
Age, years (a)		
n	664	670
Mean (std dev)	38.8 (15.83)	40.2 (16.05)
Median	35.0	37.0
Min, max	18, 82	18, 83
Age categories, years, n (%) (a)		
<45	451 (68)	423 (63)
45-59	129 (19)	145 (22)
60-64	24 (4)	40 (6)
≥65	60 (9)	62 (9)
Weight, kg		
n	663	669
Mean (std dev)	73.59 (17.777)	76.52 (20.473)
Median	71.00	72.80
Min, max	41.0, 165.5	39.0, 181.2
Missing	1	1

Source: Table 15.1.1.2.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, ITT=intent-to-treat, max=maximum, min=minimum, std dev=standard deviation.
(a) Age on date of informed consent.

The demographic characteristics of patients in the ITT population with extranodal involvement, Stage III disease or Stage IV disease were comparable with that of the ITT population as a whole.

Baseline disease characteristics were generally balanced between the 2 treatment arms in the ITT population (Table 5). The initial time since diagnosis was <1 month in both arms, and the majority of patients had nodular sclerosis classical HL (~61%), with Ann Arbor Stage IV at diagnosis (~63%). The majority of patients had at least 2 IPFP risk factors (~78%), and an ECOG performance score of 0 (57%) or 1 (39%).

Table 5 Study C25003: Baseline Disease Characteristics (ITT population)

	A+AVD N=664	ABVD N=670
Time since initial diagnosis, months (a)		
n	662	659
Mean (std dev)	1.09 (1.12)	1.18 (3.34)
Median	0.92	0.89
Min, max	0.1, 21.4	0.0, 81.4
Missing	2	11
Disease type		
Hodgkin lymphoma (HL)	661 (100)	664 (99)
Nodular lymphocyte predominant Hodgkin lymphoma	0	0
Classical Hodgkin lymphoma (b)	144 (22)	140 (21)
Nodular sclerosis classical Hodgkin lymphoma	425 (64)	386 (58)
Lymphocyte-rich classical Hodgkin lymphoma	12 (2)	20 (3)
Mixed-cellularity classical Hodgkin lymphoma	78 (12)	111 (17)
Lymphocyte-depleted classical Hodgkin lymphoma	2 (<1)	7 (1)
Other (c)	3 (<1)	6 (<1)
Ann Arbor Stage at initial diagnosis n (%)		
Stage II (d)	1 (<1)	0
Stage III	237 (36)	246 (37)
Stage IV	425 (64)	421 (63)
Not applicable	1 (<1)	1 (<1)
Missing	0	2
Number of IPFP risk factors		
0-1	141 (21)	141 (21)
2-3	354 (53)	351 (52)
4-7	169 (25)	178 (27)
ECOG performance status n (%)		
0	376 (57)	378 (57)
1	260 (39)	263 (39)
2	28 (4)	27 (4)
Missing	0	2
Bone marrow involvement at initial diagnosis or study entry n (%)		
Yes	147 (22)	151 (23)
No	502 (76)	509 (76)
Unknown	15 (2)	9 (1)
Missing	0	1

Evidence of extranodal involvement at initial diagnosis n (%)		
Yes	411 (62)	416 (62)
1 extranodal site	217 (33)	223 (33)
>1 extranodal sites	194 (29)	193 (29)
No	217 (33)	228 (34)
Unknown	36 (5)	25 (4)
Missing	0	1
B Symptoms (e)		
Number of patients with any B symptom, n (%)	400 (60)	381 (57)
Unexplained weight loss of >10% of the body weight n (%)		
Yes	206 (31)	185 (28)
No	457 (69)	483 (72)
Not done/missing	1 (<1)	2 (<1)
Unexplained, persistent, or recurrent fever with temperatures >38°C n (%)		
Yes	167 (25)	178 (27)
No	496 (75)	490 (73)
Not done/missing	1 (<1)	2 (<1)
Recurrent drenching night sweats n (%)		
Yes	336 (51)	307 (46)
No	327 (49)	361 (54)
Not done/missing	1 (<1)	2 (<1)

Source: C25003 Table 15.1.1.3.
Percentages are based on nonmissing values in the ITT population in each column.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, cHL=classical Hodgkin lymphoma, ECOG=Eastern Cooperative Oncology Group, IPFP=International Prognostic Factor Project, ITT=Intent-to-Treat, max=maximum, min=minimum, NOS=not otherwise specified, std dev=standard deviation.
(a) Time since initial diagnosis=(first dose date of study drug – date of initial diagnosis)/30.4375.
(b) Classical Hodgkin lymphoma included patients who were diagnosed with cHL NOS.
(c) Patients whose initial diagnosis was HL, then subsequently found to have been misdiagnosed.
(d) Stage II disease was captured as a protocol violation.
(e) Patients who present with a B symptom for ≥ 1 visit prior to the start of study drug administration.

Concomitant medication

A higher use of myeloid growth factors was reported for the A+AVD patients possibly as concomitant medication or secondary prophylaxis for neutropenia. At least 1 myeloid growth factor (immunostimulant) was reported as a concomitant medication for 536 A+AVD patients (81%) and 373 ABVD patients (57%). Filgrastim was the most commonly reported growth factor for patients in both treatment arms, and was reported for 405 A+AVD patients (61%) and 286 ABVD patients (43%).

Numbers analysed

Primary and secondary efficacy analysis were based on the ITT analysis set, defined as all 1334 randomized patients. A summary of all study populations is provided in Table 6.

Table 6 Study C25003: Study Populations

	A+AVD N=664 n (%)	ABVD N=670 n (%)	Total N=1334 n (%)
Intent-to-Treat (ITT) population (a)	664 (100)	670 (100)	1334 (100)
Per-Protocol (PP) population (b)	650 (98)	652 (97)	1302 (98)
Response-Evaluable population (c)	643 (97)	642 (96)	1285 (96)
Safety population (d)	662 (100)	659 (98)	1321 (99)
Patients Completing Study Treatment Per Protocol*	628 (95)	634 (95)	1262 (95)
Completed frontline therapy**	608 (92)	622 (93)	1230 (92)
Randomized regimen only	594 (89)	613 (91)	1207 (90)
Randomized regimen with alternate frontline regimen	14 (2)	9 (1)	23 (2)
Experienced PD or died before completion of frontline therapy	20 (3)	12 (2)	32 (2)

Outcomes and estimation

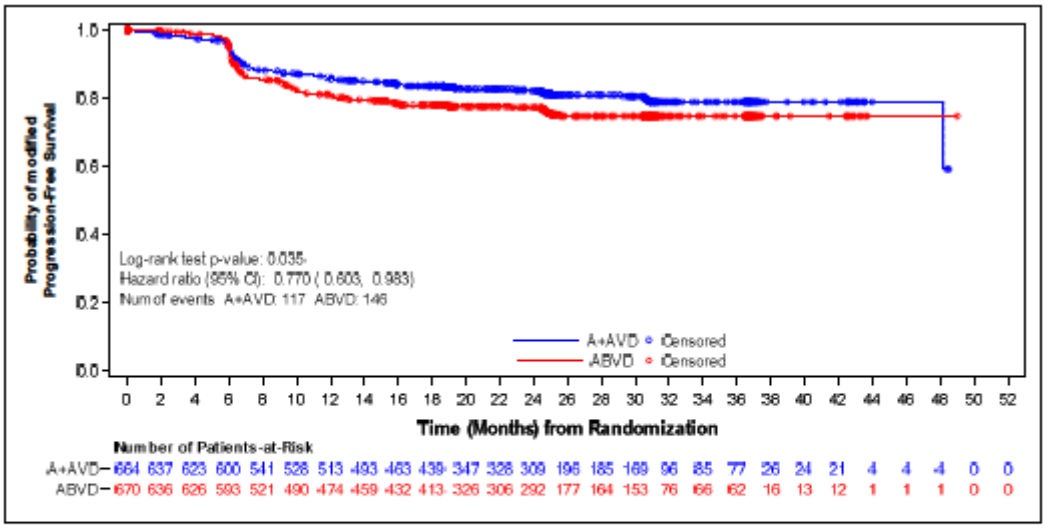
Primary endpoint – modified Progression-Free Survival per IRF

Primary analysis - As of the 20 April 2017 data cut-off date for the primary analysis of the primary endpoint, median mPFS was not reached in either treatment arm. At this time, 117 mPFS events had been observed in the A+AVD arm and 146 mPFS events had been observed in the ABVD arm. A+AVD was associated with a 23.0% reduction in the risk of an mPFS event versus ABVD (HR=0.770; 95% CI, 0.603-0.983). This improvement was statistically significant (p=0.035). The proportion of patients free from an mPFS event at 2 years after randomization was 82.1% in the A+AVD arm versus 77.2% in the ABVD arm (95% CI, 78.8-85.0% versus 73.7-80.4%; Table 7; Figure 3).

Table 7 Study C25003: Modified PFS per IRF Response Assessment (ITT population)

	A+AVD N=664	ABVD N=670
mPFS, months		
Number with events (%)	117 (18)	146 (22)
Reason leading to mPFS event		
Progressive disease	90 (14)	102 (15)
Death due to any cause	18 (3)	22 (3)
Receipt of additional therapy after non-CR (a)	9 (1)	22 (3)
Number censored (%)	547 (82)	524 (78)
25th percentile (95% CI)	48.2 (30.9, NE)	25.6 (15.8, NE)
Median (95% CI)	NE (48.2, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (48.2, NE)	NE (NE, NE)
Min, max	0.0*, 48.5*	0.0*, 49.0*
Hazard Ratio (95% CI)(b)	0.770 (0.603, 0.983)	
P-value	0.035	
Kaplan-Meier estimates (95% CI) (c)		
1 Year	85.8 (82.8, 88.3) [n=513]	80.7 (77.4, 83.6) [n=474]
2 Years	82.1 (78.8, 85.0) [n=309]	77.2 (73.7, 80.4) [n=292]
2.5 Years	80.4 (76.8, 83.6) [n=169]	74.7 (70.8, 78.2) [n=153]
3 Years	78.8 (74.8, 82.3) [n=77]	74.7 (70.8, 78.2) [n=62]
Median mPFS follow up (months) (d)	24.6	24.6
(95% CI)	(24.44, 24.84)	(24.48, 24.87)
Reason for censoring		
No Baseline and/or no post-Baseline assessment	11 (2)	24 (4)
mPFS event after more than 1 missed visit	1 (<1)	3 (<1)
Treatment discontinuation for undocumented disease progression	4 (<1)	4 (<1)
Loss to follow-up	14 (2)	22 (3)
Withdrawal by subject	24 (4)	24 (4)
No documented mPFS event	493 (74)	447 (67)

Source: Module 2.7.3 – ECHELON-1, Table 3.g.
* indicates a censored observation.
mPFS per IRF assessment was defined as the time from the date of randomization to the date of the first of (1) documentation of progressive disease by IRF overall response assessment; (2) death due to any cause; (3) for patients who are confirmed noncomplete responders per IRF, receipt of anticancer chemotherapy or radiotherapy for HL after completion of frontline therapy, as defined in the SAP Table 5-1; these patients' mPFS event date was the date of the first PET scan post completion of frontline therapy demonstrating the absence of a CR, defined as a Deauville score of ≥3. Detailed definitions of the censoring rules are provided in the SAP Table 5-2.
p-value was calculated using stratified log-rank test to compare mPFS between the 2 treatment arms. Stratification factors included region and number of IPFP risk factors at Baseline.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, IRF=independent review facility, IPFP=International Prognostic Factor Project, mPFS=modified progression-free survival, NE=not estimable.
(a) Confirmed noncomplete responders with receipt of additional anticancer treatment after completion of frontline therapy.
(b) Hazard ratio (A+AVD/ABVD region and number of IPFP risk factors at Baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD arm.
(c) Based on Kaplan-Meier product limit estimates [n=number of subjects at risk].
(d) Median mPFS follow-up is calculated from the Kaplan-Meier method, switching the mPFS event/censored status, ie, mPFS event as censored and censored as mPFS event.



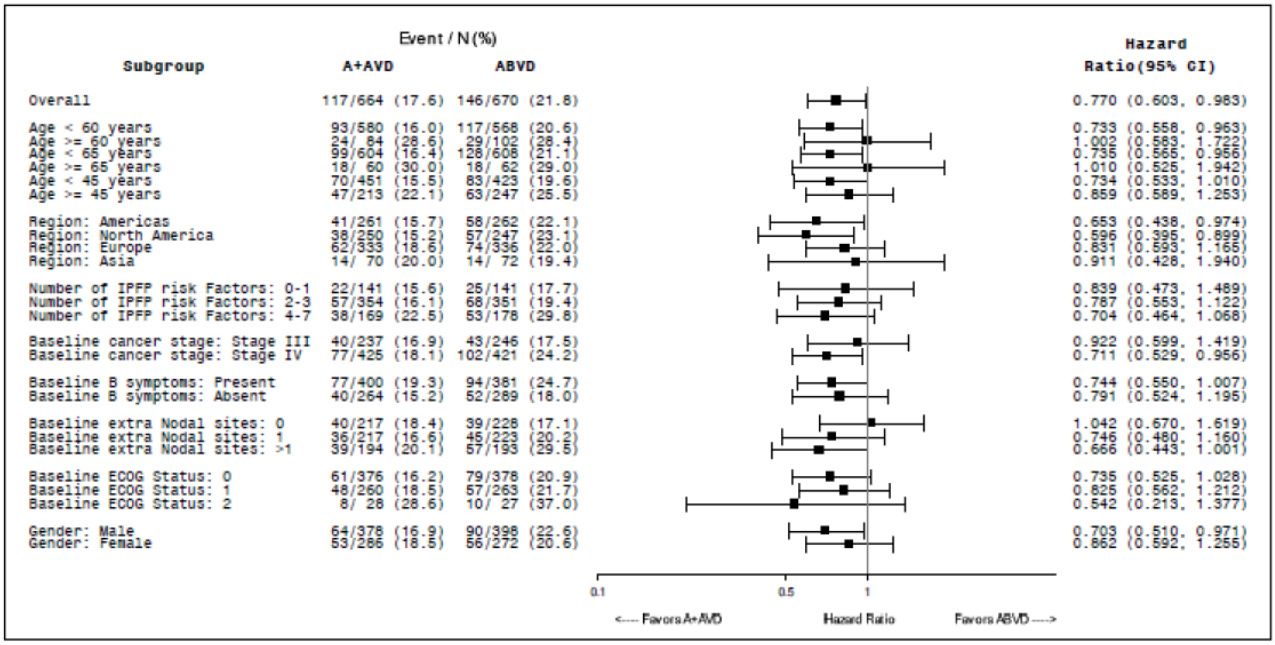
Source: Figure 15.2.4.1.
Hazard ratio (A+AVD/ABVD) and 95% CI were based on a stratified Cox's proportional hazard regression model with stratification factors region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD arm.
A+AVD=brentuximab vedotin (Adcetris) plus AVD (doxorubicin [Adriamycin], vinblastine, and dacarbazine), ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, CI=confidence interval, IPFP=International Prognostic Factor Project, IRF=independent review facility, mPFS=modified progression-free survival.

Figure 3 Study C25003: KM Plot of mPFS per IRF Assessment (ITT)

Sensitivity analyses of mPFS in which 'treatment discontinuation for undocumented disease progression after the last adequate assessment' or 'an event after more than 1 missed visit' were considered events were consistent with the primary analysis. This also applied to mPFS per investigator and additional sensitivity analyses investigating alterations in handling of missing assessments and censoring. PFS by investigator for Stage III patients was 0.766 (0.507, 1.156; p=0.203) and for Stage IV patients 0.705 (0.530, 0.937; p=0.016)

Subgroup analyses at the time of the 2017 primary analysis generally supported the primary endpoint. For patients ≥65 years of age (N=122; HR=1.010; 95% CI: 0.525, 1.942) patients ≥60 years of age (N=186; HR=1.002; 95% CI: 0.583, 1.722), and patients without extranodal disease at baseline (N=445; HR=1.042; 95% CI: 0.670, 1.619) the HR point estimate was around 1 (Figure 4).

For patients with Stage III disease, the mPFS per IRF HR was 0.922 (95% CI: 0.599, 1.419; p=0.712) and for patients with Stage IV disease, the unstratified HR was 0.711 (95% CI: 0.529, 0.956; p=0.023).



Source: C25003 Figure 15.2.3.3.

The following prespecified subset analyses were not included in the statistical analysis plan: age dichotomized around 45 and 65, ECOG status 0 vs 1 vs 2, and gender. The hazard ratio (A+AVD/ABVD) and 95% CI are based on an unstratified Cox's proportional hazard regression model with treatment as the explanatory variable. A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, CI=confidence interval, IRF=independent review facility, NE=not estimable.

Figure 4. Forest plot of mPFS per IRF assessment by baseline risk factor subgroup (ITT, primary analysis 2017)

2021 data cut-off – not performed for mPFS per IRF, due to discontinuation of independent review. Results of a prespecified sensitivity analysis of PFS per investigator are described below.

Sensitivity analysis 2021 data cut-off: PFS per investigator

As of the 2021 analysis, median PFS per investigator was not estimable (NE) for either treatment arm. The stratified HR was 0.678 (95% CI, 0.532-0.863, descriptive 2-sided p=0.002 based on a stratified log rank test; Table 8, Figure 5). Results showed a difference in the estimated PFS rate of 6.9% at 60 months and 7.8% at 72 months for A+AVD patients compared with ABVD patients.

Table 8. Study C25003: PFS per Investigator (ITT Population)

	A+AVD N=664	ABVD N=670
PFS, months		
Number with events (%)	112 (17)	159 (24)
Number censored (%)	552 (83)	511 (76)
25th percentile (95% CI)	NE (NE, NE)	66.0 (30.5, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 100.6*	0.0*, 97.9*
Hazard ratio (95% CI) [a]	0.678 (0.532, 0.863)	
P-value	0.002	
Kaplan-Meier estimates, % (95% CI) [b]		
48 months	82.7 (79.5, 85.4) [n=463]	76.3 (72.8, 79.5) [n=414]
60 months	82.3 (79.1, 85.0) [n=428]	75.4 (71.8, 78.6) [n=371]
72 months	82.3 (79.1, 85.0) [n=305]	74.5 (70.8, 77.7) [n=245]
84 months	82.3 (79.1, 85.0) [n=86]	74.5 (70.8, 77.7) [n=67]
Median PFS follow-up, months (95% CI) [c]	73.2 (72.48, 74.05)	71.6 (70.37, 72.87)
Reason leading to PFS event		
Progressive disease	96 (14)	129 (19)
Death due to any cause	16 (2)	30 (4)
Reason for censoring, n (%)		
No baseline and/or no postbaseline assessment	9 (1)	22 (3)
PFS event after more than 1 missed visit	10 (2)	8 (1)
Treatment discontinuation for undocumented PD	0	0
Lost to follow-up	73 (11)	72 (11)
Withdrawal by patient	98 (15)	101 (15)
No documented PFS event	362 (55)	308 (46)

Source: T15.2.5.2.

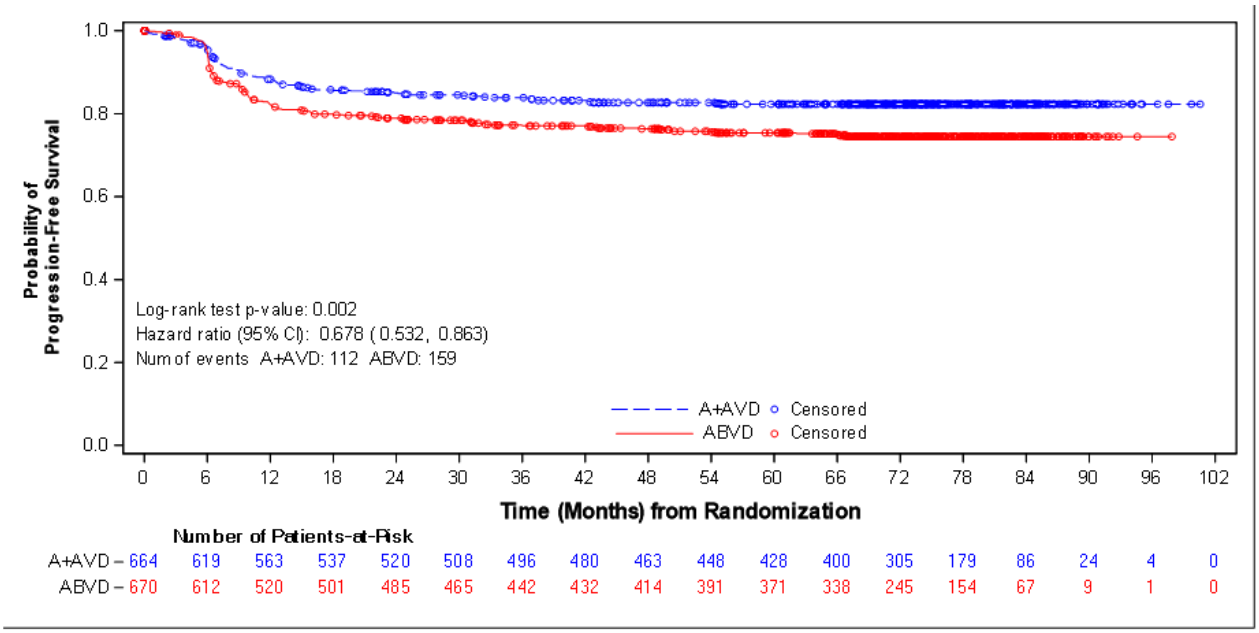
A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; NE: not estimable; PFS: progression-free survival; PFSINV: PFS per investigator assessment.

P-value was calculated using stratified log-rank test to compare PFS between the 2 treatment arms. The stratification factors included region and number of IPFP risk factors at baseline.

[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on a stratified Cox's proportional hazard regression model with stratification factors region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD patients.

[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].

[c] Median PFS follow-up was calculated from the Kaplan-Meier method switching the PFSINV event/censored status, ie, PFSINV event as censored and censored as PFSINV event.



Source: F15.2.5.2.

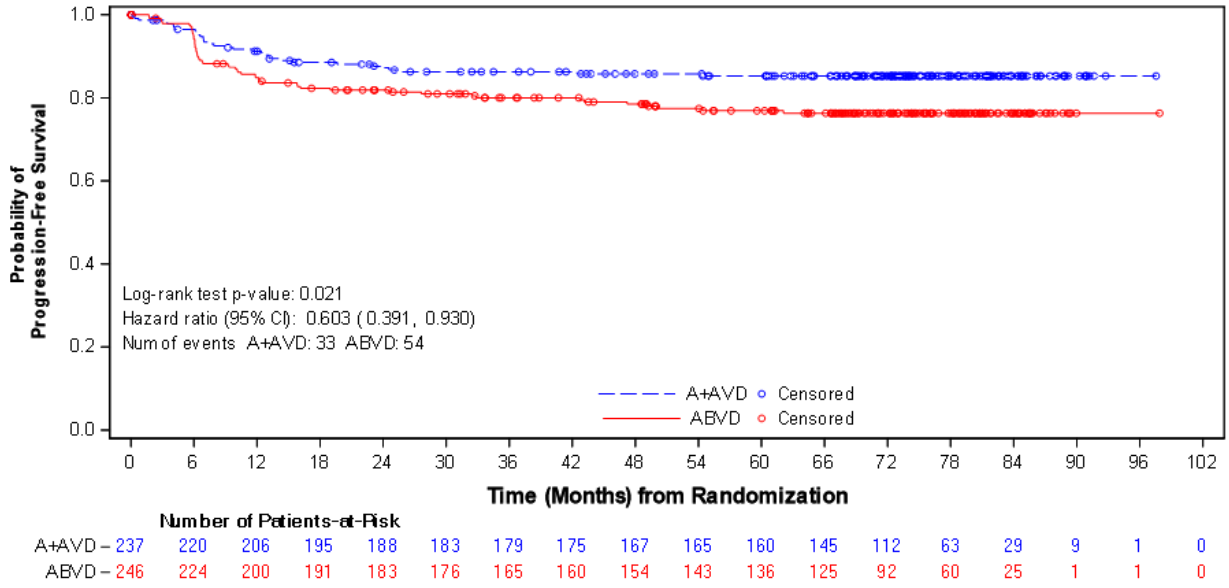
A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; K-M: Kaplan-Meier; NE: not estimable; PFS: progression-free survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on a stratified Cox's proportional hazard regression model with the stratification factors, region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD arm.

Figure 5. Study C25003: K-M Plot of PFS per Investigator (ITT Population)

PFS per investigator for patients with Stage III cHL at Baseline – 2021 data cut-off

In total 237 patients in the A+ AVD arm and 246 patients in the ABVD arm had Stage III cHL at baseline. By investigator assessment, median PFS was NE for patients across the 2 treatment arms for Stage III cHL patients (Figure 6). The unstratified HR was 0.603 (95% CI, 0.391-0.93; descriptive p=0.021).



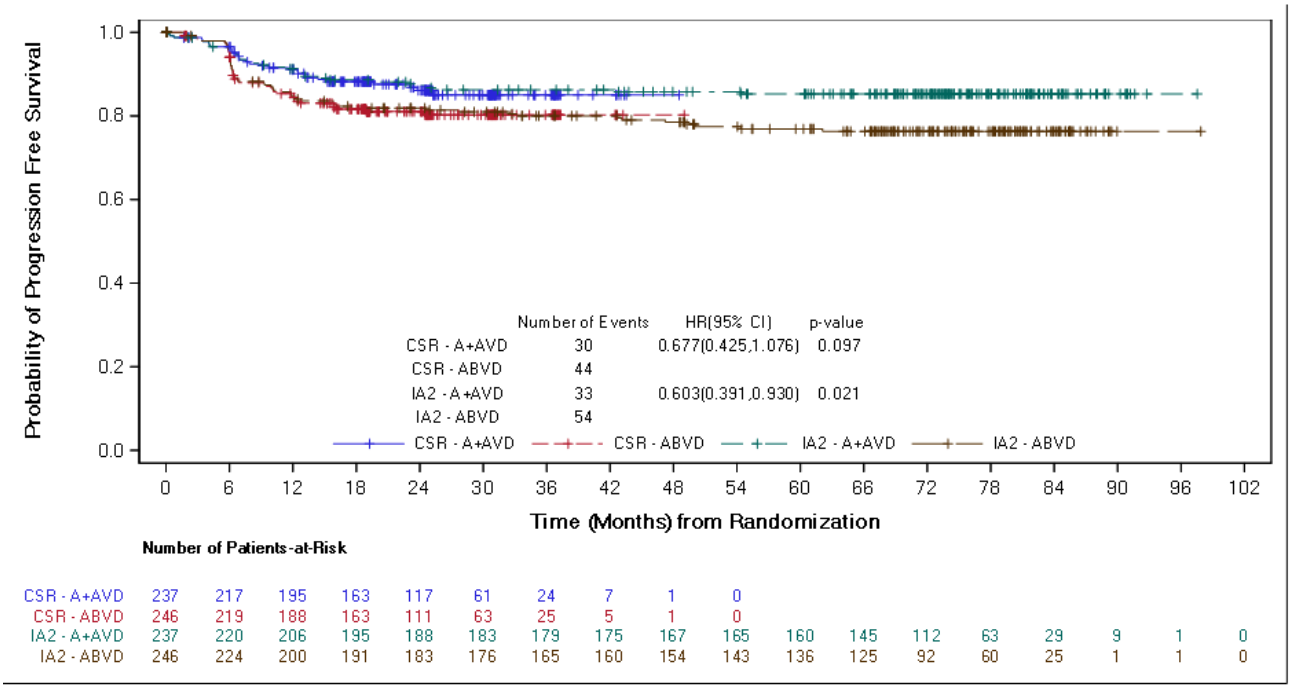
Source: F15.2.5.3a.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; ITT: intent-to treat; K-M: Kaplan-Meier; PFS: progression-free survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patents.

Figure 6. Study C25003: K-M Plot of PFS per Investigator (ITT Population; Stage III cHL at Baseline)

In Figure 7, overlays are shown of the 2017 and 2021 KM-curves for PFS per investigator for patients with Stage III cHL.

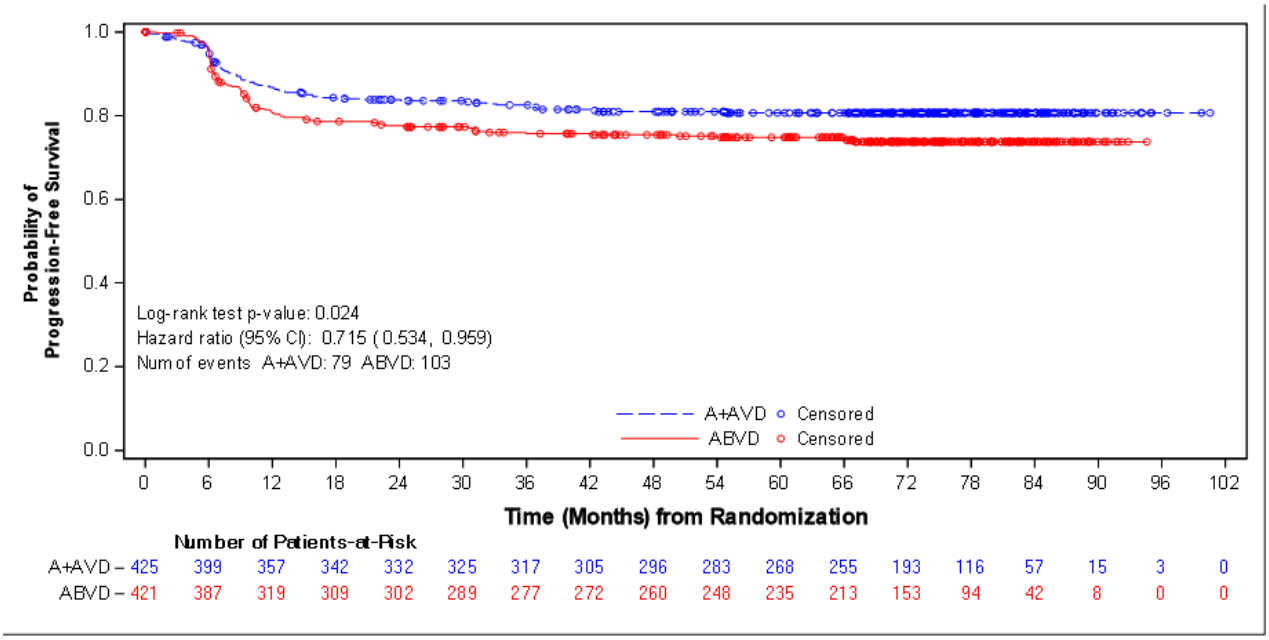


Source: Figure 99.2.9.1A, data cutoffs 20 April 2017 and 01 June 2021.
Hazard ratio (A+AVD/ABVD) and 95% CI based on unstratified Cox's proportional hazard regression model.
Hazard ratio <1 favors A+AVD arm.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CSR, clinical study report 2017 primary endpoint analysis; IA2, interim analysis 2 long-term follow up 2021 analysis as of 103 deaths.

Figure 7. ECHELON-1: PFS per Investigator at Primary Analysis vs. Interim Analysis 2 (IA2) (ITT Subset with Stage III HL)

PFS per investigator for patients with Stage IV cHL at Baseline

In total 425 patients in the A+ AVD arm and 421 patients in the ABVD arm had Stage IV cHL at baseline By investigator assessment, median PFS was NE (endpoints of the 95% CI NE) for either subgroup of A+AVD or ABVD Stage IV cHL patients (Figure 8). The unstratified HR was 0.715 (95% CI, 0.534 0.959; descriptive p=0.024)



Source: F15.2.5.3b.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; ITT: intent-to treat; K-M: Kaplan-Meier; PFS: progression-free survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patents.

Figure 8. Study C25003: K-M Plot of PFS per Investigator (ITT Population; Stage IV cHL at Baseline)

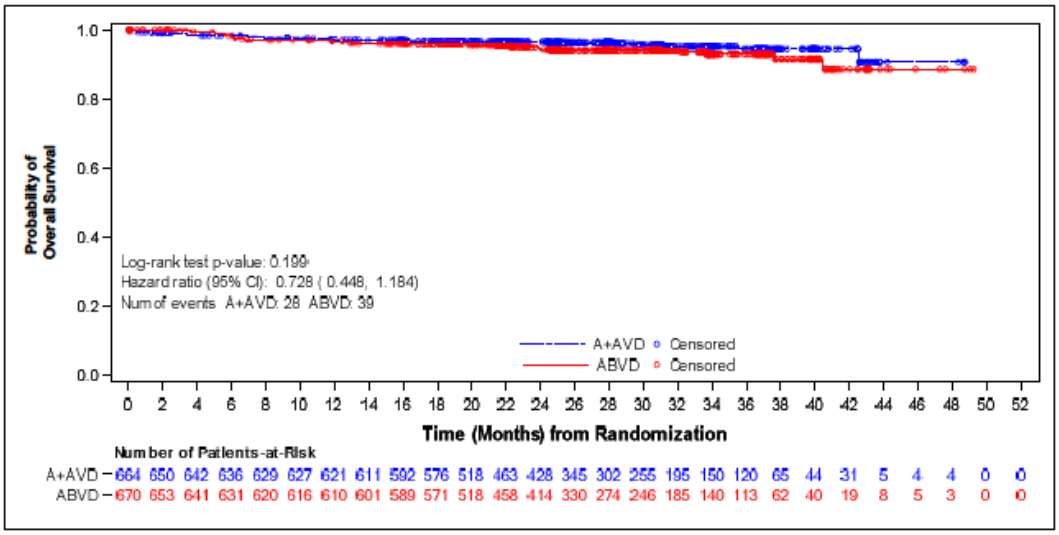
Key secondary endpoint OS

2017 IA1 ITT population- After a median follow-up of approximately 28 months, 28 deaths (4%) were reported in the A+AVD treatment arm and 39 deaths (6%) in the ABVD treatment arm. Median OS was not reached for either treatment arm (Figure 9). The stratified HR was 0.728, (95% CI, 0.448; 1.184), with statistical significance not met (p=0.199). The estimated OS rate was 96.6% for the A+AVD patients vs 94.2% for ABVD patients at 2 years; and 94.4% for A+AVD patients vs 92.9% for ABVD patients at 3 years. A forest plot with OS subgroup analysis was not yet presented at the 2017 IA1.

Table 9. Study C25003: OS at the 2017 IA1 (ITT Population)

	A+AVD N=664	ABVD N=670
OS, months		
Number with events (%)	28 (4)	39 (6)
Number censored (%)	636 (96)	631 (94)
Reason for censoring		
End of study	61 (9)	81 (12)
Lost to follow up	16 (2)	27 (4)
Withdrawal by subject	34 (5)	44 (7)
Other	11 (2)	10 (1)
Still alive at date of last contact	575 (87)	550 (82)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, max	0.0*, 48.8*	0.0*, 49.2*
Hazard ratio (95% CI) (a)	0.728 (0.448, 1.184)	
P-value	0.199	
Kaplan-Meier estimates (95% CI) (b)		
1 Year	97.2 (95.7, 98.3) [n=621]	96.7 (95.0, 97.9) [n=610]
2 Years	96.6 (94.8, 97.7) [n=428]	94.2 (92.0, 95.9) [n=414]
2.5 Years	95.6 (93.5, 97.1) [n=255]	94.0 (91.7, 95.7) [n=246]
3 Years	94.4 (91.4, 96.4) [n=120]	92.9 (90.0, 95.0) [n=113]
Median OS follow-up, months (95% CI) (c)	27.8 (25.99, 28.09)	27.4 (25.53, 27.83)

Source: Table 15.2.9.1.
* indicates a censored observation.
p-value was calculated using stratified log-rank test to compare OS between the 2 treatment arms. The stratification factors included region and number of IPFP risk factors at baseline.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, HR=hazard ratio, IPFP=International Prognostic Factor Project, ITT=intent-to-treat, max=maximum, min=minimum, NE=not estimable, OS=overall survival.
(a) Hazard ratio (A+AVD/ABVD) and 95% CI were based on a stratified Cox's proportional hazard regression model with stratification factors region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model.
(b) Based on Kaplan-Meier product limit estimates [n=number of subjects at risk].
(c) Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, i.e. OS event as censored and censored as OS event.



Source: Figure 15.2.9.1
Hazard ratio (A+AVD/ABVD) and 95% CI was based on a stratified Cox's proportional hazard regression model with stratification factors region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD arm.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, ITT=intent-to-treat, OS=overall survival.

Figure 9. Study C25003: KM-Plot of OS at the 2017 IA1 (ITT population)

2021 IA2 ITT population - After a median follow-up of approximately 73 months, 39 deaths (6%) were reported in the A+ AVD treatment arm and 64 deaths (10%) in the ABVD treatment arm (Table 10, Figure 10). Median OS was not reached for either treatment arm. The stratified OS HR was 0.59 (95% CI, 0.396-0.879), corresponding to a 41% reduction in the risk of death for A+AVD patients compared with ABVD patients. Results met statistical significance based on the stratified log-rank test and the prespecified boundary determined by O'Brien-Fleming method with a Lan-DeMets alpha spending function (p=0.009).

Table 10. Study C25003: OS (ITT Population), 2021 IA2

	A+AVD N=664	ABVD N=670
OS, months		
Number with events (%)	39 (6)	64 (10)
Number censored (%)	625 (94)	606 (90)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 100.6*	0.0*, 97.9*
Hazard ratio (95% CI) [a]	0.59 (0.396, 0.879)	
P-value	0.009	
Kaplan-Meier estimates (95% CI) [b]		
48 months	94.9 (92.9, 96.4) [n=538]	92.1 (89.7, 94.0) [n=505]
60 months	94.8 (92.7, 96.2) [n=494]	91.2 (88.6, 93.2) [n=454]
72 months	93.9 (91.6, 95.5) [n=350]	89.4 (86.6, 91.7) [n=308]
84 months	93.3 (90.7, 95.2) [n=97]	88.7 (85.6, 91.1) [n=84]
Median OS follow-up, (95% CI) months [c]	73.3 (72.61, 74.05)	72.4 (71.10, 73.63)
Reason leading to OS event		
Death due to any cause	39 (6)	64 (10)
Reason for censoring, n (%)		
End of study	210 (32)	234 (35)
Lost to follow-up	65 (10)	76 (11)
Withdrawal by patient	126 (19)	141 (21)
Other	19 (3)	17 (3)
Alive on date of last contact	415 (63)	372 (56)

Source: T15.2.9.1.

A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; NE: not estimable; OS: overall survival.

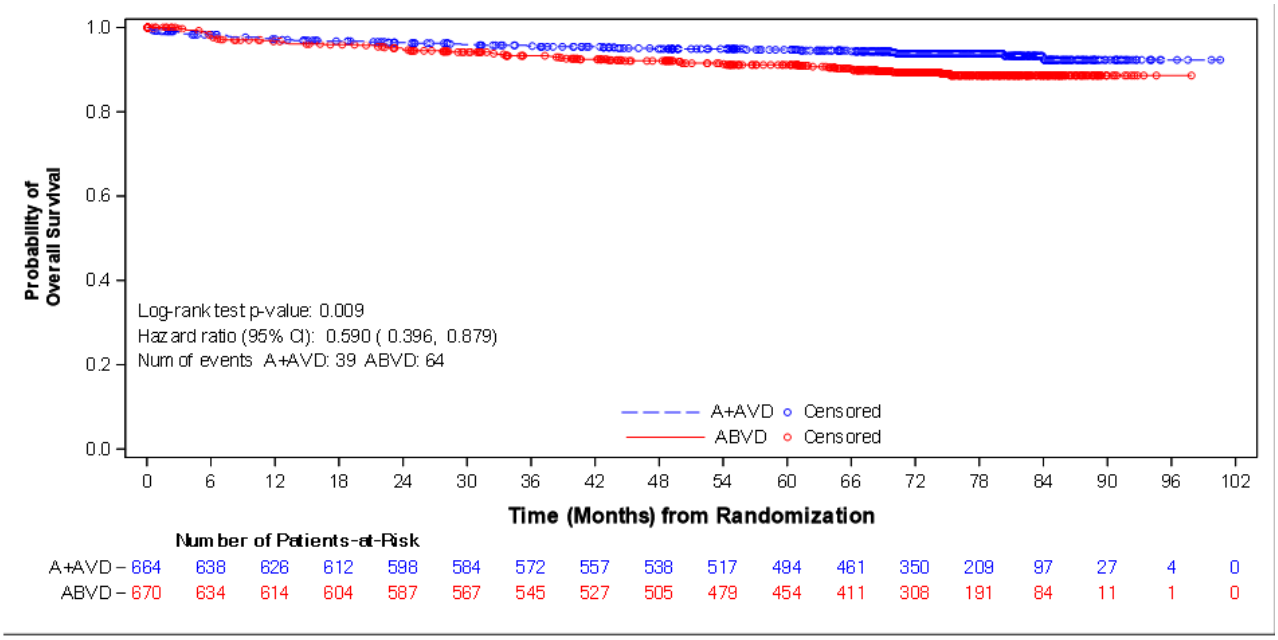
P-value was calculated using stratified log-rank test to compare OS between the 2 treatment arms. The stratification factors include region and number of IPFP risk factors at baseline.

* Indicates a censored observation.

[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on a stratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patients.

[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].

[c] Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, ie, OS event as censored and censored as OS event.



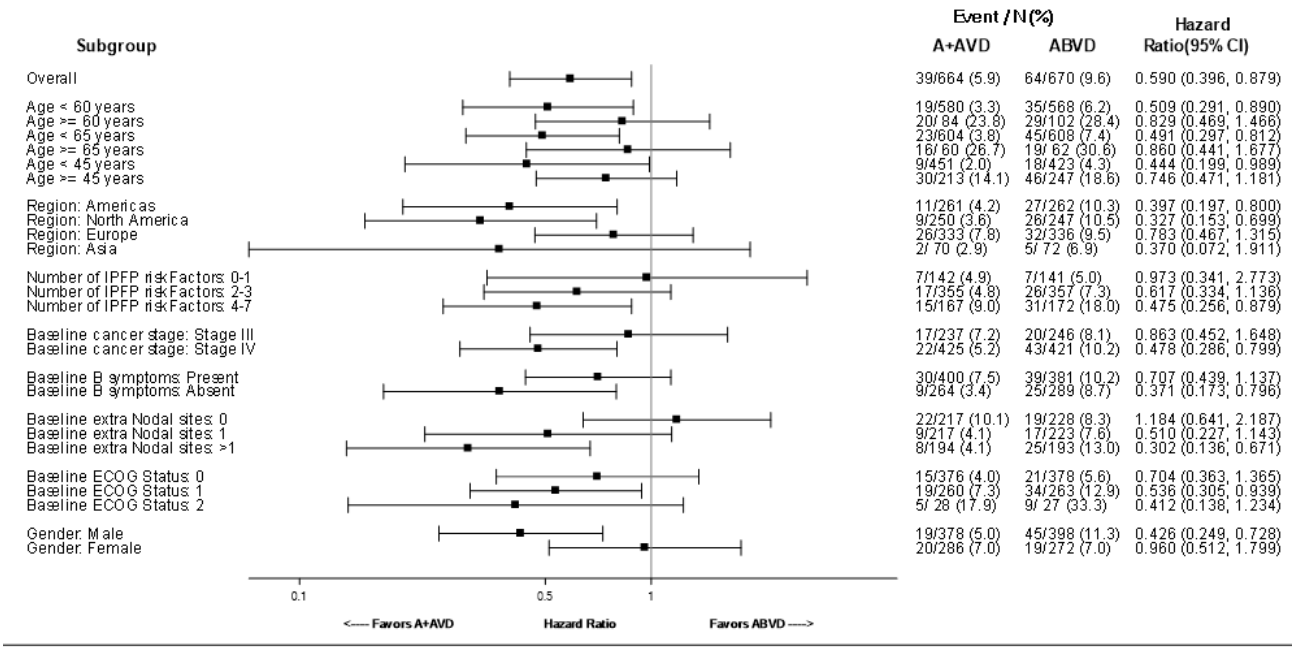
Source: F15.2.9.1.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; K-M: Kaplan-Meier; OS: overall survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on a stratified Cox's proportional hazard regression model with the stratification factors, region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD arm.

Figure 10. Study C25003: KM Plot of OS at the 2021 IA2 (ITT Population)

2021 IA2 OS Subgroup Analysis - A forest plot of the HR for prespecified subgroup analyses of OS generally showed a treatment benefit for A+AVD patients compared with ABVD patients (Figure 11). The OS HR point estimate crossed 1 in patients without baseline extra nodal sites and was close to 1 in the subgroup of patients with 0-1 IPFP risk factors and females.



Source: F15.2.11.2.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; ECOG: Eastern Cooperative Oncology Group: HR: hazard ratio; IPFP: International Prognostic Factor Project; ITT: intent-to treat; PFS: progression-free survival.

Figure 11. Study C25003: Forest Plot of HR in OS for Subgroup Analyses (ITT Population)

2021 IA2 OS for patients with Stage III cHL at Baseline - Among A+AVD-randomized patients in the ITT population with Stage III cHL at baseline, the median OS follow-up duration was approximately 73 months. At that time, 17 deaths (7%) were reported in the A+ AVD arm and 20 deaths (8%) in the ABVD arm (Table 11, Figure 12). Median OS was not reached for either treatment arm. The unstratified HR was 0.863 (95% CI, 0.452-1.648, descriptive p=0.654).

Table 11. Study C25003: OS (ITT Population; Stage III Disease at Baseline)

	A+AVD N=237	ABVD N=246
OS, months		
Number with events (%)	17 (7)	20 (8)
Number censored (%)	220 (93)	226 (92)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 97.5*	0.1*, 97.9*
Hazard ratio (95% CI) [a]	0.863 (0.452, 1.648)	
P-value	0.654	
Kaplan-Meier estimates (95% CI) [b]		
48 months	93.9 (89.8, 96.3) [n=185]	93.8 (89.8, 96.3) [n=186]
60 months	93.9 (89.8, 96.3) [n=177]	93.3 (89.1, 95.9) [n=167]
72 months	92.0 (87.4, 95.0) [n=120]	90.8 (85.9, 94.1) [n=117]
84 months	92.0 (87.4, 95.0) [n=32]	89.9 (84.6, 93.5) [n=36]
Median OS follow-up, (95% CI) months	72.8 (71.49, 74.02)	72.6 (69.75, 74.71)
Reason leading to OS event		
Death due to any cause	17 (7)	20 (8)
Reason for censoring, n (%)		
End of study	78 (33)	92 (37)
Lost to follow-up	26 (11)	39 (16)
Withdrawal by patient	46 (19)	48 (20)
Other	6 (3)	5 (2)
Alive on date of last contact	142 (60)	134 (54)

Source: T15.2.9.2a.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; ITT: intent-to treat; NE: not estimable; OS: overall survival.

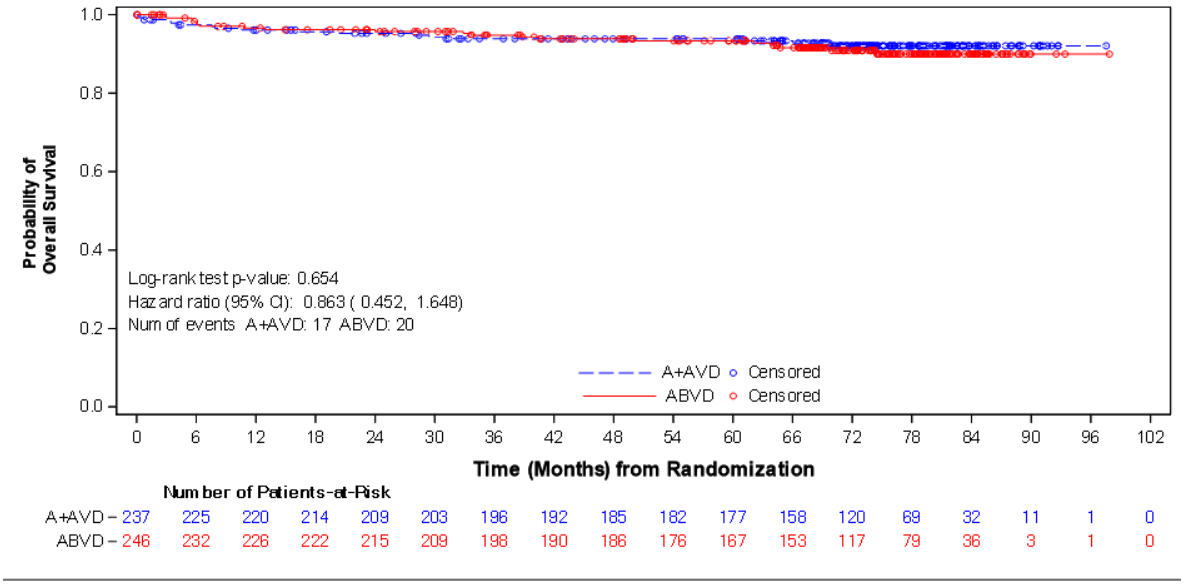
P-value was calculated using an unstratified log-rank test to compare OS between the 2 treatment arms.

* Indicates a censored observation.

[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on an unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patients.

[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].

[c] Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, ie, OS event as censored and censored as OS event.



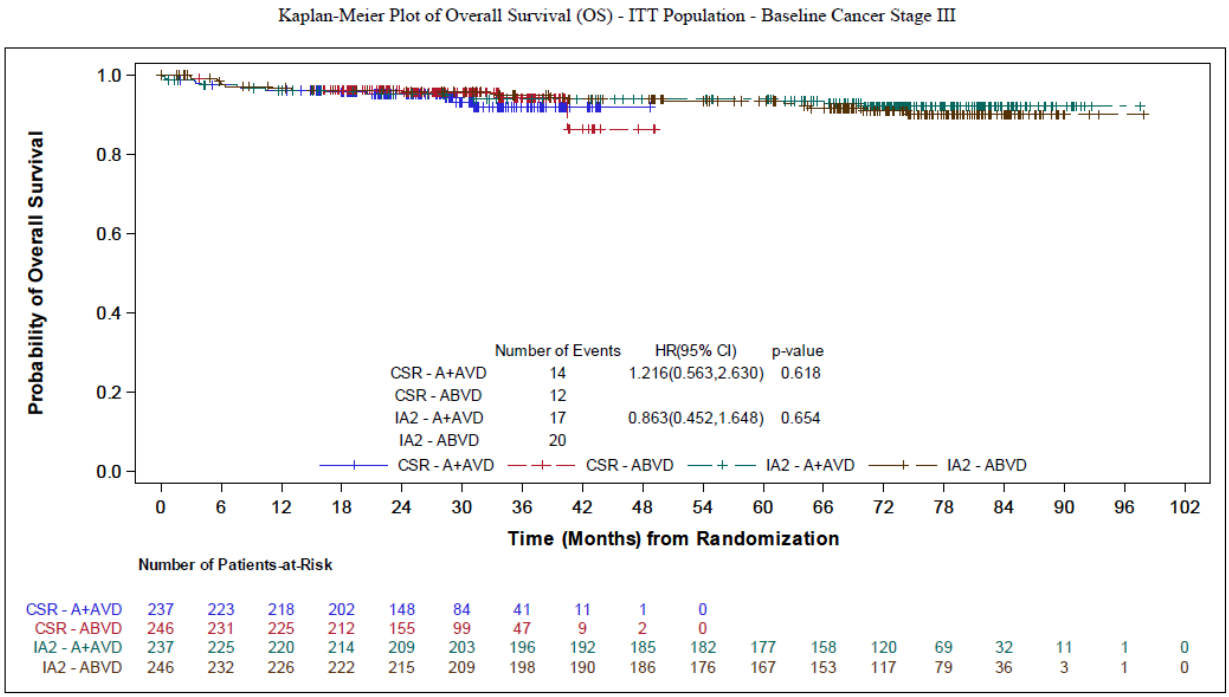
Source: F15.2.9.2a.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; cHL: classical Hodgkin lymphoma; CI: confidence interval; ITT: intent-to treat; K-M: Kaplan-Meier; OS: overall survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD arm.

Figure 12. Study C25003: K-M Plot of OS (ITT Population; Stage III cHL at Baseline)

A comparison of the observed OS during the CSR (IA1) analysis and the IA2 analysis is provided in Figure 13 below.



A+AVD: Brentuximab Vedotin (ADCETRIS) plus AVD (Doxorubicin [Adriamycin], Vinblastine, and Dacarbazine)

ABVD: ABVD (Doxorubicin (Adriamycin), Bleomycin, Vinblastine, and Dacarbazine)

Hazard ratio (A+AVD/ABVD) and 95% CI is based on unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD arm.

Data Cutoff: CSR: 04/20/2017, IA2: 06/01/2021

Figure 13. Study C25003: K-M Plots of the CSR analysis vs the IA-2 analysis in stage III

2021 IA2 OS for patients with Stage IV cHL at Baseline - Among A+AVD-randomized patients in the ITT population with Stage IV cHL at baseline, the median OS follow-up duration was approximately 73 months. A total of 22 deaths (5%) were reported in the A+ AVD arm and 43 deaths (10%) in the ABVD arm (Table 12, Figure 14). Median OS was not reached for either treatment arm. The unstratified HR was 0.478 (95% CI, 0.286-0.799) for A+AVD patients compared with ABVD patients (descriptive p=0.004).

Table 12. Study C25003: OS (ITT Population; Stage IV Disease at Baseline)

Stage IV cHL at Baseline	**A+AVD N=425**	**ABVD N=421**
OS, months		
Number with events (%)	22 (5)	43 (10)
Number censored (%)	403 (95)	378 (90)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.3, 100.6*	0.0*, 94.6*
Hazard ratio (95% CI) [a]	0.478 (0.286, 0.799)	
P-value	0.004	
Kaplan-Meier estimates (95% CI) [b]		
48 months	95.6 (93.0, 97.2) [n=353]	91.4 (88.1, 93.8) [n=319]
60 months	95.3 (92.7, 97.0) [n=317]	90.2 (86.8, 92.8) [n=287]
72 months	94.9 (92.2, 96.7) [n=230]	88.8 (85.1, 91.6) [n=191]
84 months	94.0 (90.5, 96.2) [n=65]	88.2 (84.2, 91.2) [n=48]
Median OS follow-up, (95% CI) months [c]	73.6 (72.67, 74.68)	72.3 (70.87, 73.63)
Reason leading to OS event		
Death due to any cause	22 (5)	43 (10)
Reason for censoring, n (%)		
End of study	130 (31)	140 (33)
Lost to follow-up	39 (9)	37 (9)
Withdrawal by patient	79 (19)	93 (22)
Other	12 (3)	10 (2)
Alive on date of last contact	273 (64)	238 (57)

Source: T15.2.9.2b.

A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; ITT: intent-to treat; OS: overall survival.

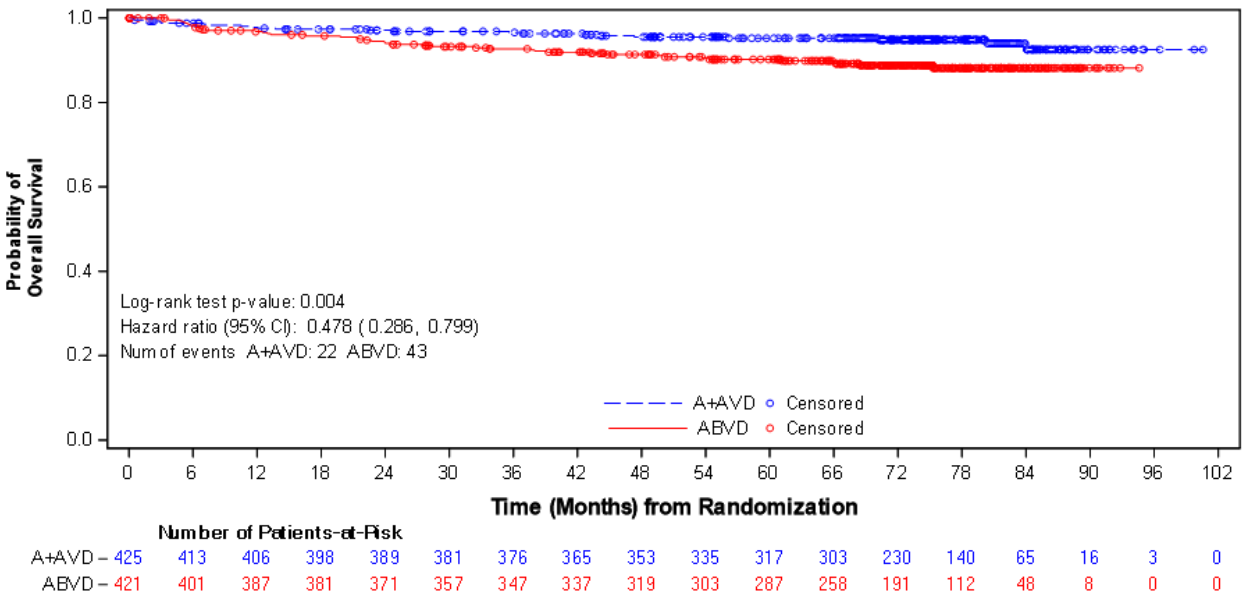
P-value was calculated using an unstratified log-rank test to compare OS between the 2 treatment arms.

* Indicates a censored observation.

[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on an unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patients.

[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].

[c] Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, ie, OS event as censored and censored as OS event.



Source: F15.2.9.2b.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; cHL: classical Hodgkin lymphoma; CI: confidence interval; ITT: intent-to treat; K-M: Kaplan-Meier; NE: not estimable; OS: overall survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD arm.

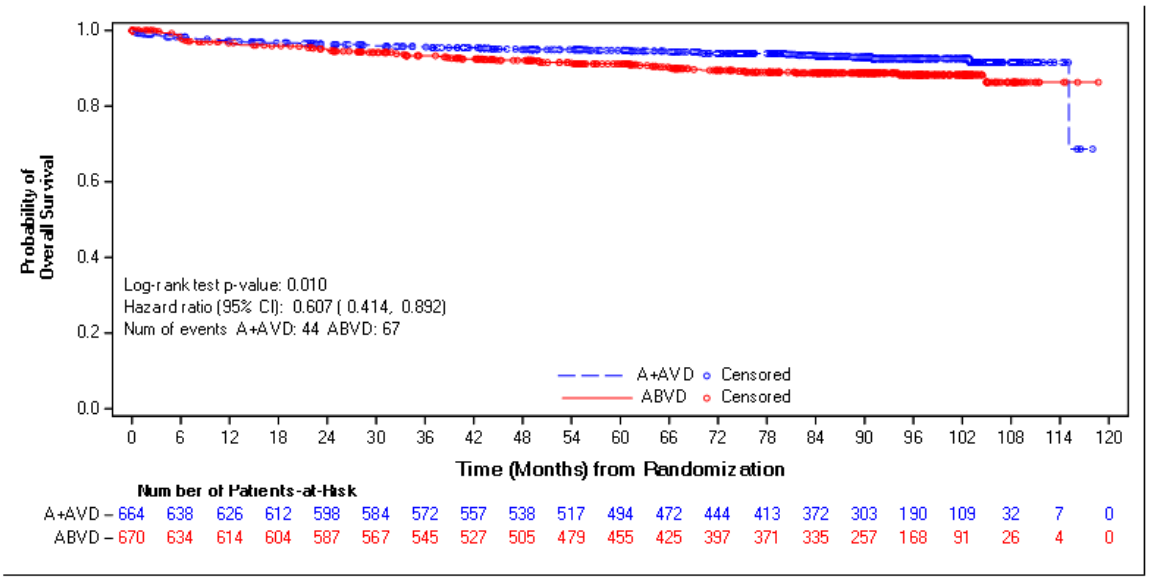
Figure 14. Study C25003: K-M Plot of OS (ITT Population; Stage IV cHL at Baseline)

2023 descriptive analysis ITT population: In response to the request for supplementary information, a descriptive OS analysis (2023 descriptive analysis) was performed with data cut-off 11 March 2023 and including 111 OS events. - After a median follow-up of approximately 88 months, 44 deaths (7%) were reported in the A+ AVD treatment arm and 67 deaths (10%) in the ABVD treatment arm. Median OS was not reached for either treatment arm (Table 13. Study C25003 OS at 2023 descriptive analysis (ITT population) Figure 15). The stratified OS HR was 0.61 (95% CI, 0.414-0.892, descriptive p=0.010), corresponding to a 39% reduction in the risk of death for A+AVD patients compared with ABVD patients.

Table 13. Study C25003 OS at 2023 descriptive analysis (ITT population)

	A+AVD N=664	ABVD N=670
OS, months		
Number with events (%)	44 (7)	67 (10)
Number censored (%)	620 (93)	603 (90)
25th percentile (95% CI)	115.1 (115.1, NE)	NE (NE, NE)
Median (95% CI)	NE (115.1, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (115.1, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 118.0*	0.0*, 118.7*
Hazard ratio (95% CI) [a]	0.607 (0.414, 0.892)	
Descriptive P-value	0.010	
Kaplan-Meier estimates (95% CI) [b]		
48 months	94.9 (92.9, 96.4)	92.1 (89.7, 94.0)
60 months	94.8 (92.7, 96.2)	91.2 (88.6, 93.2)
72 months	93.9 (91.7, 95.6)	89.5 (86.7, 91.7)
84 months	93.5 (91.1, 95.2)	88.8 (85.8, 91.1)
96 months	92.6 (90.0, 94.5)	88.3 (85.2, 90.8)
Median OS follow-up, (95% CI) months [c]	89.7 (86.57, 90.55)	86.3 (84.53, 89.33)
Reason leading to OS event		
Death due to any cause	44 (7)	67 (10)
Reason for censoring, n (%)		
End of study	247 (37)	255 (38)
Lost to follow-up	86 (13)	86 (13)
Withdrawal by patient	142 (21)	149 (22)
Other	19 (3)	20 (3)
Alive on date of last contact	373 (56)	348 (52)

Source: Table 99.3.9.1, data cutoff date 11 March 2023, run 31 May 2023.
A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; NE: not estimable; OS: overall survival.
P-value was calculated using stratified log-rank test to compare OS between the 2 treatment arms. The stratification factors include region and number of IPFP risk factors at baseline.
* Indicates a censored observation.
[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on a stratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patients.
[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].
[c] Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, ie, OS event as censored and censored as OS event.



Source: Figure 99.3.9.1, data cutoff date 11 March 2023, run 31 May 2023.
A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; K-M: Kaplan-Meier; OS: overall survival.

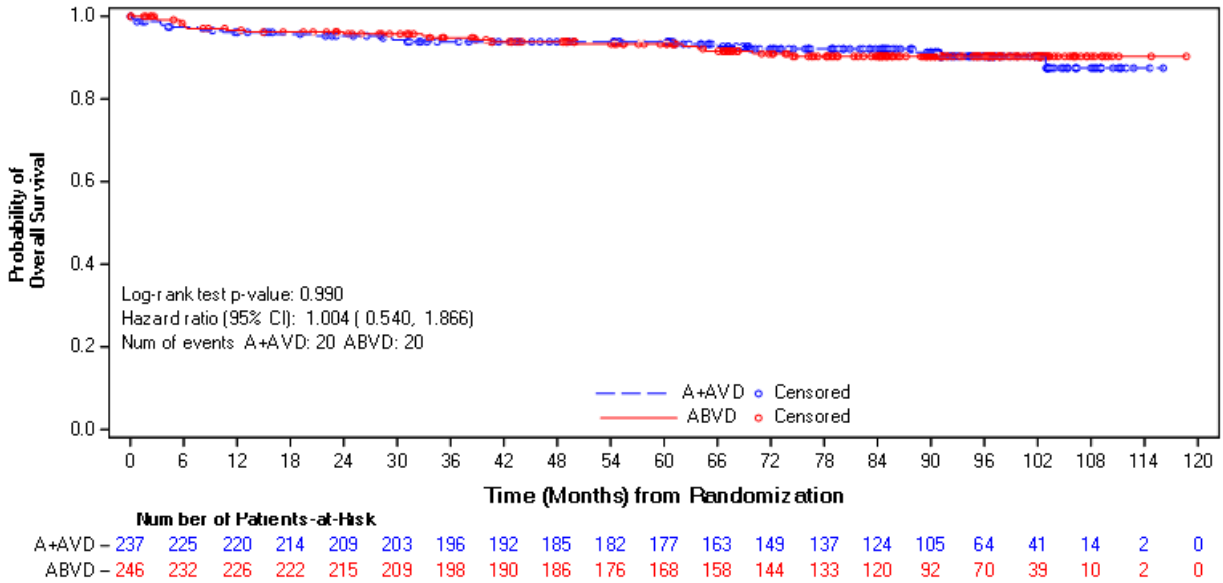
Figure 15. KM-plot of OS at the 2023 descriptive analysis (ITT population)

2023 descriptive analysis OS for patients with Stage III cHL at Baseline - Among A+AVD-randomized patients in the ITT population with Stage III cHL at baseline, the median OS follow-up duration was approximately 90 months. At that time, 20 deaths (8.4%) were reported in the A+ AVD arm and 20 deaths (8.1%) in the ABVD arm (Table 14, Figure 16). Median OS was not reached for either treatment arm. The unstratified HR was 1.004 (95% CI, 0.540-1.866, descriptive p=0.990).

Table 14. Study C25003 OS at 2023 descriptive analysis (Stage III cHL at Baseline)

	A+AVD N=237	**ABVD N=246**
OS, months		
Number with events (%)	20 (8)	20 (8)
Number censored (%)	217 (92)	226 (92)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 116.1*	0.1*, 118.7*
Hazard ratio (95% CI) [a]	1.004 (0.540, 1.866)	
Descriptive P-value	0.990	
Kaplan-Meier estimates (95% CI) [b]		
48 months	93.9 (89.8, 96.3)	93.8 (89.8, 96.3)
60 months	93.9 (89.8, 96.3)	93.3 (89.1, 95.9)
72 months	92.1 (87.6, 95.1)	91.0 (86.1, 94.2)
84 months	92.1 (87.6, 95.1)	90.3 (85.3, 93.7)
96 months	90.3 (84.9, 93.8)	90.3 (85.3, 93.7)
Median OS follow-up, (95% CI) months [c]	89.6 (83.75, 90.87)	85.0 (81.35, 89.53)
Reason leading to OS event		
Death due to any cause	20 (8)	20 (8)
Reason for censoring, n (%)		
End of study	90 (38)	100 (41)
Lost to follow-up	32 (14)	45 (18)
Withdrawal by patient	52 (22)	50 (20)
Other	6 (3)	5 (2)
Alive on date of last contact	127 (54)	126 (51)

Source: Table 99.3.9.2A, data cutoff date 11 March 2023, run 31 May 2023.
A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; NE: not estimable; OS: overall survival.
P-value was calculated using an unstratified log-rank test to compare OS between the 2 treatment arms.
* Indicates a censored observation.
[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on an unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patients.
[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].
[c] Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, ie, OS event as censored and censored as OS event.



Source: Figure 99.3.9.2a, data cutoff date 11 March 2023, run 26 May 2023.
A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; K-M: Kaplan-Meier; OS: overall survival.
Hazard ratio (A+AVD/ABVD) and 95% CI based on an unstratified Cox's proportional hazard regression model.
Hazard ratio <1 favors A+AVD arm.

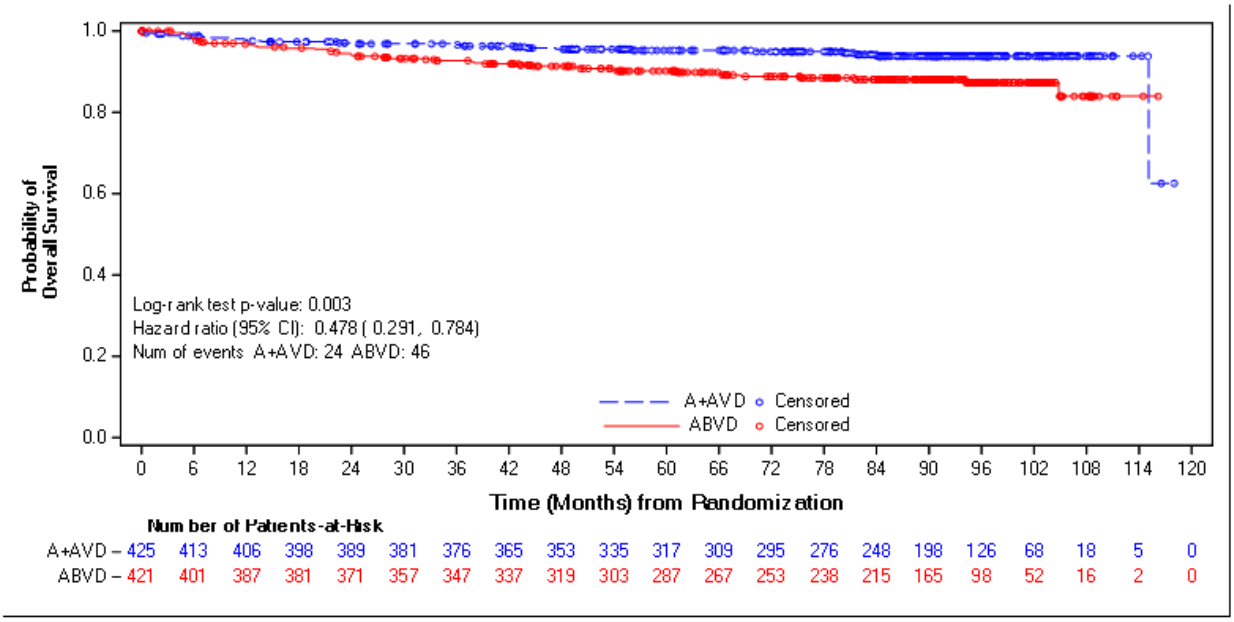
Figure 16. KM-plot of OS at the 2023 descriptive analysis (Stage III cHL disease at Baseline)

2023 descriptive analysis OS for patients with Stage IV cHL at Baseline - Among A+AVD-randomized patients in the ITT population with Stage IV cHL at baseline, the median OS follow-up duration was approximately 89 months. A total of 24 deaths (6%) were reported in the A+ AVD arm and 46 deaths (11%) in the ABVD arm (Table 15, Figure 17). Median OS was not reached for either treatment arm. The unstratified HR was 0.48 (95% CI, 0.291-0.784) for A+AVD patients compared with ABVD patients (descriptive p=0.003).

Table 15. Study C25003 OS at 2023 descriptive analysis (Stage IV cHL at Baseline)

	A+AVD N=425	ABVD N=421
OS, months		
Number with events (%)	24 (6)	46 (11)
Number censored (%)	401 (94)	375 (89)
25th percentile (95% CI)	115.1 (115.1, NE)	NE (104.8, NE)
Median (95% CI)	NE (115.1, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (115.1, NE)	NE (NE, NE)
Minimum, maximum	0.3, 118.0*	0.0*, 116.2*
Hazard ratio (95% CI) [a]	0.478 (0.291, 0.784)	
Descriptive P-value	0.003	
Kaplan-Meier estimates (95% CI) [b]		
48 months	95.6 (93.0, 97.2)	91.4 (88.1, 93.8)
60 months	95.3 (92.7, 97.0)	90.2 (86.8, 92.8)
72 months	94.9 (92.3, 96.7)	88.9 (85.2, 91.7)
84 months	94.2 (91.3, 96.2)	88.1 (84.3, 91.0)
96 months	93.8 (90.8, 95.9)	87.3 (83.2, 90.5)
Median OS follow-up, (95% CI) months [c]	89.7 (86.77, 90.87)	88.2 (85.16, 89.92)
Reason leading to OS event		
Death due to any cause	24 (6)	46 (11)
Reason for censoring, n (%)		
End of study	155 (36)	153 (36)
Lost to follow-up	54 (13)	41 (10)
Withdrawal by patient	89 (21)	99 (24)
Other	12 (3)	13 (3)
Alive on date of last contact	246 (58)	222 (53)

Source: Table 99.3.9.2b, data cutoff date 11 March 2023, run 31 May 2023.
A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; NE: not estimable; OS: overall survival.
P-value was calculated using unstratified log-rank test to compare OS between the 2 treatment arms.
* Indicates a censored observation.
[a] Hazard ratio (A+AVD/ABVD) and 95% CI were based on an unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD patients.
[b] Based on Kaplan-Meier product limit estimates [n=number of patients at risk].
[c] Median OS follow-up was calculated from the Kaplan-Meier method switching the OS event/censored status, ie, OS event as censored and censored as OS event.



Source: Figure 99.3.9.2b, data cutoff date 11 March 2023, run 31 May 2023.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; IPFP: International Prognostic Factor Project; ITT: intent-to treat; K-M: Kaplan-Meier; OS: overall survival.

Hazard ratio (A+AVD/ABVD) and 95% CI based on an unstratified Cox's proportional hazard regression model. Hazard ratio <1 favors A+AVD arm.

Figure 17. KM-plot of OS at the 2023 descriptive analysis (Stage III cHL disease at Baseline).

Other secondary endpoints (analysed at primary data cut-off in 2017)

Complete Remission (CR) rate by IRF

At the end of randomized treatment, the CR rate was 73% in the A+AVD arm vs. 70% in the ABVD arm (Table 1). At the end of frontline treatment, the CR rate was 73% vs. 71%, respectively. At the end of cycle 2, 69% and 67%, respectively, achieved CR. The CR rate and ORR by disease stage are shown in Table 17 and Table 18.

Table 16. CR Rate, ORR, PET negativity Rate and Deauville Score per IRF (ITT)

	A+AVD N=664 n (%)	ABVD N=670 n (%)	Relative Risk (95% CI)
CR rate at the end of randomized regimen (a)	488 (73)	472 (70)	1.042 (0.97, 1.11)
CR rate at the end of frontline therapy (b)	488 (73)	474 (71)	1.038 (0.97, 1.11)
ORR at the end of randomized regimen (c)	569 (86)	553 (83)	1.038 (0.99, 1.09)
PET negativity rate at Cycle 2 (d)	588 (89)	577 (86)	1.028 (0.99, 1.07)
Summary of Deauville score at Cycle 2 (e)			
1	435 (66)	414 (62)	
2	131 (20)	133 (20)	
3	22 (3)	30 (4)	
4	26 (4)	28 (4)	
5	21 (3)	30 (4)	
Rate of Deauville score ≤3 at the end of frontline therapy	570 (86)	551 (82)	1.044 (1.00,1.09)
Rate of Deauville score ≤2 at the end of frontline therapy	563 (85)	537 (80)	1.058 (1.01,1.11)

Table 17. CR Rate, ORR, PET negativity Rate and Deauville Score per IRF (ITT population with Stage III HL)

	A+AVD N=237 n (%)	ABVD N=246 n (%)	Relative risk (95% CI)
CR rate at the end of randomized regimen (a)	189 (80)	183 (74)	1.072 (0.97,1.18)
CR rate at the end of frontline therapy (b)	189 (80)	184 (75)	1.066 (0.97,1.17)
ORR at the end of randomized regimen (c)	206 (87)	205 (83)	1.043 (0.97,1.12)
PET negativity rate at Cycle 2 (d)	209 (88)	219 (89)	0.991 (0.93,1.06)
Summary of Deauville score at Cycle 2 (e)			
1	150 (63)	159 (65)	
2	55 (23)	49 (20)	
3	4 (2)	11 (4)	
4	7 (3)	10 (4)	
5	6 (3)	5 (2)	
Rate of Deauville score ≤3 at the end of frontline therapy	211 (89)	208 (85)	1.053 (0.98,1.13)
Rate of Deauville score ≤2 at the end of frontline therapy	207 (87)	204 (83)	1.053 (0.98,1.13)

Table 18. CR Rate, ORR, PET negativity Rate and Deauville Score per IRF (ITT population with Stage IV HL)

	A+AVD N=425 n (%)	ABVD N=421 n (%)	Relative risk (95% CI)
CR rate at the end of randomized regimen (a)	298 (70)	289 (69)	1.021 (0.93, 1.12)
CR rate at the end of frontline therapy (b)	298 (70)	290 (69)	1.018 (0.93, 1.11)
ORR at the end of randomized regimen (c)	362 (85)	348 (83)	1.030 (0.97, 1.09)
PET negativity rate at Cycle 2 (d)	379 (89)	358 (85)	1.049 (1.00, 1.10)
Summary of Deauville score at Cycle 2			
1	285 (67)	255 (61)	
2	76 (18)	84 (20)	
3	18 (4)	19 (5)	
4	19 (4)	18 (4)	
5	15 (4)	24 (6)	
Rate of Deauville score ≤3 at the end of frontline therapy	358 (84)	342 (81)	1.037 (0.97,1.10)
Rate of Deauville score ≤2 at the end of frontline therapy	355 (84)	333 (79)	1.056 (0.99,1.13)

Event-free survival (EFS)

The median EFS by IRF assessment was not estimable for either treatment arm. The stratified HR indicated no significant difference between treatment arms: 0.900 (95% CI, 0.726; 1.117, p=0.339). An estimated 76.5% of A+AVD patients vs. an 73.7% of ABVD patients were event free at 2 years; at 3 years, the frequencies were 73.9% and 71.5%, respectively.

Disease-free survival (DFS)

The median DFS by IRF assessment was not estimable (NE) for either treatment arm. The stratified hazard ratio was 0.701 (95% CI, 0.504, 0.976; p=0.034), favouring the A+ AVD arm. An estimated 88% of patients achieving CR on the A+AVD arm (95% CI, 84-90%) versus an estimated 82% of patients achieving CR on the ABVD arm (95% CI, 78-86%) were DFS-event free at 2 years. At 3 years 86% vs. 81% of patients achieving CR were DFS-event free, respectively.

Objective Response Rate (ORR) by IRF

The ORR at the end of randomization regimen was also similar between treatment arms: 86% (A+AVD) vs. 83% (ABVD).

Concordance between IRF and INV assessments of CR and ORR

CR and ORR results by investigator assessment are shown in Table 16. The IRF and INV ORR assessments were concordant for 1215 of 1334 patients (91%) and the concordance rates were similar for each of the treatment arms. A lower overall concordance rate of 75% was noted for the CR assessments at the end of the randomized regimen treatment period and at the end of frontline therapy.

Table 19. CR Rate and ORR per INV (ITT)

	A+AVD N=664 n (%)	ABVD N=670 n (%)	Relative Risk (95% CI)
CR rate at the end of randomized regimen (a)	438 (66)	426 (64)	1.036 (0.96,1.12)
CR rate at the end of frontline therapy (b)	439 (66)	428 (64)	1.033 (0.95,1.12)
ORR at the end of randomized regimen (c)	582 (88)	545 (81)	1.077 (1.03,1.13)

Duration of response (DOR) by IRF

The median DOR by IRF assessment was not estimable for either treatment arm. A total of 628 of 664 A+AVD patients (95%) and 623 of 670 ABVD patients (93%) achieved a best overall response of PR or better. Among them, almost similar frequencies of patients had disease progression after objective response (86 patients [14%] versus 99 patients [16%], respectively).

Duration of complete remission (DOCR) by IRF

By IRF assessment, median DOCR was not estimable for either treatment arm of the ITT population who had a best response of CR. After a median follow-up of 22.7 months, the number of patients who progressed after achieving a best response of CR was 59 of 543 A+AVD patients (11%) and 72 of 528 ABVD patients (14%).

Rate of Patients Not in CR Who Received Irradiation and/or Chemotherapy

Among patients not attaining a CR, a numerical lower proportion of A+AVD-randomized patients required radiation or subsequent chemotherapy than similar patients randomized to ABVD (Table 20). Among the 132 A+AVD patients (20%) and 157 ABVD patients (23%) in the ITT population who were determined to be not in CR by IRF assessment at the end of frontline therapy, 11 A+AVD patients (8%) and 20 ABVD

patients (13%) subsequently received radiotherapy. Subsequent chemotherapy was reported for 43 A+AVD patients (33%) and 65 ABVD patients (41%) in this subgroup.

Table 20. Study C25003: Patients Not in CR Receiving Subsequent Radiation and Chemotherapy After Completion of Frontline Therapy (ITT Population)

	A+AVD N=664	ABVD N=670	descriptive p-value [a]
Patients not in CR after completion of frontline therapy	132 (20)	157 (23)	
Subsequent radiation after completion of frontline therapy *	11 (8)	20 (13)	p=0.381
Subsequent chemotherapy after completion of frontline therapy *	43 (33)	65 (41)	P=0.226

Source: T15.2.18.2.

A+AVD: brentuximab vedotin (ADCETRIS) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CR: complete remission; IPFP: International Prognostic Factor Project; IRF: independent review facility; ITT: intent-to treat.

The first subsequent therapy after completion of frontline therapy was considered in the summary.

* Percentages are based on number of patients not in CR per IRF after completion of frontline therapy.

[a] P-value was calculated using a CMH test stratified by the stratification factors, region and number of IPFP risk factors at baseline.

PET negativity at Cycle 2 and Deauville Scores

At the end of Cycle 2, the PET negativity rate was 89% versus 86% (RR 1.028 [95% CI, 0.99; 1.07]).

At the end of frontline therapy, the rates of Deauville scores ≤3 were 86% vs 82% (RR 1.044 [95% CI, 1.00; 1.09]) and the rates of scores ≤2 were 85% vs 80% (RR 1.058 [95% CI, 1.01; 1.11]).

Patient-reported outcomes (PRO) per European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30.

Over time, compliance (the number of forms actually completed as a proportion of those anticipated) ranged from 86% to 98% across treatment arms. The mean EORTC QLQ-C30 summary scores (ITT) are shown in Figure 18.

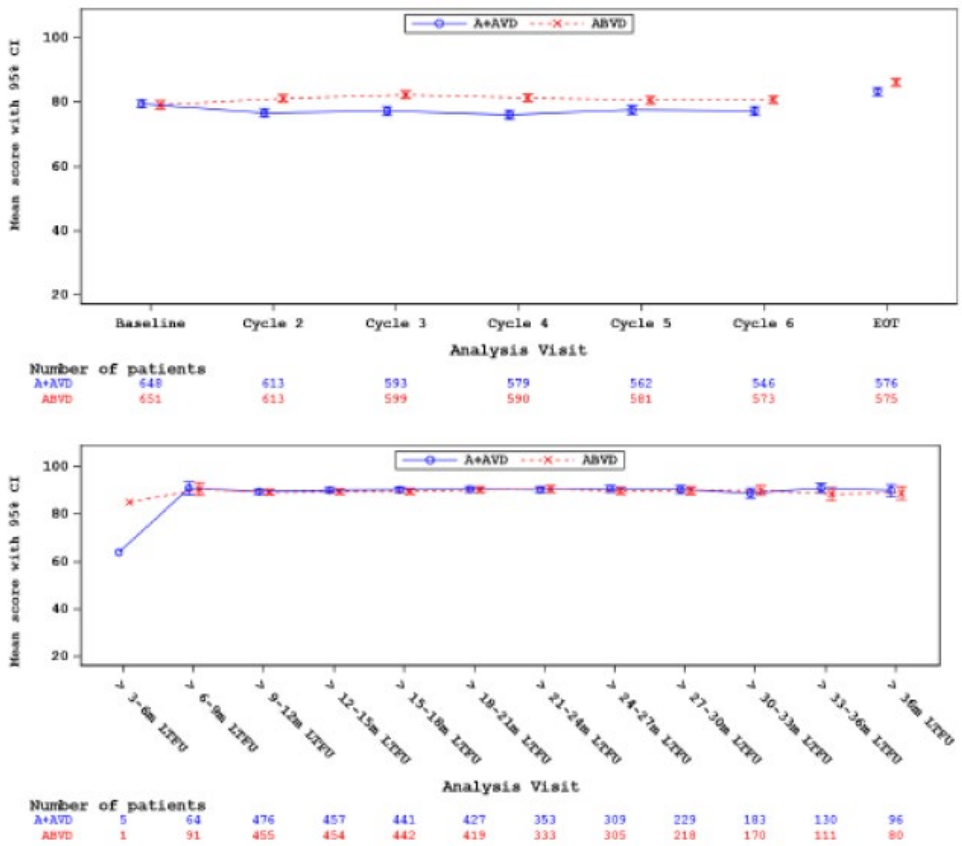


Figure 18. Study C25003: Mean EORTC-QLQ-C30 Summary Scores over Time (ITT)

Antitherapeutic antibodies (ATA)

At the end of frontline therapy, immunogenicity status and response rates were examined in the 632 immunogenicity-evaluable patients of the A+AVD-treated safety population. Of these, 109 patients (17.2%) were anti-therapeutic antibody (ATA) positive at any time post-baseline.

Response per IRF was calculated for the subset of transiently ATA-positive patients (positive in 1 or 2 post-baseline samples) and the subset of persistently ATA-positive patients (positive in >2 post-baseline samples).

The majority of transiently ATA-positive patients (87 patients, 83%) achieved CR at the end of frontline therapy, whereas 1 of 4 persistently ATA-positive patients achieved CR at the end of frontline therapy. All 4 persistently ATA positive patients achieved an objective response at the end of frontline therapy.

Response rates by ATA titer status

Of the 108 patients with a positive ATA status who had their titer assessed, 106 patients had a low ATA titer and 2 patients had a high ATA titer. Most of the patients with a low titer achieved a response of CR or PR (99 of 106) and both patients with a high titer achieved a response of CR at the end of frontline therapy.

Response rates by ATA neutralizing antibody (nATA) response status (positive/negative)

The proportion of patients who achieved a CR at the end of frontline therapy was similar for neutralizing antibody (nATA)- positive (83%) and nATA-negative (80%) patients; 2 of the 12 patients (17%) who were nATA positive achieved a PR at the end of frontline therapy compared with 11 of 95 (12%) patients who were nATA negative.

Exploratory endpoints

PRO per FACIT-Dyspnea 10 (lung-specific PRO, ITT)

Mean subscale scores for dyspnoea generally were higher in the A+AVD arm than in the ABVD arm from Cycles 3 through 6, indicating a higher impact of dyspnoea in the A+AVD arm. A trend of worsening dyspnoea was observed in both treatment arms across treatment cycles, although there is no established minimum clinically important difference (MCID).

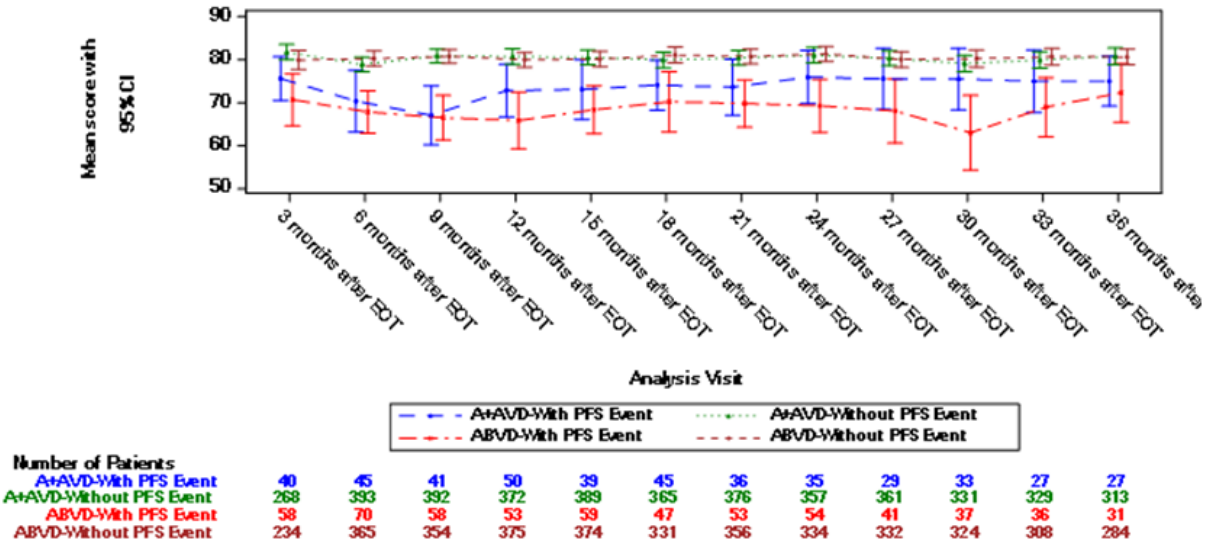
PRO per Functional Assessment of Cancer Therapy – Neurotoxicity

Mean subscale scores were lower in the A+AVD treatment arm compared with the ABVD arm over the course of the study and at EOT. A difference between treatment arms was observed in favour of ABVD across Cycles 2 through 6. The differences in FACT/GOG-Ntx at Cycles 4, 5, and 6 were clinically meaningful according to the MAH.

Patient-reported health utility values per EuroQoL (EQ)-5D-3L

2017 primary data cut-off - Overall, mean scores over time were not different between the 2 treatment arms on the basis of the MCID of 0.07 established for the UK TTO score.

2021 updated analysis - Figure 19 illustrates patients' quality of life for the long-term follow-up period as assessed per EORTC QLQ-30/QoL subscale scores by treatment arm and the presence or absence of a PFS event per investigator. EORTC QLQ-C30 data were collected for 3 years after the last dose of frontline therapy ending at posttreatment follow-up (PTFU) Visit 12 or until the first of documented disease progression or subsequent anticancer therapy. Absence of a PFS per investigator event is according to the MAH associated with higher quality of life at each posttreatment time point.



Source: m2.7.3 Appendix 1, Figure 99.2.1.1, data cutoff 01 June 2021.
Baseline is defined as the value collected at the time closest to, but before, the start of study drug administration.
Long-term follow-up visits indexed from study Day 1. Patients on study treatment are excluded.
The score range is 0-100. A high score represents a high QoL.
A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; EOT, end of treatment.

Figure 19. ECHELON-1: Mean EORTC QLQ-C30 Global Health Status/QoL Subscale Scores Over Time by Progression-Free Survival per Investigator Status (ITT Population)

Utilization of medical resources

At least 1 hospitalization was reported for a higher number of patients in the A+ AVD arm (n= 242, 36%) compared to the ABVD arm (n=186 ABVD, 28%).

The median number of days of hospitalization among patients who were hospitalized at least once was similar across treatment arms (9 vs. 8 days, respectively).

The hospitalization visit rate per patient-year was 0.3363 (95% CI: 0.31, 0.37) for A+AVD patients and 0.2277 (95% CI: 0.20, 0.25) for ABVD patients. An AE or toxicity was the most commonly reported reason for hospitalization.

Percent of patients alive without HL at 3 and 5 years

As of the 20 April 2017 data cutoff date, approximately one quarter of patients have had the opportunity to be followed for 3 years and no patient has yet to have been followed for 5 years.

There was no statistically significant difference (p=0.795) in the estimated proportion of patients in the ITT population alive without HL at 3 years between the A+AVD treatment arm (70%) and the ABVD treatment arm (71%).

Percent of patients switching therapy after Cycle 2 and before EOT

After the Cycle 2 PET assessment, patients could be switched to an AFM of physician's choice for the remainder of planned frontline therapy without the switch being considered an mPFS event. While this was permitted, in practice, very few patients were switched to an AFM.

A total of 15 A+AVD patients (2%) and 9 ABVD patients (1%) received an AFM. All patients receiving AFM switched to another form of chemotherapy. The reason for switching was primarily an adverse event (54%) or Deauville score (21%).

Ancillary analyses

The choice of subsequent therapy for CD30+ HL after first line brentuximab vedotin was discussed at the time of approval, as brentuximab vedotin is also indicated following autologous stem cell transplant in adult patients with at increased risk of relapse, and in relapsed or refractory patients. As next line anticancer therapies continued to be followed, the updated data are presented below.

Subsequent anticancer therapy

At least 1 subsequent anticancer therapy was reported for 135 A+AVD patients (20%) and 157 ABVD patients (24%) in the safety population. Chemotherapy was the most commonly reported subsequent anticancer therapy across treatment arms. At least 1 anticancer chemotherapeutic regimen was reported for 79 A+AVD patients (12%) and 111 ABVD patients (17%) and included high-dose chemotherapy and transplantation in 3% of patients across treatment arms. The type of first subsequent anticancer therapy in both treatment arms is shown in Table 21. Three patients in the A+AVD arm received subsequent brentuximab vedotin-containing anticancer therapy compared to 23 patients in the ABVD arm.

Table 21. Study C25003: First Subsequent Anticancer Therapy Reported for ≥2 Patients in Either Treatment Arm (Safety Population)

	A+AVD N=662	ABVD N=659
Patients with at least 1 subsequent anticancer therapy	135 (20)	157 (24)
Type of therapy, n (%)		
Chemotherapy	72 (11)	94 (14)
Carboplatin + etoposide + ifosfamide	12 (2)	18 (3)
Cisplatin + cytarabine + dexamethasone	17 (3)	8 (1)
Brentuximab vedotin	3 (<1)	12 (2)
Cisplatin + cytarabine + etoposide + methylprednisolone	5 (<1)	6 (<1)
Ifosfamide + gemcitabine + vinorelbine	3 (<1)	4 (<1)
Doxorubicin + bleomycin + vinblastine + dacarbazine	3 (<1)	3 (<1)
Brentuximab vedotin + bendamustine	0	5 (<1)
Gemcitabine + cisplatin + dexamethasone	2 (<1)	2 (<1)
Brentuximab vedotin + nivolumab	0	3 (<1)
Etoposide + ifosfamide + mesna + carboplatin	1 (<1)	2 (<1)
Ifosfamide + gemcitabine + vinorelbine + prednisone	0	3 (<1)
Bendamustine	2 (<1)	0
Cyclophosphamide + vincristine + procarbazine + prednisone	1 (<1)	1 (<1)
Dexamethasone + cisplatin + gemcitabine	0	2 (<1)
Gemcitabine + carboplatin	0	2 (<1)
Gemcitabine + cisplatin	0	2 (<1)
Ifosfamide + carboplatin + etoposide	0	2 (<1)
Rituximab + bendamustine	0	2 (<1)
Radiation	45 (7)	41 (6)
High-dose chemotherapy + transplantation	18 (3)	19 (3)
Carboplatin + etoposide + ifosfamide + ASCT	5 (<1)	1 (<1)
Carboplatin + etoposide + ifosfamide + SCT	0	3 (<1)
Gemcitabine + cisplatin + dexamethasone + ASCT	3 (<1)	0
Etoposide + cytarabine + carmustine + gemcitabine + ifosfamide + melphalan + vinorelbine + ASCT	0	2 (<1)
Ifosfamide + gemcitabine + vinorelbine + ASCT	0	2 (<1)
Stem cell transplant	0	2 (<1)
Immunotherapy	4 (<1)	4 (<1)
Brentuximab vedotin + nivolumab	0	3 (<1)
Pembrolizumab	2 (<1)	1 (<1)
Nivolumab	2 (<1)	0
Hormonal	0	2 (<1)

Source: Table 15.3.4.7a.

A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; ASCT: autologous stem cell transplantation; SCT: stem cell transplantation.

The first subsequent anticancer therapy that patient received after frontline therapy was included in the summary.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial C25003: ECHELON-1

Title: A Randomized, Open label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma			
Study identifier	C25003 (ECHELON-1); IND Number:110,636; EudraCT Number:2011 005450 60; NCT Number:NCT01712490; Universal Trial Number: U1111 1161 4937		
Design	Open-label, randomized, 2-arm, multicenter, phase 3 study had the primary objective of comparing the mPFS obtained with A+AVD versus that obtained with ABVD.		
	Study initiation date: Primary completion date: Final OS analysis:		9 Nov 2012 20 April 2017 After 112 deaths or 10 years after randomisation of the last patient, whichever occurs first.
Hypothesis	Superiority		
Treatments groups	A+AVD		IV infusion on day 1 and 15 of each 28 day cycle, for up to 6 cycles of: A (brentuximab vedotin): 1.2 mg/kg A (doxorubicin [Adriamycin]): 25 mg/m2 V (vinblastine): 6 mg/m2 D (dacarbazine): 375 mg/m2
	ABVD		IV infusion on day 1 and 15 of each 28 day cycle, for up to 6 cycles of: A (doxorubicin [Adriamycin]): 25 mg/m2 B (bleomycin): 10 units/m2 V (vinblastine): 6 mg/m2 D (dacarbazine): 375 mg/m2
Endpoints and definitions	Primary endpoint	mPFS	Time from randomization to PD, death due to any cause; or for patients who failed to achieve a CR per **IRF**, receipt of subsequent anticancer therapy for HL after completion of frontline therapy.
			Sensitivity analysis primary endpoint: PFS by **investigator**
	Key secondary endpoint	OS	Time from randomization to date of death.
Database lock	Primary analysis and first OS interim analysis: 20 April 2017 (previously reviewed in first line HL indication application) Second OS interim analysis: 1 June 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Data cut-off 20 April 2017 for primary endpoint, 1 June 2021 for key secondary endpoint OS and sensitivity analysis PFS by investigator.		
Descriptive statistics and estimate variability	Treatment group	A+AVD	ABVD
	Number of subject	664	670
	Median PFS (by IRF)	NE	NE

	95% CI	(48.2, NE)	(NE, NE)
	Exploratory sensitivity analysis - median PFS (by Inv)	NE	NE
	95% CI	(NE, NE)	(NE, NE)
	Median OS	NE	NE
	95% CI	(NE, NE)	(NE, NE)
Effect estimate per comparison	Primary endpoint mPFS by IRF at 2017 primary analysis*	Comparison groups	A+AVD vs. ABVD
		Hazard Ratio (HR)	0.77
		95% CI	(0.603, 0.983)
		P-value	0.035
	Exploratory sensitivity analysis PFS by Inv at 2021 IA2	Comparison groups	A+AVD vs. ABVD
		HR	0.678
		95% CI	(0.532, 0.863)
		Descriptive P-value	0.002
	Key secondary endpoint OS at 2023 descriptive analysis	Comparison groups	A+AVD vs. ABVD
		HR	0.607
		95% CI	(0.414, 0.892)
		P-value	0.009
Notes	* The primary comparison of mPFS was IRF based on the ITT set, with a stratified log rank test at the two-sided 5% significance level, adjusted for stratification factors region and number of IPFP risk factors at baseline. *CI: Confidence Interval, CR: complete remission, Inv: investigator, IRF: independent (radiologic) review facility, NE: not estimable, OS: Overall Survival, PD: progressive disease, PET: positron emission tomography, mPFS: modified Progression Free Survival, PR: partial remission, PRO: patient reported outcome.*		
Analysis description	**Prespecified subgroup analysis Stage III HL**		
Analysis population and time point description	*Stage III HL* *Data cut-off: 1 June 2021*		
Descriptive statistics and estimate variability	Treatment group	A+AVD	ABVD
	Number of subjects	237	246
	PFS by Inv	NE	NE
	95% CI	(NE, NE)	(NE, NE)
	Median OS	NE	NE
	95% CI	(NE, NE)	(NE, NE)
Effect estimate per comparison	Exploratory endpoint PFS by Inv	Comparison groups	A+AVD vs. ABVD
		HR	0.603
		95% CI	(0.391, 0.930)
		Descriptive P-value	0.021
	Key secondary endpoint OS (data cut-off 2023 descriptive analysis)	Comparison groups	A+AVD vs. ABVD
		HR	1.004
		95% CI	(0.540, 1.866)
		Descriptive P-value	0.990
Analysis description	**Prespecified subgroup analysis Stage IV HL**		

Analysis population and time point description	*Stage IV HL* *Data cut-off: 1 June 2021*		
Descriptive statistics and estimate variability	Treatment group	A+AVD	ABVD
	Number of subjects	425	421
	PFS by Inv	NE	NE
	95% CI	(NE, NE)	(NE, NE)
	Median OS	NE	NE
	95% CI	(NE, NE)	(NE, NE)
Effect estimate per comparison	Exploratory endpoint PFS by Inv	Comparison groups	A+AVD vs. ABVD
		HR	0.715
		95% CI	(0.534, 0.959)
		Descriptive P-value	0.024
	Key secondary endpoint OS (data cut-off 2023 descriptive analysis)	Comparison groups	A+AVD vs. ABVD
		HR	0.478
		95% CI	(0.291, 0.784)
		Descriptive P-value	0.003

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses or meta-analysis have been submitted.

Clinical studies in special populations

Elderly

In the pivotal study, 84 patients (13%) in the A+AVD arm, and 102 patients (15%) in the ABVD arm were ≥60 years of age. Approximately 61 patients in both arms (9%) were ≥ 65 years of age.

2017 primary analysis data cut-off - The percentage of patients age 60 years or older receiving subsequent anticancer therapy was similar across treatment arms (A+AVD 19% [n=16 of 83] versus ABVD 17% [n=17 of 98]) as of the 2017 data cut-off. In the safety population slightly fewer A+AVD arm patients (121 patients, 18%) received at least 1 subsequent anticancer therapy compared with ABVD patients (144 patients, 22%).

As of the 20 April 2017 data cut-off and after a median follow-up of 28 months, 32 deaths had occurred among patients who were age 60 years or older: 15 deaths (18% of this subgroup of older patients) on the A+AVD arm and 17 deaths (17% of this subgroup of older patients) on the ABVD arm. No data has been presented for patients <60 years of age. In the ITT, a slightly larger difference between treatment arms was observed: 28 deaths (4%) were reported in the A+AVD treatment arm and 39 deaths (6%) in the ABVD treatment arm after a median follow-up of approximately 28 months.

Elderly Stage IV patients

2017 primary analysis data cut-off - The mPFS (HR 0.804, 95% CI: 0.42 to 1.53, p = 0.506) and OS (HR 0.616, 95% CI: 0.245, 1.546, p=0.297) results for elderly patients with Stage IV HL are shown in Table 22 and Table 23.

Table 22. ECHELON-1: Summary of mPFS per IRF (ITT Population Patients Aged 60 Years or More, Subset with Stage IV HL)

	A+AVD N=51	ABVD N=67
mPFS (months)		
Number with Events (%)	16 (31)	22 (33)
Number Censored (%)	35 (69)	45 (67)
25th Percentile (95% CI)	11.7 (6.4, NE)	8.9 (6.0, 24.3)
Median (95% CI)	NE (29.2, NE)	NE (24.3, NE)
75th Percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 48.5*	0.0*, 39.1*
Hazard Ratio[a] (95% CI)	0.804 (0.422, 1.532)	
P-value	0.506	
Kaplan-Meier Estimates[b] % (95% CI)		
1 Year	73.4 (58.6, 83.6) [n=35]	70.8 (57.3, 80.8) [n=38]
2 Years	71.3 (56.3, 81.9) [n=26]	66.1 (51.8, 77.1) [n=24]
2.5 Years	66.5 (49.4, 79.0) [n=14]	57.3 (41.7, 70.2) [n=11]
3 Years	59.9 (39.5, 75.3) [n=6]	57.3 (41.7, 70.2) [n=4]
Median mPFS follow-up[c] (months) (95% CI)	25.2 (24.38, 30.69)	24.6 (18.83, 25.10)
Reason Leading to mPFS Event		
Progressive disease	11 (22)	14 (21)
Death due to any cause	5 (10)	7 (10)
Receipt of additional therapy after non-CR[d]	0	1 (1)
Reason for Censoring		
No baseline and/or no post-baseline assessment	1 (2)	6 (9)
mPFS event after more than one missed visit	0	1 (1)
Treatment discontinuation for undocumented disease progression	0	1 (1)
Lost to follow-up	0	1 (1)
Withdrawal by subject	2 (4)	1 (1)
No documented mPFS event	32 (63)	35 (52)

Table 23. ECHELON-1: Summary of OS (ITT Population Patients Aged 60 Years or More, Subset with Stage IV HL)

	A+AVD N=51	ABVD N=67
OS (months)		
Number with Events (%)	8 (16)	13 (19)
Number Censored (%)	43 (84)	54 (81)
25th Percentile (95% CI)	42.5 (35.6, NE)	NE (19.8, NE)
Median (95% CI)	42.5 (42.5, NE)	NE (NE, NE)
75th Percentile (95% CI)	NE (42.5, NE)	NE (NE, NE)
Min, Max	1.4, 42.5	0.0*, 39.1*
Hazard Ratio[a] (95% CI)	0.616 (0.245, 1.546)	
P-value	0.297	
Kaplan-Meier Estimates[b] % (95% CI)		
1 Year	92.1 (80.2, 97.0) [n=46]	90.2 (79.4, 95.5) [n=55]
2 Years	88.1 (75.4, 94.5) [n=36]	76.9 (63.3, 86.0) [n=35]
2.5 Years	88.1 (75.4, 94.5) [n=20]	76.9 (63.3, 86.0) [n=20]
3 Years	80.1 (56.0, 91.8) [n=10]	76.9 (63.3, 86.0) [n=8]
Median OS follow-up[c] (months) (95% CI)	28.1 (26.25, 31.01)	27.6 (24.94, 30.16)
Reason Leading to OS Event		
Death due to any cause	8 (16)	13 (19)
Reason for Censoring		
End of Study	3 (6)	7 (10)
Lost to follow-up	0	1 (1)
Withdrawal by subject	3 (6)	5 (7)
Other	0	1 (1)
Still alive at date of last contact	40 (78)	47 (70)

Source: /bdm/tbos/SGN-035/C25003/CSR2/rsi aor2018/Tables/T97.2.10.3-Summary OS StageIV Elder. run date

2021 IA2: As of the 1 June 2021 data cut-off, 49 deaths had occurred among patients who were aged 60 years or older. Based on OS subgroup data presented in Figure 11, 20 events (23.8% of this elderly subgroup) occurred in the A+ AVD arm and 29 events (28.4% of this subgroup) in the ABVD arm. Data for elderly patients has not been updated by disease stage.

2023 descriptive OS analysis : In response to the request for supplementary information, data for elderly Stage IV patients were presented with the 2023 descriptive analysis data cut-off. A further 13 OS events had occurred in patients aged ≥60 years since the 2017 OS IA1 (4 A+AVD, 9 ABVD). The OS HR of 0.634 (0.314, 1.282; p=0.201), supported the 2017 IA1.

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

With this application, an extension of indication (EoI) is requested for brentuximab vedotin in patients with previously untreated CD30+ HL, i.e. from '**Stage IV** HL' to '**advanced** HL'.

Main clinical data to support this variation is derived from Phase 3 Study ECHELON-1. This is a randomized, open-label trial comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin + AVD (Adcetris plus doxorubicin [Adriamycin], vinblastine and dacarbazine, abbreviated A+ AVD; n=664) versus that obtained with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine, n=670). Patients were required to have treatment-naïve histologically confirmed classical HL, with Ann Arbor Stage III or IV. Overall survival (OS) was the key secondary endpoint.

This study has been reviewed as pivotal trial for the EoI II/55 in previously untreated CD30+ **Stage IV** HL. In that EoI, the MAH initially applied for an indication in advanced HL (which is the same as the current proposed target population), as the trial included HL patients with Ann Arbor Stage III and Stage IV. During review of the data from the 2017 primary analysis of ECHELON-1, the MAH changed the applied indication to Stage IV cHL, based on OS results for patients with Stage III cHL. As of the 2017 primary analysis, overall survival (OS) yielded a hazard ratio in excess of 1 (HR=1.216, 95% CI 0.563 to 2.630).

Results of a second interim analysis (IA2) of OS data (data cut-off 01 June 2021) were reviewed as part of a variation to update SmPC section 4.8 and 5.1 with long-term follow-up data from ECHELON-1 (II/0103). In this procedure, it was concluded that the updated data confirm the benefit of treatment in the approved first line Stage IV HL indication. Based on the same data, the MAH is now seeking an extension of indication in advanced HL, i.e. including Stage III HL patients. This since updated OS results of the second interim analysis in 2021 showed a HR point estimate below 1 in patients with Stage III HL. While IA2 results have been presented before, the study population of interest for review of the data is now changed from Stage IV patients to **advanced** (Stage III and IV) patients.

As per the previous EoI review, the comparator arm, endpoints and statistical methods of the ECHELON-1 trial are considered acceptable. The 2021 IA2 repeated the time-to-event analyses for PFS and OS considered valuable in the long-term follow-up period. As it was not meaningful to repeat an analysis of mPFS per IRF due to discontinuation of independent review, PFS per investigator, a prespecified sensitivity analysis around the mPFS primary endpoint, replaced the function of mPFS per IRF in IA2. This is acknowledged. Secondary endpoints event free survival, disease free survival, duration of response and duration of CR have not been updated, which is acceptable as OS is the key secondary endpoint and the potential OS detriment in Stage III patients was the main concern at the previous EoI review.

There are currently no fully concordant definitions of the term 'advanced HL' in Europe. In some guidelines, patients with clinical Stage IIB with the risk factors large mediastinal mass and/or extranodal disease also belong to 'advanced' patients. Therefore, a similar definition as used in the pivotal trial is preferred in the indication: 'Stage III or IV'. (see SmPC section 4.1).

No changes to the existing dosing recommendation in previously untreated HL have been proposed, which is agreed.

Efficacy data and additional analyses

All patients were already included at the time of the primary analysis with a data cut-off in 2017, therefore, baseline characteristics were the same at the 2021 IA2. In the ITT population, a slightly higher proportion of patients across treatment arms were male (~58%), most patients were white (~83%) and the median age was approximately 36 years. Most patients had Stage IV HL (~64%) and 36% had Stage III disease in the ITT. The demographic characteristics of patients in the ITT population with extranodal involvement, Stage III disease or Stage IV disease were comparable with that of the ITT population as a whole.

Results of the prespecified exploratory sensitivity analysis of PFS by investigator at the 2021 data cut-off (HR 0.678 (95% CI, 0.532 0.863, descriptive 2-sided p=0.002) supported the primary 2017 mPFS by IRF analysis (HR 0.770; 95% CI, 0.603-0.983; p=0.035). With longer follow up in the subgroup of patients with Stage III disease, the PFS by investigator HR improved from 0.766 at the 2017 data cut-off, to 0.603 (95% CI, 0.391 0.93; descriptive p=0.021) at the 2021 data cut-off. In patients with Stage IV disease, the PFS HR remained similar with a HR of ~0.71.

Key secondary endpoint OS reached statistical significance at the 2021 IA2 (0.59 (95% CI, 0.396 0.879, p=0.0009), while this was not (yet) the case at IA1 (HR of 0.728 [95% CI, 0.448; 1.184], p=0.199). After a median OS follow-up duration of 73.3 months, 39 deaths (6%) were reported in the A+ AVD treatment arm and 64 deaths (10%) in the ABVD treatment arm. Median OS was not reached in either treatment arm, the latter is to be expected considering the prognosis of HL patients.

For patients with Stage IV cHL, the OS HR shifted from 0.507 (95% CI 0.265-0.971) as of the 2017 IA1 to 0.478 (95% CI 0.286-0.0.799) with the 2021 IA2. In patients with Stage III cHL, the OS HR changed from 1.216 (95% CI 0.563-2.630) in the 2017 first interim analysis, to 0.863 (95% CI 0.452-1.648) in the 2021 second interim analysis. The censoring reasons were quite similar between treatment arms, except lost to follow-up: 26 out of 237 (10.9%) in A+AVD vs. 39 out of 246 (15.9%) in ABVD (Table 11). If this censoring is informative of an upcoming OS event, it seems more to favour the control arm. The change of HR from >1 to <1 can be understood as Figure 13 shows that the detriment in the A+AVD arm was seen in a part of the survival curve with much censoring, which has disappeared with longer follow-up. Therefore, the updated OS analysis seems more reliable than at IA1, within the constraints of few events. Before 72 months, virtually no difference in survival rates seems to be present in Stage III patients, at 72 months this is 1.2% and at 84 months 2.1%, in favour of A+AVD (Table 11). Therefore, the updated OS results do not indicate a detriment for Stage III patients, which is reassuring. The proportion of patients with Stage III cHL experiencing an OS event is still quite low as of the 2021 IA2 (7% of A+AVD patients and 8% of ABVD patients), however this can be acceptable considering the prognosis of these patients. Overall (complete ITT), 41% (A+AVD) and 48% (ABVD) patients have discontinued the study, and will not provide further follow-up data. In response to the request for supplementary information, the MAH indicated that the 112th OS event to trigger the final OS analyses was recorded, but data analyses is in progress as one date of death is still missing from the additional 9 patients who died since the second interim OS analysis (with 103 OS events). This patient had Stage IV cHL and was randomized to the ABVD arm. A descriptive OS analysis (2023 descriptive analysis) was presented without this OS event (i.e. with 111 OS events). Updated 2023 descriptive OS data for the ITT (HR 0.61, corresponding with approximately 4 percent points OS difference) and Stage IV patients (HR 0.48, corresponding to up to 6 percent points OS difference) supported the 2021 IA2 analyses. For patients with Stage III disease, the proportion of patients experiencing an OS event is still quite low (8%) and the HR shifted from 0.86 (95% CI, 0.452 1.648) to 1.004 (95% CI, 0.540 1.866). There is no survival advantage of A+ AVD, but still no sign of a potential detrimental effect either as the HR is ~1 and KM curves are overlapping (within the constraints of few events). Similar OS results are acceptable

considering the substitution setting and different safety profile (see safety section). Updated OS data were reflected in SmPC section 5.1.

Altogether, clinical relevant efficacy in terms of mPFS by investigator and OS is considered demonstrated for the studied HL patients. Considering the substitution trial setting, similar efficacy compared to the active control arm would be acceptable as well and it is most important to exclude a potential detrimental effect on OS. Updated IA2 results indicate that this has been done for Stage III patients as well.

Subgroup analyses of mPFS by IRF at the primary analysis data cut-off showed that for patients ≥60 or ≥65 and patients without extranodal sites no clear benefit of A+AVD over ABVD in terms of mPFS could be demonstrated as the HR point estimate was ~1. These analyses have not been updated due to discontinuation of independent review, which is acknowledged. The current presented OS subgroup analysis confirmed this observation for patients without extranodal sites, as the HR in this subgroup crossed 1 (HR 1.184, 95% CI: 0.641, 2.187). A trend for a smaller difference between treatment arms has been observed for patients with Stage III disease and 0-1 IPFP risk factors relative to the respective more advanced counterparts as well. Results of these subgroup analyses should be interpreted with caution due to the low number of events, wide confidence intervals and high censoring rates. Results of the mPFS subgroup analyses were reflected in SmPC section 5.1, including the absence of a clinically meaningful difference between treatment arm in elderly patients and patients without extranodal sites. OS Subgroup analyses suggest lower efficacy in females compared to males, as is shown by an OS HR of 0.96 in females vs. 0.43 in males, though results are still considered clinically relevant for both gender subsets in this substitution setting.

As of the previous data cut-off in 2017, mPFS results in elderly patients with Stage IV disease showed a trend towards a larger benefit of A+AVD treatment over ABVD compared to elderly in the ITT (HR~1): patients aged ≥60, n=118, mPFS per IRF: HR of 0.804 (95% CI: 0.42 to 1.53; p=0.506) and patients aged ≥65, n=78, HR of 0.777 (95% CI: 0.36 to 1.67; p=0.515). OS data for this subgroup with the 2023 descriptive analysis data cut-off supported these observations. However, the number of patients within the elderly stage IV subgroup is relatively small and the number of events was low with a high censoring rate. This leads to uncertainty in the HR point estimates of these subgroups, as illustrated by the wide confidence intervals.

A descriptive analysis of OS was performed using data with median follow up of over 7 years for OS. In the ITT population, a lower proportion of patients randomized to A + AVD (44 deaths, 7%) had died compared with patients randomized with ABVD (67 deaths, 10%) [HR = 0.61, 95% CI (0.414, 0.892)]. Similar proportions of Stage III patients randomized to A+AVD (20 deaths, 8%) and ABVD (20 deaths, 8%) had died [HR =1.004, 95% CI (0.540, 1.866)]. A lower proportion of Stage IV patients randomized to A + AVD (24 deaths, 6%) had died compared with patients randomized with ABVD (46 deaths, 11%) [HR = 0.48, 95% CI (0.291, 0.784)].

Results of secondary and exploratory endpoints analysed at the 2017 data cut-off were more or less similar between treatment arms (a.o. CR, ORR, EFS, PET negativity at Cycle 2) or slightly in favour of A+AVD (DFS, rate of patients not in CR who received irradiation and/or chemotherapy, subsequent anticancer therapy).

From previous studies it is known that retreatment with brentuximab vedotin after ASCT is still effective. With the current proposed indication, brentuximab vedotin could in theory be considered three times during the course of the disease (frontline, after ASCT if at increased risk of relapse, and at relapse after ASCT). As of the 2021 data cut-off, only 3 patients in the A+AVD arm received subsequent brentuximab vedotin-containing anticancer therapy, while this applied to 23 patients in the ABVD arm. These data suggest very limited use of brentuximab vedotin in case this antibody-drug conjugate was included in the front-line therapy. As such, a thorough assessment of efficacy of retreatment is not feasible.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

2.4.4. Conclusions on the clinical efficacy

Clinical efficacy of brentuximab vedotin in first line Stage III or IV HL treatment is considered demonstrated by a statistically significant difference in mPFS and OS as shown by a HR of 0.770 and 0.59, respectively, in favour of A+AVD over ABVD in the studied population. This difference seems mainly driven by Stage IV patients. With updated OS data (HR 1.004 (95% CI, 0.540-1.866), as of the 2023 descriptive analysis) there seems no survival advantage in Stage III patients, but no detrimental effect is observed either. The MAH agreed to submit final OS data in the context of a future Type II variation.

2.5. Clinical safety

Introduction

With this EoI application, updated clinical safety findings have been submitted for the ECHELON-1 (Study C25003) safety population after approximately 6 years of posttreatment follow-up (PTFU). Ongoing safety assessments during posttreatment follow-up (PTFU) included deaths, treatment-related serious adverse events (SAEs), treatment-emergent neuropathy events, second malignancies, and pregnancy. Investigators were required to report any deaths and any SAEs that were considered treatment related according to investigator assessment.

The safety results are based on cumulative data from the second interim analysis as of the 01 June 2021 cut-off for data analysis and are presented coincided with the results of the second interim analysis of the study's key secondary endpoint, overall survival (OS). The ECHELON-1 study has been reviewed as pivotal trial for the EoI in previously untreated CD30+ *Stage IV* HL as well using a data cutoff of 20 April 2017 (II/0055). Safety data as of the 01 June 2021 cut-off have been subject of the EMEA/H/C/002455/II/0103 procedure.

Patient exposure

The safety population consisted of 662 A+AVD patients and 659 ABVD patients from pivotal study ECHELON-1, including 237 A+AVD patients and 246 ABVD patients with Stage III cHL. Patients in ECHELON-1 were randomized 1:1 to receive up to 6 cycles of either A+AVD or ABVD on Days 1 and 15 of each 28 day treatment cycle. The relative dose intensity, duration of treatment, and number of maximum completed cycles of individual regimen components was similar between treatment arms. Patients in both treatment groups received a median of 6 cycles of study treatment per patient over a median of approximately 24 weeks. As the maximum number of cycles to be administered was 6, exposure data with the currently presented safety update with data cut-off 01 June 2021 remained the same as those

presented using a data cutoff of 20 April 2017 (II/0055). A median of 6 cycles (range 1 to 6 cycles) was reported for both treatment arms, administered over a similar median duration of approximately 24 weeks (range 2.0 to 48.9 weeks).

Adverse events

For reference, an overview is presented of the safety results for ECHELON-1 from the treatment-emergent period of the study (from administration of the first dose of study drug through 30 days after the last dose of frontline therapy) with data cut-off 20 April 2017. These results have been reviewed as part of the EoI in first line Stage IV cHL (II/0055). An overview of the safety is presented in Table 24.

Table 24 Study C25003: Overview of Safety (Safety Population)

Number of Patients (%)	A+AVD N=662	ABVD N=659
Any AE	653 (99)	646 (98)
Drug-related AE	646 (98)	623 (95)
Grade 3 or higher AE	549 (83)	434 (66)
Drug-related Grade 3 or higher AE	528 (80)	393 (60)
SAE	284 (43)	178 (27)
Drug-related SAE	240 (36)	125 (19)
AEs resulting in study drug discontinuation	87 (13)	104 (16)
AE resulting in dose modification	423 (64)	293 (44)
Dose held	45 (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 drug-related adverse events	8 (1)	7 (1)

Source: Table 15.3.1.1.
A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, and dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event.
MedDRA Version 22.0 was applied.
A patient was counted once for each type of adverse event.
On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.
Drug or dose discontinued permanently indicated at least 1 individual drug within frontline therapy discontinued.
Dose modification included dose held, dose interrupted, dose reduced and dose delayed.

TEAEs: Any Grade

The most frequently reported TEAEs (≥20%) of any grade for ABVD patients were nausea (56% of patients), neutropenia (45%), constipation (37%), fatigue (32%), vomiting (28%), and pyrexia and alopecia (22% each; Table 25).

Table 25. Study C25003: TEAEs Reported for at Least 10% of Patients in Either Treatment Arm by preferred term (PT) (Safety Population)

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)
Febrile neutropenia	128 (19)	52 (8)
Bone pain	126 (19)	66 (10)
Insomnia	126 (19)	82 (12)
Decreased appetite	118 (18)	76 (12)
Cough	97 (15)	123 (19)
Headache	95 (14)	94 (14)
Arthralgia	89 (13)	78 (12)
Neutrophil count decreased	86 (13)	79 (12)
Dyspepsia	84 (13)	75 (11)
Paraesthesia	84 (13)	73 (11)
Back pain	83 (13)	49 (7)
Dyspnoea	82 (12)	124 (19)
Myalgia	81 (12)	71 (11)
Pain in extremity	81 (12)	67 (10)
Oropharyngeal pain	72 (11)	55 (8)
Upper respiratory tract infection	70 (11)	70 (11)
Alanine aminotransferase increased	68 (10)	26 (4)

Source: C25003 Table 15.3.1.18.
TEAEs were defined as any AE that occurred after administration of the first dose of the study drug and up through 30 days after the last dose of frontline therapy.
MedDRA Version 19.0 was applied.
A patient was counted once for each preferred term.
Percentages determined using the number of patients in the treatment arm as the denominator.
Preferred terms sorted by decreasing frequency of the A+AVD treatment arm.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, TEAE=treatment-emergent adverse event.

Treatment-Related TEAEs: Any Grade

The most frequently reported drug-related TEAEs (≥20%) of any grade for the A+AVD patients were neutropenia (55% of patients), nausea (48%), constipation (33%), vomiting and peripheral sensory neuropathy (27% each), fatigue (26%), PN (25%) and alopecia (24%; Table 26).

Table 26. Study C25003: Drug-Related TEAEs Reported for at Least 10% of Patients in Either Treatment Arm by PT (Safety Population)

Preferred Term	A+AVD N=662 n (%)	ABVD N=659 n (%)
Patients with at least 1 drug-related TEAE	641 (97)	617 (94)
Neutropenia	366 (55)	270 (41)
Nausea	319 (48)	342 (52)
Constipation	216 (33)	168 (25)
Vomiting	182 (27)	156 (24)
Peripheral sensory neuropathy	180 (27)	107 (16)
Fatigue	169 (26)	178 (27)
Neuropathy peripheral	163 (25)	73 (11)
Alopecia	159 (24)	135 (20)
Diarrhoea	120 (18)	61 (9)
Febrile neutropenia	120 (18)	46 (7)
Stomatitis	118 (18)	93 (14)
Pyrexia	113 (17)	91 (14)
Anaemia	107 (16)	51 (8)
Abdominal pain	91 (14)	30 (5)
Weight decreased	90 (14)	21 (3)
Decreased appetite	86 (13)	60 (9)
Neutrophil count decreased	84 (13)	75 (11)
Paraesthesia	75 (11)	63 (10)
Dyspnoea	43 (6)	82 (12)

Source: C25003 Table 15.3.1.3.
TEAEs were defined as any AE that occurred after administration of the first dose of the study drug and up through 30 days after the last dose of frontline therapy.
MedDRA Version 19.0 was applied.
A patient was counted once for each preferred term.
Percentages determined using the number of patients in the treatment arm as the denominator.
Relatedness was attributed to any of the study drugs in the combination regimen.
Preferred terms sorted by decreasing frequency of the A+AVD treatment arm.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, TEAE=treatment-emergent adverse event.

Grade 3 or Higher Treatment-Emergent Adverse Events

At least 1 Grade 3 or higher TEAE was reported for 549 patients (83%) in the A+AVD treatment arm and 434 patients (66%) in the ABVD treatment arm. The Grade 3 or higher TEAEs reported for at least 10% of the A+AVD patients were neutropenia (54% of patients), febrile neutropenia (19%), and decreased neutrophil count (13%). The Grade 3 or higher TEAEs reported for at least 10% of ABVD patients were neutropenia (39%) and decreased neutrophil count (10%).

Drug-Related Grade 3 or Higher Treatment-Emergent Adverse Events

At least 1 Grade 3 or higher drug-related TEAE was reported for 525 patients (79%) in the A+AVD treatment arm and 389 patients (59%) in the ABVD treatment arm. The Grade 3 or higher drug-related TEAEs reported for at least 5% of the A+AVD patients were neutropenia (52%), febrile neutropenia (18%), decreased neutrophil count (12%) and anemia (7%). The Grade 3 or higher drug-related TEAEs reported for at least 5% of ABVD patients were neutropenia (37%), decreased neutrophil count (10%), and febrile neutropenia (7%).

Serious adverse event/deaths/other significant events

Updated results for the safety assessments that continued during posttreatment follow-up (PTFU) are provided in the following sections.

SAEs

2017 data cut-off – At least 1 treatment-emergent SAE was reported for 284 A+AVD patients (43%) and 178 ABVD patients (27%; Table 27). The most frequently reported treatment-emergent SAEs for the

A+AVD patients were febrile neutropenia (17% of patients), pyrexia (7%), and neutropenia and pneumonia (3% each).

Table 27. Study C25003: Treatment-Emergent SAEs Reported for at Least 5 Patients in Either Treatment Arm by PT (Safety Population)

Preferred Term	A+AVD N=662 n (%)	ABVD N=659 n (%)
Patients with at least 1 treatment-emergent SAE	284 (43)	178 (27)
Febrile neutropenia	114 (17)	43 (7)
Pyrexia	44 (7)	28 (4)
Neutropenia	19 (3)	4 (<1)
Pneumonia	18 (3)	15 (2)
Abdominal pain	14 (2)	4 (<1)
Sepsis	14 (2)	4 (<1)
Constipation	11 (2)	6 (<1)
Diarrhoea	11 (2)	1 (<1)
Pulmonary embolism	11 (2)	9 (1)
Vomiting	11 (2)	3 (<1)
Dehydration	10 (2)	3 (<1)
Neutropenic sepsis	8 (1)	2 (<1)
Anaemia	7 (1)	3 (<1)
Device related infection	7 (1)	2 (<1)
Nausea	7 (1)	3 (<1)
Cellulitis	5 (<1)	2 (<1)
Deep vein thrombosis	5 (<1)	2 (<1)
Pneumocystis jirovecii pneumonia	5 (<1)	2 (<1)
Dyspnoea	3 (<1)	5 (<1)
Pneumonitis	2 (<1)	12 (2)
Pulmonary toxicity	0	5 (<1)

Source: C25003 Table 15.3.1.22.
MedDRA Version 19.0 was applied.
A patient was counted once for each PT.
Percentages were determined using the number of patients in the treatment arm as the denominator.
PTs sorted by decreasing frequency for the A+AVD treatment arm.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, SAE=serious adverse event.

At least 1 drug-related SAE was reported for 240 patients (36%) in the A+AVD treatment arm and 125 patients (19%) in the ABVD treatment arm. The most frequently reported drug-related SAEs for the A+AVD patients were febrile neutropenia (17% of patients); pyrexia (6%); neutropenia (3%); and pneumonia, sepsis, abdominal pain, constipation, and vomiting (2% each).

2021 data cut-off – During PTFU, investigators were required to report to the sponsor any SAE that they considered to be treatment related. Drug relationship was ascribed to any of the anticancer regimens in the combination therapy. SAEs reported during PTFU were identified from a review of the clinical and global safety databases. During PTFU, peripheral motor neuropathy was reported for 1 A+AVD patient (<1%). Peripheral motor neuropathy was initially reported as a drug-related SAE during the treatment period of the study and persisted beyond 30 days from the last dose of frontline therapy.

A treatment-related SAE was identified from a review of the sponsor's global safety database for 3 patients each across the 2 treatment arms. Pain, suicidal ideation, and malignant lung neoplasm were the treatment-related SAE PTs reported for 1 A+AVD patient each and diffuse large B-cell lymphoma, trisomy 18 (Edward's syndrome [child]), and acute promyelocytic leukemia were the treatment-related SAE PTs reported for 1 ABVD patient each.

Per protocol, any occurrence of progressive multifocal leukoencephalopathy (PML) in a patient was to be reported on an SAE form, regardless of treatment arm or causal relationship, from administration of the first dose of study drug through death or termination of the study by the sponsor.

PML was reported for 1 A+AVD patient during PTFU. PML was considered to be not drug related, according to the investigator assessment and was attributed to the patient's immunosuppressive state subsequent to allogeneic stem cell transplantation. The patient's condition was reported to be resolving.

Deaths

2017 data cut-off – On-study deaths (i.e. within 30 days of last dose of frontline therapy), were reported for 9 patients (1%) in the A+AVD arm and 13 patients (2%) in the ABVD arm at the time of the primary analysis. At this 2017 data cut-off, 19 patients had died during post treatment follow up (PTFU, i.e. after 30 days of the last dose of frontline therapy) in the A+AVD arm and 26 patients in the ABVD arm.

2021 data cut-off – As of the 01 June 2021 cut-off for data analysis, 39 deaths (6%) were reported for A+AVD patients and 64 deaths (10%) were reported for ABVD patients in the safety population (Table 28).

Deaths during the 2021 PTFU were reported for 30 patients (5%) in the A+AVD arm and 51 patients (8%) in the ABVD arm. Death was considered disease related for 15 patients (2%) vs. 24 patients (4%), respectively. The primary cause of death for the non–disease related deaths during the PTFU (N=15; 2% vs. N=27; 4%) was different for all cases, except for cardiac arrest that was reported for 2 patients (<1%) and 3 hemorrhage related deaths (hemorrhage following a fall at home, intracerebral hemorrhage, intracranial hemorrhage; one case for each) in the A+AVD arm. Of note, one death is attributed to AE and 3 deaths are attributed to deceased. In the ABVD arm N=5 deaths were related to pulmonary toxicity/infections.

Table 28 Study C25003: Deaths (Safety Population)

Number of Patients (%)	**A+AVD N=662**	**ABVD N=659**
All deaths	39 (6)	64 (10)
Disease related	18 (3)	28 (4)
Not disease related	21 (3)	36 (5)
Primary cause of death		
Deaths within 30 days of last dose of frontline therapy	9 (1)	13 (2)
Disease related	3 (<1)	4 (<1)
Pneumonia	0	2 (<1)
Cardiopulmonary failure	0	1 (<1)
Haemophagocytic lymphohistiocytosis	1 (<1)	0
Myocardial infarction	1 (<1)	0
Pneumocystis jirovecii pneumonia	0	1 (<1)
Septic shock	1 (<1)	0
Non-disease related	6 (<1)	9 (1)
Cardiac arrest	0	2 (<1)
Death	1 (<1)	1 (<1)
Acute respiratory distress syndrome	0	1 (<1)
Cardiorespiratory arrest	1 (<1)	0
Cerebrovascular accident	0	1 (<1)
Multiple organ dysfunction syndrome	1 (<1)	0

Number of Patients (%)	A+AVD N=662	ABVD N=659
Myocardial infarction	1 (<1)	0
Neutropenic sepsis	1 (<1)	0
Pneumonia	0	1 (<1)
Pneumonitis	0	1 (<1)
Pulmonary toxicity	0	1 (<1)
Respiratory disorder	0	1 (<1)
Respiratory failure	1 (<1)	0
Deaths >30 days of last dose of frontline therapy	30 (5)	51 (8)
Disease related	15 (2)	24 (4)
Related to disease under study or complications thereof	15 (2)	24 (4)
Non-disease related	15 (2)	27 (4)
Unknown	1 (<1)	6 (<1)
Deceased	3 (<1)	1 (<1)
Cardiac arrest	2 (<1)	0
Acute myeloid leukemia	0	1 (<1)
Acute promyelocytic leukemia	0	1 (<1)
Adverse event	1 (<1)	0
Cancer of bile ducts	0	1 (<1)
Clostridial myonecrosis (autopsy pending)	0	1 (<1)
Complications secondary to second transplantation	0	1 (<1)
Death caused by DLBCL	0	1 (<1)
Due to lymphoma progression; T-cell lymphoma	1 (<1)	0
Gallbladder cancer	0	1 (<1)
Haematological phagocytosis	0	1 (<1)
Haemorrhage following a fall at home	1 (<1)	0
Heart failure	1 (<1)	0
Hepatocellular carcinoma	0	1 (<1)
Information not available	0	1 (<1)
Intracerebral hemorrhage	1 (<1)	0
Intracranial hemorrhage	1 (<1)	0
Lower respiratory tract infection	0	1 (<1)
Metastatic prostate cancer	0	1 (<1)
Myelodysplastic syndrome	0	1 (<1)
Suicide	1 (<1)	0
HL, which eventually transformed to DLBCL	1 (<1)	0
Peripheral T-cell lymphoma	0	1 (<1)
Pneumocystis pneumonia	0	1 (<1)
Pneumonia	1 (<1)	0
Pneumonitis	0	1 (<1)
Pulmonary hemorrhage/pneumonia	0	1 (<1)
SARS-CoV2 infection	0	1 (<1)
Sudden death without symptoms	0	1 (<1)
T-cell lymphoma	0	1 (<1)

Source: C25003 Table 15.3.1.28.

A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, and dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin lymphoma; SARS-CoV2: severe acute respiratory syndrome coronavirus 2.

Number of Patients (%)	A+AVD N=662	ABVD N=659

Follow-up deaths were defined as deaths that occurred after 30 days of the last dose of frontline therapy.

Follow-up death collected on disposition page do not have Preferred Terms but primary cause of death. Terms under Disease related or Non-disease related are displayed as reported.

On 11 March 2023, the 112th overall survival (OS) event required to trigger the final analysis of OS (OS FA) was recorded. Data cleaning and site queries toward the OS FA are now in progress, with no date of death yet available for 1 of the 9 patients who died since the second interim OS analysis (OS IA2).The available data on the 9 additional deaths is presented in Table 29.

Table 29 ECHELON-1: Listing of Deaths (Safety Population Patients Who Died Between OS IA2 [103 Events] and Final OS Analysis [112 Events])

Patient ID	Disease Stage	Cause of Death	Death Date
A+AVD Patients			
02010-301	Stage III	Esophageal cancer	13 Oct 2022
04003-303	Stage III	Related to disease under study or complications thereof	08 Jul 2022
63007-303	Stage III	Possibly related to disease under study or complications thereof (details unknown)	13 Dec 2022
58009-301	Stage IV	Nurse verified patient died of respiratory failure caused by pneumothorax of both lungs (per hospital notes)	11 Mar 2023
63006-301	Stage IV	Related to disease under study or complications thereof	15 Jun 2021
ABVD Patients			
07005-303	Stage IV	Adenocarcinoma of the lung	21 Oct 2022
42009-351	Stage IV	Death	Unknown
58003-321	Stage IV	Biliary obstruction, liver damage, was on hospice	28 Aug 2022
63001-301	Stage IV	Related to disease under study or complications thereof	12 Jun 2022

Source: Extract performed 23 May 2023 on preliminary data.

All safety population patients herein were also in the intent-to-treat (ITT) population (Listing 16.2.3.1).

Stage III cHL

As of the 01 June 2021 cut-off for data analysis, 17 deaths (7%) were reported for A+AVD patients and 20 deaths (8%) were reported for ABVD patients in the safety population. On-study death was reported for 4 A+AVD patients and 5 ABVD patients (2% each) in the Stage III cHL subset of the safety population.

Death during 2021 PTFU was reported for 13 A+AVD patients and 15 ABVD patients (6% each) in the Stage III subset of patients in the safety population. PTFU death was considered disease related or attributed to the primary disease and associated complications for 8 A+AVD patients (3%) vs. 6 ABVD treated patients (2%) and non–disease related for 5 A+AVD patients (2%) vs. 9 ABVD patients (4%) in this subset.

The reported non-disease related primary causes of death in the A+AVD arm (n=5) were AE, intracerebral hemorrhage, (completed) suicide, deceased NOS, and pneumonia. AE, intracerebral haemorrhage, and deceased NOS were considered complications of the primary disease, cHL. Pneumonia was considered a complication of a second malignancy.

The reported primary non-disease related causes of death in the ABVD arm (n=9) were clostridial myonecrosis, lower respiratory tract infection, hematological phagocytosis, pulmonary hemorrhage/pneumonia, acute promyelocytic leukemia, hepatocellular carcinoma, T-cell lymphoma and unknown for 2 patients.

Stage IV cHL

On-study death was reported for 5 A+ AVD patients (1%) and 8 ABVD patients (2%) in the Stage IV cHL subset of the safety population. Deaths due to drug-related adverse events were reported in 5 patients in each arm (1%). Data were not presented separately for this subgroup.

Other significant AEs

Updated results for the safety assessments AEs of special interest that continued during PTFU (peripheral neuropathy and second malignancy) are described below. For comparison, results with the 2017 data cut-off are presented as well.

Peripheral neuropathy

Peripheral neuropathy is a well characterized side effect of brentuximab vedotin treatment and is considered an adverse event of special interest for patients who treated with brentuximab vedotin. Patients with an ongoing PN event at the end of frontline therapy were to be followed during PTFU every 3 months for 36 months and every 6 months thereafter to assess changes in severity of PN events until the sooner of resolution to baseline or study closure.

2017 data cut-off – As of the 20 April 2017 cut-off for data analysis, at least 1 PN (SMQ) event of any grade was reported for 442 patients (67%) in the A+AVD treatment arm and 286 patients (43%) in the ABVD treatment arm. The most frequently reported PN PTs (≥5%) of any grade for the A+AVD patients were peripheral sensory neuropathy (29% of patients), PN (26%), paraesthesia (13%), PMN (6%), and muscular weakness (5%). The most frequently reported PN PTs of any grade for ABVD patients were peripheral sensory neuropathy (17% of patients), PN (13%), paraesthesia (11%), and hypoesthesia (5%).

For patients with at least 1 treatment-emergent PN (SMQ) event, PN continued to improve over time and resolution or improvement was reported for 295 A+AVD patients (67%) and 214 ABVD patients (75%) at the time of last follow-up. At EOT, an ongoing PN (SMQ) event was reported for 320 A+AVD patients (72%) and 147 ABVD patients (51%), the majority of which were either Grade 1 or Grade 2 events. At the time of the last follow-up, an ongoing PN event was reported for 251 A+AVD patients (57%) and 112 ABVD patients (39%), the highest proportion of which were Grade 1 events.

2021 data cut-off – As of the 01 June 2021 cut-off, at least 1 PN (SMQ) event of any grade was reported for 443 A+AVD patients (67%) and 286 ABVD patients (43%) in the safety population.

The most commonly reported PN (SMQ) events of any grade for A+AVD patients were peripheral sensory neuropathy (29% of patients), peripheral neuropathy (26%), paraesthesia (13%), and peripheral motor

neuropathy (6%). For ABVD patients, the most commonly reported PN (SMQ) events of any grade were peripheral sensory neuropathy (17% of patients), peripheral neuropathy (13%), and paraesthesia.

Among the 443 A+AVD and 286 ABVD patients for whom at least 1 PN (SMQ) event was reported during frontline therapy, resolution was reported for 318 A+AVD patients (72%) and 227 ABVD patients (79%), and resolution or improvement for 379 A+AVD patients (86%) and 249 ABVD patients (87%) at last follow-up.

At last follow-up, a PN (SMQ) event was reported to be ongoing for 125 A+AVD patients (28%) and 59 ABVD patients (21%). Among A+AVD patients with an ongoing PN (SMQ) event, Grade 1 was reported for 71 patients (16%), Grade 2 for 38 patients (9%), and Grade 3 for 15 patients (3%). Grade 4 polyneuropathy was the only Grade 4 PN (SMQ) event reported in the study and was reported to be ongoing for the affected A+AVD patient at the time of the patient's death. Among the ABVD patients with an ongoing PN (SMQ) event, Grade 1 was reported for 39 patients (14%), Grade 2 for 16 patients (6%), and Grade 3 for 4 patients (1%).

Table 30. Study C25003: Resolution and Improvement of Treatment-Emergent Peripheral Neuropathy (SMQ) (Safety Population)

Patients With Treatment-emergent PN (SMQ) Event, (%)	A+AVD (N=443)	ABVD (N=286)
At EOT [a]		
Patients with resolution or improvement in PN events [b, c]	236 (53)	180 (63)
Patients with resolution of all PN events [b]	133 (30)	145 (51)
Patients with improvement in PN events [c]	103 (23)	35 (12)
Patients with no resolution or improvement of any PN events	207 (47)	106 (37)
Patients with ongoing PN events [d]	310 (70)	140 (49)
Grade 1	178 (40)	101 (35)
Grade 2	91 (21)	33 (12)
Grade 3	40 (9)	6 (2)
Grade 4	1 (<1)	0
At last follow-up		
Patients with resolution or improvement in PN events [b, c]	379 (86)	249 (87)
Patients with resolution of all PN events [b]	318 (72)	227 (79)
Patients with improvement in PN events [c]	61 (14)	22 (8)
Patients with no resolution or improvement of any PN events	64 (14)	37 (13)
Patients with ongoing PN events [e]	125 (28)	59 (21)
Grade 1	71 (16)	39 (14)
Grade 2	38 (9)	16 (6)
Grade 3	15 (3)	4 (1)
Grade 4	1 (<1)	0

A+AVD: brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, and dacarbazine; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; EOT: end of treatment; MedDRA: Medical Dictionary for Regulatory Activities; PN: peripheral neuropathy; SMQ: standardised MedDRA query.

Only patients who experienced any treatment-emergent PN (SMQ) event within PN SMQ broad included in table.

One patient had ongoing Grade 4 PN reported at time of death 87 days after first dose.

[a] For patients without EOT date, the date was imputed as last dose of frontline therapy +30 days.

[b] Resolution was defined as event outcome of "resolved" or "resolved with sequelae". Patients with resolution of all PN events at EOT (or last follow-up) were patients with all PN resolved and all the resolution dates were on or before EOT or last follow-up date.

[c] Resolution implies improvement. In addition, for events that were not resolved, improvement was defined as decrease by at least 1 grade from the worst grade with no higher grade thereafter. Patients with improvement in any event at EOT or at last follow-up were those with at least 1 improved event and date of improvement was before EOT date or last follow-up date. Patients with all PN events resolved were excluded.

[d] Ongoing event at EOT was defined as event end date was after the EOT date if event end date was not missing or last follow-up date was on or after the EOT date if event end date is missing. Maximum severity is the maximum among grades that were occurring at EOT.

[e] Ongoing event at last follow-up was defined as event outcome of "unresolved" or "unknown" or events without an end date. Maximum severity is the maximum among grades that were occurring at last follow-up.

Among patients for whom at least 1 treatment-emergent PN (SMQ) event of any grade was reported during frontline therapy, the median time to resolution was 16 weeks (range, 0-283 weeks) for A+AVD patients vs. 10 weeks (range, 0-343 weeks) for ABVD patients.

Among the subgroup of patients for whom a PN (SMQ) event was reported to be ongoing at the end of frontline therapy, resolution was reported for 185 A+AVD patients (42%) and 82 ABVD patients (29%) at last follow-up. Resolution was reported at a median of 34 weeks (range, 0-270 weeks) after end of treatment (EOT) for A+AVD patients and 16 weeks (range, 0-318 weeks) after EOT for ABVD patients.

Peripheral motor neuropathy: Among the 74 A+AVD patients and 29 ABVD patients for whom at least 1 treatment-emergent PMN (SSQ) event of any grade was reported during frontline therapy, resolution was reported for 55 A+AVD patients (74%) and 26 ABVD patients (90%), and resolution or improvement for 62 A+AVD patients (84%) and 26 ABVD patients (90%) at last follow-up. At last follow-up, a PMN (SSQ) event was reported to be ongoing for 19 A+AVD patients (26%) and 3 ABVD patients (10%). Resolution was reported at a median of 49 days (range, 0-237 days) after EOT for A+AVD patients and 18 days (range, 4-240 days) after EOT for ABVD patients.

Secondary malignancy

2017 data cut-off – As of the 20 April 2017 data cut-off date, 10 of 662 patients receiving A+AVD (1.5%) and 14 of 659 patients receiving ABVD (2.1%) experienced a second malignancy. The onset day for second malignancies following the last dose of the study treatment ranged from 24 to 624 days for the A+AVD arm and from 14 to 857 days for the A+AVD arm.

2021 data cut-off – A second malignancy was reported for 23 A+AVD patients (3%) and 32 ABVD patients (5%) in the safety population. After a categorisation as to what was reported in the CSR, the number of patients with a solid (2%) or hematological (2%) malignancy was comparable across the treatment arms in the A+AVD versus ABVD arm. No A+AVD patient (0%) had a malignancy that could not be categorized as opposed to 3 ABVD patients (<1%).

Table 31 ECHELON-1: Second Malignancy as of 2021 OS IA2, Categorized by Solid or Heme Malignancy Type (Safety Population)

Disease Type CE/AE Term	A+AVD N = 662 n (%)	ABVD N = 659 n (%)
Patients with second/secondary malignancy	23 (3)	32 (5)

Table 31 ECHELON-1: Second Malignancy as of 2021 OS IA2, Categorized by Solid or Heme Malignancy Type (Safety Population)

Disease Type CE/AE Term	A+AVD N = 662 n (%)	ABVD N = 659 n (%)
Solid Neoplasm	14 (2)	13 (2)
Prostate	3 (<1)	2 (<1)
Melanoma	1 (<1)	2 (<1)
Thyroid	1 (<1)	1 (<1)
Anal angiomyxoma	0	1 (<1)
Appendiceal carcinoma	1 (<1)	0
Basal cell carcinoma in left ear	0	1 (<1)
Breast	1 (<1)	0
Cancer of bile ducts	0	1 (<1)
Cervical	0	1 (<1)
Colon	0	1 (<1)
Gall bladder	0	1 (<1)
Invasive adenocarcinoma in the right lower lobe of lung	0	1 (<1)
Liver	0	1 (<1)
Metastatic gastrointestinal stromal tumor	1 (<1)	0
Metastatic lung cancer	1 (<1)	0
Rectal	1 (<1)	0
Renal cell carcinoma	1 (<1)	0
Skin basal cell carcinoma, excised.	1 (<1)	0
Squamous cell carcinoma (lesion removed)	0	1 (<1)
Stomach	0	1 (<1)
Undetermined nodule right lung lobe	1 (<1)	0
Urothelial carcinoma	1 (<1)	0
Hematological Neoplasm	10 (2)	16 (2)
Follicular lymphoma	1 (<1)	4 (<1)
Acute myeloid leukaemia or related precursor neoplasm	2 (<1)	1 (<1)
Diffuse large b-cell lymphoma NOS	1 (<1)	2 (<1)
Angioimmunoblastic t-cell lymphoma	1 (<1)	1 (<1)
Peripheral t-cell lymphoma NOS	1 (<1)	1 (<1)
'Double hit' DLBCL	1 (<1)	0
Acute promyelocytic leukemia	0	1 (<1)
Diffuse large B-cell lymphoma of lymph nodes of multiple regions	0	1 (<1)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (malt)	0	1 (<1)
Mycosis fungoides	1 (<1)	0
Myelodysplastic syndrome	0	1 (<1)
Non-Hodgkin lymphoma	1 (<1)	0
Precursor B-acute lymphoblastic leukemia/lymphoblastic lymphoma (LBL)	0	1 (<1)
Primary cutaneous marginal zone lymphoma	1 (<1)	0
Primary mediastinal (thymic) large B-cell lymphoma	0	1 (<1)
Subject was found to have diffuse B cell lymphoma in September 2015	0	1 (<1)
Unknown	0	3 (<1)
Atypical Langerhans cell proliferation	0	1 (<1)
Granulomatous disease sarcoidosis like	0	1 (<1)
Unknown, during diagnostics	0	1 (<1)

Data cutoff date 01 June 2021, run 02 June 2023.
One patient experienced both a heme (mycosis fungoides) and solid (prostate) malignancy.

Fertility/pregnancy

Any pregnancy in patients or their partners from the date of first dose until the date of study closure was to be reported and the pregnancy was to be followed for the final pregnancy outcome.

At least 1 pregnancy was reported for 49 female A+AVD patients (17%) with 39 live births (80%) reported as the most recent pregnancy outcome for these patients, and for 28 female ABVD patients (10%) with 19 live births (68%) reported as the most recent pregnancy outcome for these patients.

At least 1 pregnancy was reported for 33 partners each of A+AVD patients (9%) and ABVD patients (8%) with 31 live births (94%) reported as the most recent pregnancy outcome for the partners of A+AVD patients and 26 live births (79%) reported as the most recent pregnancy outcome for the partners of ABVD patients.

No stillbirths were reported for either female patients or partners of male patients across the 2 treatment arms

Subgroup analyses

2017 data cut-off – On-treatment safety data have been presented separately for subgroups of patients with Stage III and Stage IV cHL disease. The incidence of SAEs, treatment-related SAEs and AEs resulting in study drug discontinuation was higher in patients with Stage III cHL compared to the incidence observed in patients with Stage IV cHL (Table 28, Table 29).

Table 32. ECHELON-1: Overview of Safety (Safety Population With Stage III cHL)

	A+AVD N=236 n (%)	ABVD N=244 n (%)
Any AE	235 (100)	241 (99)
Treatment-related AE	231 (98)	232 (95)
Grade 3 or higher AE	196 (83)	155 (64)
Treatment-related Grade 3 or higher AE	188 (80)	139 (57)
SAE	113 (48)	63 (26)
Treatment-related SAE	99 (42)	42 (17)
AEs resulting in study drug discontinuation	44 (19)	39 (16)
AE resulting in dose modification	155 (66)	109 (45)
Dose held	18 (8)	10 (4)
Dose interrupted	10 (4)	13 (5)
Dose reduced	70 (30)	24 (10)
Dose delayed	114 (48)	79 (32)
On-study deaths	4 (2)	5 (2)
Deaths due to study treatment-related AEs	3 (1)	2 (<1)

Source: 0114\mpi\0068\ICR_BIO\dev\primary\programs\tables\ADt15.3.1.1E-teae_stagiii.sas, run date 29 May 2018: 11:53.
TEAEs were defined as any AE that occurred after administration of the first dose of study drug and through 30 days after the last dose of frontline therapy.
A patient was counted once for each type of event.
AEs were coded using the MedDRA dictionary Version 19.0.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PTFU=posttreatment follow-up, TEAE=treatment-emergent adverse event.
(a) On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.
(b) PTFU deaths were defined as deaths that occurred after 30 days of the last dose of frontline therapy.

Table 33. ECHELON-1: Overview of Safety (Safety Population With Stage IV cHL)

	A+AVD N=424 n (%)	ABVD N=413 n (%)
Any adverse event	416 (98)	403 (98)
Drug-related adverse event	408 (96)	383 (93)
Grade 3 or higher adverse event	352 (83)	278 (67)
Drug-related Grade 3 or higher adverse event	336 (79)	250 (61)
Serious adverse event	170 (40)	114 (28)
Drug-related serious adverse event	140 (33)	83 (20)
Adverse events resulting in study drug or dose discontinuation	44 (10)	66 (16)
Adverse event resulting in dose modification	268 (63)	184 (45)
Dose held	26 (6)	22 (5)
Dose interrupted	12 (3)	20 (5)
Dose reduced	121 (29)	41 (10)
Dose delayed	204 (48)	138 (33)
On-study deaths	5 (1)	8 (2)
Deaths due to drug-related adverse events	5 (1)	5 (1)

Source: m2.7.4 – ECHELON-1, Table 4.a.

The incidence of TEAEs of Grade 3 or higher is similar between patients with Stage III or IV cHL (83%). The most common TEAEs of Grade 3 or higher are similar between treatment arms, except for a slightly lower frequency of neutropaenia in patients with Stage III cHL (50%) compared to Stage IV patients (56%; Table 30, Table 31).

Table 34. Most Common (At Least 10% in Either Arm) Treatment-Emergent Grade 3 or Higher Adverse Events by MedDRA Preferred Term (Safety Population with Stage III cHL)

Preferred Term	A+AVD N=236 n (%)	ABVD N=244 n (%)
Patients with at least 1 Grade 3 or higher TEAE	196 (83)	155 (64)
Neutropenia	117 (50)	91 (37)
Febrile neutropenia	48 (20)	17 (7)
Neutrophil count decreased	31 (13)	28 (11)

Source: 0114\mpi\0068\ICR_BIO\dev\primary\programs\tables\ADt15.3.1.19C-comm10_gegr3_stagiii.sas, run date 29 May 2018: 11:53.
Treatment-emergent adverse events are defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of frontline therapy.
MedDRA dictionary Version 19.0 was applied.
Patient Incidence: A patient counts once for each preferred term.
Percentages use the number of treated patients as the denominator.

Table 35. Most Common (At Least 10% in Either Arm) Treatment-Emergent Grade 3 or Higher Adverse Events by MedDRA Primary System Organ Class and Preferred Term (Safety Population with Stage IV cHL)

Preferred Term	A+AVD N=424 n (%)	ABVD N=413 n (%)
Patients with at least 1 Grade 3 or higher TEAE	352 (83)	278 (67)
Neutropenia	239 (56)	169 (41)
Febrile neutropenia	80 (19)	35 (8)
Neutrophil count decreased	52 (12)	39 (9)

Source: m2.7.4 – ECHELON-1, Table 4.c

Laboratory findings

On-treatment laboratory findings for the safety population with data cut-off 01 June 2017 have been reviewed at the time of the EoI to first line Stage IV cHL and are not repeated here.

Safety in special populations

Elderly

The incidence of second malignancy was evaluated for patients aged <60 years and those aged ≥60 years.

Patients <60 years – A total of 579 A+AVD patients and 561 ABVD patients in the safety population were aged <60 years. Within the subgroup of patients across the 2 treatment arms aged <60 years, a second malignancy was reported for 14 A+AVD patients (2%) and 18 ABVD patients (3%). Tumours categorized as 'other' were the most reported of these malignancies; 'other' tumours were reported for 6 A+AVD patients and 7 ABVD patients (1% each), mature B-cell neoplasms for 1 A+AVD patient and 5 ABVD patients, solid tumours for 3 patients each and mature T-cell and natural killer–cell neoplasms for 2 patients each across the 2 treatment arms, acute myeloid leukaemia or related precursor neoplasm for 2 A+AVD patients and precursor lymphoid neoplasm for 1 ABVD patient (<1% each)

Patients ≥60 years – A total of 83 A+AVD patients and 98 ABVD patients in the safety population were aged ≥60 years. Within the subgroup aged ≥60 years, a second malignancy was reported for 9 A+AVD patients (11%) and 14 ABVD patients (14%). Solid tumours and those categorized as 'other' were reported for 5 A+AVD patients each (5%). Solid tumours were reported for 6 ABVD patients (6%) and 'other' tumours for 5 ABVD patients (5%).

Safety related to drug-drug interactions and other interactions

No new data regarding interactions have been submitted.

Discontinuation due to adverse events

2017 data cut-off – An AE resulted in premature study drug discontinuation for 88 patients (13%) in the A+AVD arm vs. 105 patients (16%) in the ABVD arm.

This data has not been updated with the 2021 data cut-off.

Post marketing experience

As of 30 January 2023, brentuximab vedotin has been approved in 79 countries and regions. As of the 18 August 2022 data-lock point for the currently approved PBRER (Periodic Benefit-Risk Evaluation Report), the cumulative estimated patient exposure to brentuximab vedotin was 119,292 patients, including 3320 patients from company-sponsored clinical studies, 4015 patients from investigator-sponsored studies, 2976 patients from various compassionate use programs, and approximately 108,981 patients from the postmarketing setting (sponsor in-house data).

No data from post marketing experience in first line HL were submitted within this application. Post marketing experience has been the subject of Periodic Safety Update Single Assessments (PSUSAs) with the latest update reporting up to 18 August 2022 (EMEA/H/C/PSUSA/00010039/202208). Here it was concluded that the benefit-risk assessment for brentuximab vedotin remains unchanged.

2.5.1. Discussion on clinical safety

Updated clinical safety findings have been submitted for pivotal Phase 3 Study C25003 (ECHELON 1) after approximately 6 years of posttreatment follow up (PTFU) with data cut-off 01 June 2021. The ECHELON-1 study has been reviewed as pivotal trial for the EoI in previously untreated CD30+ Stage IV HL as well using a data cutoff of 20 April 2017 (II/0055). PTFU assessments included deaths, treatment related SAEs, PN (SMQ) events that were ongoing at the end of frontline therapy, and secondary malignancies. PTFU safety with data cut-off 01 June 2021 have been previously submitted as part of II/0103.

Exposure – The safety population consisted of 662 A+AVD patients and 659 ABVD patients from pivotal study ECHELON-1. This population included 237 A+AVD patients and 246 ABVD patients with Stage III cHL, who comprise (next to Stage IV patients) part of the applied target indication in advanced HL. No new exposure data was provided. The maximum number of cycles to be administered was 6. As the median number of cycles of study treatment was already 6 in both treatment arms at the previously reviewed 20 April 2017 data cut-off, exposure data remained the same with the currently presented safety update with data cut-off 01 June 2021. A similar median duration of approximately 24 weeks (range 2.0 to 48.9 weeks) was observed in both arms. Of note, patients lost to follow up or by withdrawn patients (>30% in both arms) may have influenced safety reporting during the PTFU, however rates were quite similar between the two study arms.

Treatment-emergent period – An overview of the safety results for ECHELON 1 from the treatment emergent period of the study (from administration of the first dose of study drug through 30 days after the last dose of frontline therapy) with data cut-off 20 April 2017 were provided. As these have been presented as pivotal evidence in the II/0055 procedure these are only summarized here. In brief, almost all patients experienced 1 TEAE of any grade in both treatment arms (>98% in both arms). At least 1 grade 3 or higher TEAE was reported for 83% in A+AVD and 66% in the ABVD arm and at least SAE for 43% vs. 27%, respectively. The higher frequency of Grade 3 or higher TEAEs and SAEs previously reported for A+AVD patients during frontline treatment was attributed to the higher frequency of neutropenia and associated complications, primarily febrile neutropenia. The combination of A+AVD had a safety profile consistent with that of each drug individually with respect to the nature of TEAEs and SAEs observed. No new important risks were identified. The most common reported TEAE in both regimens were neutropenia, peripheral sensory neuropathy, diarrhoea, peripheral neuropathy, decreased weight, abdominal pain, anaemia, febrile neutropenia, and bone pain. The A+AVD treatment is associated with an increased risk of peripheral neuropathy and neutropenia, whereas the ABVD treatment is associated with increased risk for pulmonary toxicity. Of note, during the II/0055 procedure it was noted that a minority of the patients had received primary G-CSF prophylaxis (N=83 A+AVD patients and N=43 ABVD patients). It was supported during the II/0055 procedure that the SmPC states that adult patients with

advanced cHL treated with A+AVD should receive primary prophylactic growth factor support beginning with the first dose of study drug, as an increased tolerability of the A+AVD regimen as well as reduced neutropenia and associated complications were observed in patient having received this prophylaxis.

Stage III/IV - The type of AEs, SAEs, TEAEs was comparable across the Safety Population and did not differ with the presence of extranodal disease or disease staging (III/IV). The incidence of SAEs (48% with A+AVD in Stage III patients vs. 40% with Stage IV), treatment-related SAEs (42% vs. 33%, respectively) and AEs resulting in study drug discontinuation (19% vs. 10%) was higher in patients with Stage III cHL compared to the incidence observed in patients with Stage IV cHL. These differences were not seen in the ABVD arm. During the II/0055 procedure no differences in exposure or baseline demographics were observed between between stage III and stage IV patients in the A+AVD (and ABVD) arm. Also the frequencies of SAEs/AEs leading to discontinuation per preferred term (PT) were comparable between stage III and stage IV patients in the A+AVD. Thus, no clear cause of these differences could be found. It is considered that no further information can be requested which may clarify this issue.

Related SAEs during PTFU - Investigators were required to report to the sponsor any SAE that they considered to be treatment related during PTFU. Peripheral motor neuropathy was reported as a drug related SAE for 1 A+AVD patient (<1%). Additional treatment related PTFU SAEs were identified from a review of the sponsor's global safety database for 3 patients each across the 2 treatment arms. Pain, suicidal ideation, and malignant lung neoplasm were reported as treatment related SAE PTs for 1 A+AVD patient each vs. diffuse large B-cell lymphoma, trisomy 18 (child) and acute promyelocytic leukaemia in 1 patient each of the ABVD arm. Overall, the incidence of treatment related SAEs was low across the 2 treatment arms during PTFU and no new safety signals were observed. Of note, one case of PML was reported in the A+ AVD arm. PML was considered to be not drug related and was attributed to the patient's immunosuppressive state subsequent to allogeneic stem cell transplantation by the MAH. This is agreed upon. PML is adequately reported on in the label.

Deaths - Fewer deaths were reported for A+AVD patients in the safety population both during the on study period and PTFU compared to the ABVD arm. As of the 01 June 2021 cut-off for data analysis, 39 deaths (6%) were reported for A+AVD patients and 64 deaths (10%) were reported for ABVD patients in the safety population. In total, N=18 (3%) versus N=28 (4%) were considered disease related and N=21 (3%) versus N=36 (5%) were not. On study death was reported for 9 A+AVD patients (1%) and 13 ABVD patients (2%). Death during PTFU was reported for 30 A+AVD patients (5%) and 51 ABVD patients (8%).

During the II/0055 procedure on-study deaths patients were reported during Cycle 1 for the majority of the A+AVD patients and deaths were related to neutropenia, febrile neutropenia and its associated complications, including infections, sepsis and septic shock. Very few of these patients had received primary G-CSF prophylaxis, which is considered to reduce the complications of cytopenia. The majority of on-study deaths for ABVD patients were related to pulmonary toxicity, which is a known risk factor of bleomycine.

During the PTFU the primary cause of death for the non–disease related deaths (2% vs. 4%) was different for all cases, except for cardiac arrest that was reported for 2 patients (<1%) and 3 hemorrhage related deaths in the A+AVD arm. In the ABVD arm N=5 deaths were related to pulmonary toxicity/infections. In the A+AVD arm one death is attributed to AE and 3 deaths are attributed to "deceased". The causes of these deaths could not be retrieved after long-term follow up, which can be understood. Overall, these data are considered to be in line with the known safety profile of both drugs that deaths were mostly related to cytopenia complications for the A+AVD arm and in the ABVD arm mostly deaths related to pulmonary toxicity were observed. Updated data on deaths were provided for patients who died between OS IA2 (103 deaths) and the 112 OS event trigger for the final OS analysis (data cleaning still in progress). No new safety concerns were identified.

Stage III patients - On study death was reported for 4 A+AVD patients and 5 ABVD patients (2% each) in the Stage III cHL subset of the safety population. Death during the PTFU period in 13 vs. 15 patients (6% each), of which death was considered disease related or attributed to the primary disease and associated complications for 8 A+AVD patients (3%) vs. 6 ABVD treated patients (2%). Although the total number of deaths is limited, safety data do not indicate a detrimental effect of brentuximab vedotin for Stage III HL patients.

Stage IV patients - On-study death was reported for 5 A+ AVD patients (1%) and 8 ABVD patients (2%) in the Stage IV cHL subset of the safety population. Deaths due to drug-related adverse events were reported in 1% of each arm. Data were not presented separately for this subgroup, however since these data can be assessed by deducting stage III deaths from the total deaths, no concern is raised. Death during the PTFU period was observed in N=17 in the A+AVD arm and N=36 patients in the ABVD arm.

AEs of special interest - Updated results were presented for two AEs of special interest, namely peripheral neuropathy and second malignancy that continued during PTFU.

Peripheral neuropathy - Among the 443 A+AVD (67%) and 286 ABVD patients (43%) for whom at least 1 treatment emergent PN (SMQ) event of any grade was reported during frontline therapy, resolution or improvement was reported for 86% and 87% respectively in the safety population at last follow up. This is higher compared to the previous 2017 data cut-off, when resolution or improvement was reported for 67% and 75%, respectively, at the time of last follow-up. Despite these improvements, it needs to be considered that a minority of the patients will continue to experience peripheral neuropathy complaints. At the 2021 data cut-off, an ongoing PN event was reported for 28% and 21%, respectively, which is a substantial decrease from the 2017 data cut-off (57% and 39% respectively).

Second malignancy – While the incidence of second malignancies increased with longer follow-up, this occurred in both treatment arms and still a lower incidence of second (new primary) malignancy was reported for A+AVD patients: N=23 (3%) vs. N=32 (5%) with ABVD in the safety population. The MAH recategorized the second malignancies according to solid and haematological neoplasms indicating that 2%of the patients had a solid malignancy and 2% of the patients had a hematological malignancy in both study arms. The MAH conducted subgroup analyses which indicated that second malignancies occurred relatively more frequent in patients of 60 years and older (11% in the A+AVD arm and 14% in the ABVD arm) compared to those younger than 60 years (2% in the A+AVD arm and 3% in the ABVD arm). However, it remains uncertain what the influence of brentuximab vedotin is on these numbers.

Other- No new data was submitted for laboratory values and discontinuations. This is acceptable considering that this data is not relevant for long term post treatment follow up. Pregnancy is not an infrequent event and it can be concluded that treatment does not necessarily lead to infertility (in both arms). However, these data do not allow any conclusion regarding a possible reduction in fertility or embryotoxicity. The latest PSUSA concluded that the benefit-risk assessment for brentuximab vedotin remains unchanged.

2.5.2. Conclusions on clinical safety

Overall, the data show that the toxicity of the A+AVD regimen is substantial. Compared to ABVD a different toxicity profile is observed and toxicity is generally higher for A+AVD in cHL patients. The ABVD treatment is associated with increased risk for pulmonary toxicity, whereas the A+AVD treatment is associated with an increased risk of peripheral neuropathy and neutropenia/cytopenia. No new safety concerns were reported, and long term safety is in line with what can be expected from the initial application in HL. The type of AEs, SAEs, TEAEs was comparable across the Safety Population and did not differ with the presence of extranodal disease or disease staging (III/IV) in the A+AVD arm. It is noted that stage III patients have more SAEs and drug discontinuations compared to stage IV, however no clear

cause of these differences could be found. Overall, the data can be considered to confirm the known safety profile of brentuximab vedotin in combination with doxorubicin, vinblastine and dacarbazine.

In the II/0055 procedure, the following measures was considered necessary to address issues related to clinical safety: The MAH will provide data from a 10-year extension of the pivotal Phase 3 study C25003 (ECHELON-1) which will follow-up on safety

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18.0 is acceptable.

The updated RMP includes the newly proposed indication, and Part II has been updated with most recent epidemiology data and clinical trial and post-marketing exposure for the newly proposed and existing indications as requested. The safety concerns remain unchanged. Furthermore, the MAH took the opportunity to make editorial changes throughout the RMP. Minor inconsistencies in tables V.1 and V.3 were noted for routine risk communication of important potential risks severe hepatotoxicity and pulmonary toxicity. As the same updates have also been submitted in the ongoing procedure II/0109, the MAH will be requested to amend the RMP in that procedure.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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)

3.1.2. Available therapies and unmet medical need

Patients who present with advanced disease, are usually treated with 6 to 8 cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine), with some physicians adding limited field consolidative radiotherapy for bulky mediastinal involvement. In patients ≤ 60 years who are eligible for a more intensive treatment, 6 cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) could also be considered. Approximately 30-40% of patients relapse within 5 years after initial treatment or have immediate treatment failure. A substantial proportion of patients with relapsed or refractory HL are not eligible for autologous stem cell transplantation (ASCT), cannot be cured by ASCT, or are still subject to late ASCT-related complications. This indicates the need for more effective first line treatments with manageable toxicity profiles.

3.1.3. Main clinical studies

Main evidence to support this extension of the indication is obtained from pivotal Phase 3, randomized, open-label Study ECHELON-1 (C25003). This study compared the modified progression-free survival (mPFS) obtained with brentuximab vedotin + AVD (Adcetris plus doxorubicin [Adriamycin], vinblastine and dacarbazine, abbreviated A+ AVD, n=664) versus that obtained with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine, n=670) as frontline treatment for adult patients with CD30+ stadium III/IV HL. Primary endpoint was mPFS by independent review. Overall survival (OS) was the key secondary endpoint.

This study has been reviewed as pivotal trial for the EoI in previously untreated CD30+ Stage IV HL as well (II/0055). Results of a second interim analysis of OS data were reviewed as part of a variation to update SmPC section 4.8 and 5.1 with long-term follow-up data from ECHELON-1 (II/0103). Efficacy data presented in the current EoI application pertain to a prespecified second OS interim analysis performed in 1 June 2021 (2021 IA2) and non-prespecified 2023 descriptive analysis presented in response to the request for supplementary information. These analyses waere done for the ITT as well as several patient subgroups, including the new target population of patients with Stage III disease. Moreover, updated PFS results (by investigator due to discontinuation of independent review) and posttreatment follow-up safety assessments were presented. The safety population consisted of 662 patients in the A+AVD treatment arm and 659 patients in the ABVD treatment arm. Updated clinical safety findings have been submitted for the safety population after approximately 6 years of posttreatment follow-up (PTFU) as of the 01 June 2021 cut-off.

3.2. Favourable effects

The primary endpoint mPFS per IRF based on the ITT population, as reported after 263 mPFS events (117 mPFS events in the A+AVD arm and 146 mPFS events in the ABVD arm) at the 20 April 2017 data

cut-off, was met. A+AVD was associated with a 23.0% reduction in the risk of an mPFS event versus ABVD (stratified HR=0.770; 95% CI, 0.603-0.983, p=0.035). The mPFS effect was consistent across several sensitivity analyses. A pre-specified analysis of mPFS per IRF by disease stage showed that patients with Stage IV disease (HR 0.711 [95% CI: 0.529, 0.956], p=0.023) may experience more benefit of A+AVD relative to that seen in Stage III patients (HR 0.922 [95% CI: 0.599, 1.419], p=0.712).

Results of a prespecified exploratory sensitivity analysis of PFS by investigator at the 1 June 2021 data cut-off supported the primary analysis (HR 0.678 (95% CI, 0.532 0.863, descriptive 2-sided p=0.002). With longer follow up in the subgroup of patients with Stage III disease, the PFS by investigator HR improved from 0.766 at the 2017 data cut-off, to 0.603 (95% CI, 0.391 0.93; descriptive p=0.021) at the 2021 data cut-off. In patients with Stage IV disease, the PFS HR remained similar with a HR of ~0.71.

Key secondary endpoint OS reached statistical significance at the 2021 IA2 (0.59 (95% CI, 0.396 0.879, p=0.0009), while this was not yet the case at IA1 (HR of 0.728 [95% CI, 0.448; 1.184], p=0.199). At the 2023 descriptive analysis , the HR for the ITT was 0.61 (0.414, 0.892). For patients with Stage IV cHL, the OS HR improved from 0.507 (95% CI 0.265-0.971) as of the 2017 IA1 to 0.478 (95% CI 0.286-0.0.799) with the 2021 IA2, and remained similar at the 2023 descriptive analysis . In patients with Stage III cHL, the OS HR changed from 1.216 (95% CI 0.563-2.630) in the 2017 first interim analysis, to 0.863 (95% CI 0.452-1.648) in the 2021 second interim analysis and 1.004 (95% CI, 0.540-1.866) in the 2023 descriptive analysis.

Other secondary efficacy endpoints suggested more or less similar efficacy relative to the active control arm (a.o. CR [73% vs. 70%], ORR [86% vs. 83%], EFS [HR 0.9, 95% CI: 0.726, 1.117] and PET negativity at Cycle 2 [89% vs. 86%]) or results in favour of A+AVD (DFS [HR 0.701, 95% CI: 0.504, 0.976; p=0.034], rate of patients not in CR who received irradiation and/or chemotherapy [8% vs, 13% radiation/ 33% vs. 41% chemotherapy]).

A descriptive analysis of OS was performed using data with median follow up of over 7 years for OS. In the ITT population, a lower proportion of patients randomized to A + AVD (44 deaths, 7%) had died compared with patients randomized with ABVD (67 deaths, 10%) [HR = 0.61, 95% CI (0.414, 0.892)]. Similar proportions of Stage III patients randomized to A+AVD (20 deaths, 8%) and ABVD (20 deaths, 8%) had died [HR =1.004, 95% CI (0.540, 1.866)]. A lower proportion of Stage IV patients randomized to A + AVD (24 deaths, 6%) had died compared with patients randomized with ABVD (46 deaths, 11%) [HR = 0.48, 95% CI (0.291, 0.784)].

3.3. Uncertainties and limitations about favourable effects

Median mPFS and OS were not yet reached in either treatment arm. An update of mPFS results will not be provided, which limits the precision of the mPFS data, in particular for the subgroups with relative good prognosis due to the current high censoring rates and low event rates, reflecting high activity (or even curative) potential of front-line treatment in HL. Despite the longer follow-up for OS, the number of events for Stage III HL patients (who now form part of the target population as well) is still limited (17 events [7%] A+AVD, 20 events [8%] ABVD).

Results of prespecified mPFS by IRF analyses indicated no clinically meaningful difference between treatment arms in elderly patients and patients without extranodal sites. OS subgroup analysis confirmed this observation for patients without extranodal sites, as the HR in this subgroup crossed 1 (HR 1.184, 95% CI: 0.641, 2.187). A trend for a smaller or no difference between treatment arms has been observed for patients with Stage III disease and 0-1 IPFP risk factors relative to the respective more advanced counterparts. Results of these subgroup analyses should be interpreted with caution due to the

low number of events, wide confidence intervals and high censoring rates. Results of the respective subgroups have been reflected in SmPC section 5.1.

Efficacy of retreatment with brentuximab vedotin after ASCT is uncertain. From previous studies it is known that retreatment with brentuximab vedotin after ASCT is still effective. With the current proposed indication, brentuximab vedotin could in theory be considered three times during the course of the disease (frontline, after ASCT if at increased risk of relapse, and at relapse after ASCT), with unknown efficacy.

The MAH committed to submit final OS data as part of a separate Type II variation, when available.

3.4. Unfavourable effects

No updated exposure data and safety data from the treatment-emergent period of the study (from administration of the first dose of study drug through 30 days after the last dose of frontline therapy) for ECHELON-1 have been submitted. These data remain unchanged as those presented using a data cut-off of 20 April 2017 and are presented below for easy reference.

Patients with any TEAE of any grade were observed in N=653 (99%) and N=646 (98%) patients in the A+AVD arm and ABVD arm, respectively. At least 1 grade 3 or higher TEAE was reported for N=549 (83%) patients in A+AVD and N=434 (66%) in the ABVD arm and at least SAE for N=284 (43%) vs. N=178 (27%) patients, respectively. The higher frequency of Grade 3 or higher TEAEs and SAEs previously reported for A+AVD patients during frontline treatment was attributed to the higher frequency of neutropenia and associated complications, primarily febrile neutropenia.

The most common reported TEAE in both regimens were neutropenia, peripheral sensory neuropathy, diarrhoea, peripheral neuropathy, decreased weight, abdominal pain, anaemia, febrile neutropenia, and bone pain. The A+AVD treatment is associated with an increased risk of peripheral neuropathy and neutropenia, whereas the ABVD treatment is associated with increased risk for pulmonary toxicity. The type of AEs, SAEs, TEAEs was comparable across the Safety Population and did not differ with the presence of extranodal disease or disease staging (III/IV).

Ongoing safety assessments during the PTFU as of the 01 June 2021 cut-off for data analysis included deaths, treatment-related serious adverse events (SAEs), treatment-emergent, neuropathy events, secondary malignancies, and pregnancy.

Treatment related SAEs: during the PTFU peripheral motor neuropathy, pain, suicidal ideation, and malignant lung neoplasm were reported in 1 patient each in the A+AVD arm versus diffuse large B-cell lymphoma, trisomy 18 (child) and acute promyelocytic leukaemia in 1 patient each of the ABVD arm

Deaths: as of the 01 June 2021 cut-off 39 deaths (6%) were reported for A+AVD patients and 64 deaths (10%) were reported for ABVD patients in the safety population. Death during PTFU was reported for 30 A+AVD patients (5%) and 51 ABVD patients (8%). During the PTFU the primary cause of death for the non–disease related deaths (2% vs. 4%) was different for all cases, except for cardiac arrest that was reported for 2 patients (<1%) and 3 hemorrhage related deaths in the A+AVD arm. In the ABVD arm N=5 deaths were related to pulmonary toxicity/infections.

PN: as of the 01 June 2021 cut-off at least 1 PN (SMQ) event of any grade was reported for N=443 A+AVD patients (67%) and N= 286 ABVD patients (43%) in the safety population. Resolution or improvement was reported for 379 A+AVD patients (86%) and 249 ABVD patients (87%).

Secondary malignancy*:* as of the 01 June 2021 cut-off secondary malignancy was reported for 23 A+AVD patients (3%) and 32 ABVD patients (5%) in the safety population.

3.5. Uncertainties and limitations about unfavourable effects

The incidence of SAEs (48% with A+AVD in Stage III patients vs. 40% with Stage IV) and AEs resulting in study drug discontinuation (19% vs. 10%) was higher in patients with Stage III cHL compared to the incidence observed in patients with Stage IV cHL. It is uncertain what the cause of these differences is.

3.6. Effects Table

Table 2. Effects Table for [ADCETRIS indicated for adult patients with previously untreated CD30+ advanced Hodgkin lymphoma (HL) in combination with AVD] (data cut-off: 20 April 2017*)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
mPFS	Freedom from progression (progressive disease; death due to any cause; or for patients who failed to achieve a CR per IRF, receipt of subsequent anticancer therapy for HL after completion of frontline therapy)	Probability at 2 years (95% CI)	82.1% (78.8, 85.0) ITT: HR 0.77 (95% CI 0.6- 0.98, p=0.035) Stage III: 0.92 (0.60-1.42, p=0.712) Stage IV: HR 0.71 (0.53-0.96, p=0.0.023	77.2% (73.7, 80.4)	Active controlled study (ITT: n=1334) Medians not reached. High censoring rates in the pre-specified subgroup analysis by disease stage. HR point estimate around 1 in elderly and patients without extranodal disease at baseline.	CSR C25003
OS**	Time from randomisation to date of death	Probability of survival at 4 years (95% CI)	94.9% (92.9, 96.4)	92.1% (89.7, 94.0)	2023 descriptive analysis Medians not reached, relative small number of events per treatment arm (n=44 [7%] vs. n=67 [10%]).	CSR C25003

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			ITT: HR 0.61 (0.41-0.89), p=0.010 Stage III: 1.004 (0.54, 1.866, descriptive p=0.990) Stage IV: 0.48 (0.29, 0.784, descriptive p=0.003)			
CR	Rate at the end of randomised treatment	%	73%	70%		CSR C25003
DFS	Time from CR to disease progression or death from lymphoma or acute toxicity from treatment		HR 0.70 (95% CI 0.504-0.976, p=0.034)		Median not reached	CSR C25003
Unfavourable Effects						
SAEs	Serious adverse events	N (%)	N= 284 (43%)	N=178 (27%)	Data derived from an RCT with no difference in median exposure.	
Deaths		N (%)	N=39 (6%)	N=64 (10%)		
PN		N (%)	N=443 (67%)	N= 286 (43%)	Resolution or improvement was reported for 379 A+AVD patients (86%) and 249 ABVD patients (87%)	
Secondary malignancy		N (%)	N= 3 (3%)	N=32 (5%)		

Abbreviations: CR: complete remission, CSR: clinical study report, HL: Hodgkin Lymphoma, IRF: independent review facility, IA: interim analysis, ITT: intention to treat population, mPFS: modified Progression Free Survival, OS: Overall Survival

Notes: *Data cut-off primary analysis. ** Updated data cut-off 11 March 2023

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, clinical efficacy in terms of mPFS by IRF at the primary analysis data cut-off (HR 0.77, 95% CI: 0.603, 0.983) and OS as of the 2023 descriptive analysis data cut-off (0.61, 95% CI: 0.414, 0.892) is considered demonstrated for the ITT consisting of Stage III and IV HL patients. The OS HR in Stage III patients shifted from 1.216 at the first interim analysis (2017 IA1) to 0.863 (95% CI 0.452-1.648) at the second 2021 IA and 1.004 at the 2023 descriptive analysis with overlapping OS KM curves. Although no survival advantage was observed for Stage III patients, there is no trend for a potential detrimental effect in these patients either, which is considered most important in this substitution setting. The proportion of patients with OS events, in particular in the subgroups by disease stage is still quite low (<10%), but this can be acceptable considering the prognosis of these patients.

The observed toxicity is generally higher for A+AVD versus ABVD, however compared to ABVD a different toxicity profile is observed between the regimens. ABVD treatment is associated with increased risk for pulmonary toxicity, whereas the A+AVD treatment is associated with an increased risk of peripheral neuropathy and neutropenia /cytopenia effects. These are managed with dose modifications and primary G-CSF prophylaxis. Of note, the latter was not recommend for the majority of the study patients. G-CSF prophylaxis is recommended in the SmPC as this was considered to improve tolerability to A+AVD and reduce neutropenia and related complications.

For the long term follow up no new safety concerns were reported, and long term safety is in line with what can be expected from the known safety profile of the product in HL.

3.7.2. Balance of benefits and risks

The benefit risk balance of ADCETRIS in first line advanced HL patients is considered positive. Clinical efficacy is considered demonstrated in terms of mPFS and OS. The efficacy is considered to outweigh the known toxicity profile for A+AVD. This regimen has a higher, but differential toxicity profile compared to ABVD and thus is considered to be a clinically relevant treatment option in this setting.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Adcetris in the indication

> *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)*
>
> is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Extension of indication to include treatment of adult patients with previously untreated CD30+ Stage III Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine and dacarbazine (AVD), for ADCETRIS, based on the second interim analysis of OS data from ECHELON-1 study (C25003); this is a randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical HL. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. Version 18.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.