13 December 2018
EMA/6661/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adcetris

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/0000

Note

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

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List of abbreviations

ADC	antibody-drug conjugate
AE	adverse event
AFM	alternative frontline medication
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration versus time curve
CD30+	CD30-positive
cHL	classical HL
CR	complete response
CT	computed tomography
DBL	database lock
DFS	disease-free survival
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EQ-5D-3L	European Quality of Life 5-Dimension Three Level Version
FACIT	Functional Assessment of Chronic Illness Therapy
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (subscale)
FACT-GOG	Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group
FFS	failure-free survival
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor
HL	Hodgkin lymphoma
HU	healthcare utilization
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IPFP	International Prognostic Factors Project
iPK	Intensive PK
IRF	independent review facility
ITT	intent to treat
IV	intravenous; intravenously
KM	Kaplan-Meier
MMAE	monomethyl auristatin E
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAb	neutralizing antibody
Ntx	neurotoxicity
ORR	overall response rate

PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PP	per protocol
PR	partial response
PRO	patient-reported outcome
PTFU	Posttreatment follow-up
QoL	quality of life
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
sCD30	soluble CD30
SD	stable disease
SmPC	Summary of Product Characteristics
ULN	upper limit of the normal
VAS	visual analog scale

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 28 November 2017 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, IIIA and IIIB

Extension of the existing Hodgkin lymphoma (HL) indication to include the frontline treatment of adult patients with CD30+ advanced HL in combination with chemotherapy, based on data from ECHELON-1 (C25003), a phase 3 multi-centre, randomised, open-label study comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin, doxorubicin, vinblastine and dacarbazine versus the mPFS obtained with doxorubicin, bleomycin, vinblastine and dacarbazine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10. The MAH also submitted an updated RMP version 13.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Adcetris was designated as an orphan medicinal product in the following indications: treatment of Hodgkin lymphoma on 15/01/2009 (EU/3/08/596), treatment of anaplastic large cell lymphoma on 15/01/2009 (EU/3/08/595) and treatment of cutaneous T-cell lymphoma on 11/01/2012 (EU/3/11/939).

The new indication, which is the subject of this application, falls within the above mentioned orphan designation indication treatment of Hodgkin lymphoma.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0232/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0232/2017 was not yet completed as some measures were deferred.

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 applicant 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 applicant received Protocol assistance from the CHMP on 16 February 2012 and on 23 October 2014. The Protocol assistance pertained to clinical aspects of the dossier.

2. Scientific discussion

2.1. Introduction

Disease or condition

Hodgkins Lymphoma (HL) formerly known as Hodgkin's disease accounts for approximately 10 percent of all lymphomas and is highly curable, with 80% of patients reaching complete remission.

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 is characterized histologically 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.

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.

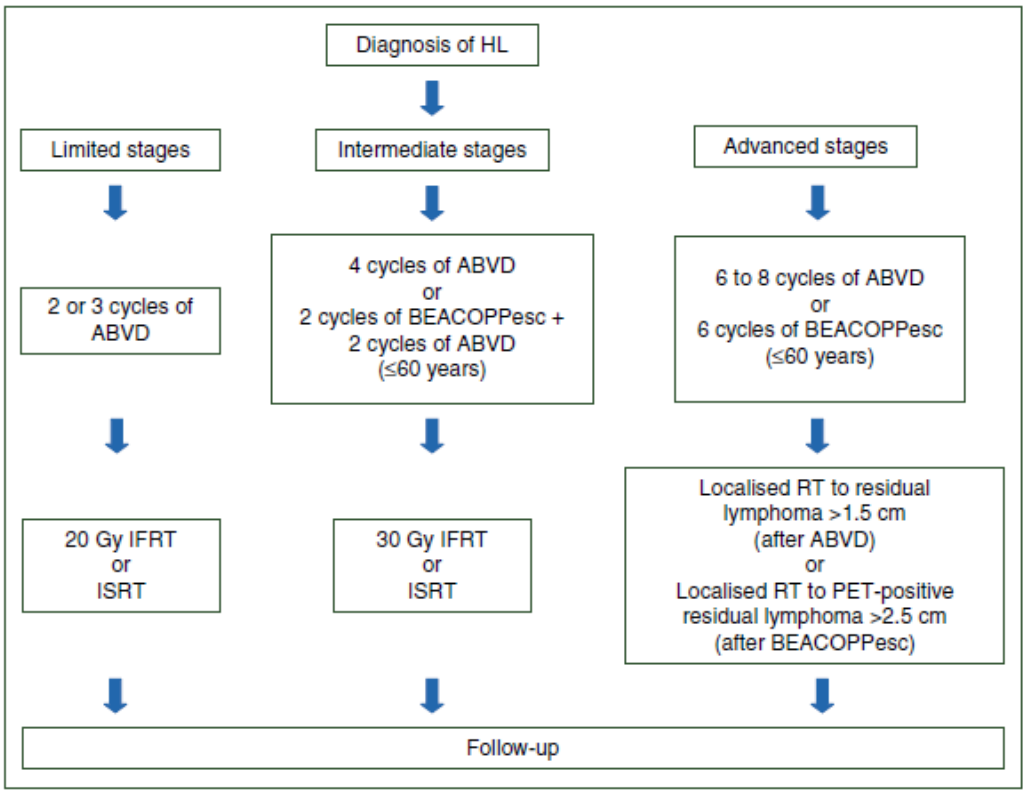
In addition to clinical staging, other clinical features can predict outcomes in these patients. The international prognostic score is a tool that assesses 7 potentially unfavourable clinical features in HL at diagnosis: serum albumin <4 g/dL, haemoglobin <10.5 g/dL, male gender, age >45 years, Stage 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. 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 Therapeutic algorithm for newly diagnosed Hodgkin's lymphoma.



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.

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.

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.

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.

Adcetris was granted a MA in the EU in October 2012 and is currently 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).

- 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.

- the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

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

The additional HL indication initially proposed for Adcetris through this variation procedure was: “the frontline treatment of adult patients with CD30+ advanced HL in combination with chemotherapy”.

The indication was finally revised to “Adcetris is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).”

Brentuximab vedotin is formulated for intravenous administration as a 50 mg powder for concentrate for solution for infusion. The recommended dose in combination with chemotherapy (doxorubicin [A],

vinblastine [V] and dacarbazine [D] [AVD]) is 1.2 mg/kg administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles.

Primary prophylaxis with growth factor support (G-CSF) is recommended for all patients with previously untreated HL receiving combination therapy beginning with the first dose.

Refer to the summary of product characteristics (SmPC) of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated HL. (see SmPC sections 4.2, 4.4 and 5.1)

2.2. Non-clinical aspects

No new non-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 applicant.

The applicant 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.

- **Table 1: 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

An overview of the clinical pharmacology of brentuximab vedotin as monotherapy was already provided in the assessment reports for the original MAA. Reference PK results for brentuximab vedotin antibody-drug conjugate (ADC) and monomethyl auristatin E (MMAE) at time of initial registration in patients with CD30 positive haematological malignancies is shown in Table 2.

Table 2. PK parameters of ADC and MMAE following first dose of brentuximab vedotin ADC 1.8 mg/kg studies SG035-0001 and SGN35-008A.

ADC	study	AUC0-inf µg.day/ml	Cmax µg/ml	Tmax day	$t_{1/2}$ day	CL L/h	Vss L
	SG035-0001	79.4 (30%)	32.0 (29%)	0.089	4.4 (38%)	0.073 (17%)	8.2 (24%)

	SGN35-008A	89.8 (25%)	36.7 (34%)	0.024	2.9 (66%)	0.068 (26%)	10.0 (34%)
MMAE	study	AUC0-inf ng.day/ml	Cmax ng/ml	Tmax day	$t_{1/2}$ day	CL L/h	Vss L
	SG035-0001	37.0 (47%)	4.97 (43)	2.1	3.6 (25%)		
	SGN35-008A	40.1 (53%)	4.98 (67%)	3.0	3.7 (19%)		

This section only summarizes additional findings from the Phase 3 study C25003 (ECHELON-1).

Unlike all previous studies for brentuximab vedotin, ECHELON-1 used the drug in combination, at a lower starting dose, and with a more frequent dosing schedule. This 1.2 mg/kg brentuximab vedotin combination starting dose given on Days 1 and 15 of each 28-day cycle was chosen to yield exposures similar to the 1.8 mg/kg monotherapy starting dose given once every 3 weeks.

Relevant pharmacokinetics (PK) and pharmacodynamics (PD) secondary and exploratory objectives of the ECHELON-1 study included:

- To describe the PK of the brentuximab vedotin antibody-drug conjugate (ADC), its monomethyl auristatin E toxin (MMAE), and total antibody (TAb) in blood.
- To determine the immunogenicity of brentuximab vedotin.
- To assess any impact of brentuximab vedotin dosing on serum concentrations of doxorubicin, vinblastine, and/or dacarbazine (AVD).
- To assess changes in tumour biomarker expression before and after treatment.

Additionally, population PK (popPK) analyses were conducted in adult patients to build predictive popPK models for the ADC and MMAE.

Sparse PK sampling was performed for all Safety Population patients, with intensive PK sampling (iPK) to be performed for a total of 100 patients, 50 patients on each treatment arm, of whom at least 20 patients on each treatment arm were to be Asian.

Bioanalysis for ADC, its MMAE, TAb, doxorubicin, vinblastine, and/or dacarbazine was conducted using validated assays.

PK Parameters for Brentuximab Vedotin ADC

The PK of the brentuximab vedotin ADC was determined from serum collected from the blood samples of patients who met the study's inclusion criteria, received brentuximab vedotin, and provided evaluable PK data. ADC PK data are presented for 661 patients (100%) in the A+AVD treatment arm, including a 59-patient intensive PK (iPK) sampling subset, and for 59 patients in the ABVD arm to permit comparisons (for AVD components).

Among 59 the iPK patients in the A+AVD arm, 4 patients from Cycle 1 Day 1 (C1D1) and 7 patients from Cycle 3 Day 1 (C3D1) were excluded from the ADC PK analysis using the non-compartmental analysis (NCA) approach because of insufficient concentration data or missing end of infusion (EOI) concentrations. One additional implausible predose ADC concentration on C1D1 was excluded.

Serum concentration-time profiles following IV infusion administration of 1.2 mg/kg brentuximab vedotin twice weekly (Q2W) are shown in Figure 2, and PK parameters are summarised in Table 2. Peak serum ADC concentrations occurred at the sampling time point close to the EOI (within 1 hour post EOI) for both C1D1 and C3D1. The geometric mean serum ADC maximum concentration (Cmax) was 22.9 µg/mL and 23.6 µg/mL for C1D1 and C3D1, respectively. The geometric mean concentration at the end of infusion (Ceoi) was comparable to Cmax. After attaining Cmax, serum ADC

concentrations declined in a multi-exponential manner with a geometric mean terminal disposition phase half-life ($t_{1/2z}$) of 3.70 days on C1D1 and 5.00 days on C3D1. Geometric mean area under the concentration-time curve from time 0 to 14 days (AUC14D) was 43.2 day*µg/mL on C1D1 and 56.1 day*µg/mL on C3D1, with an accumulation ratio of 1.27.

Figure 2. Mean (Standard Deviation) Serum Concentration-Time Profiles of ADC (Linear and Log-Linear Scales) on C1D1 and C3D1 Following 1.2 mg/kg Brentuximab Vedotin Q2W (iPK Patients, A+AVD Arm) (Study C25003)

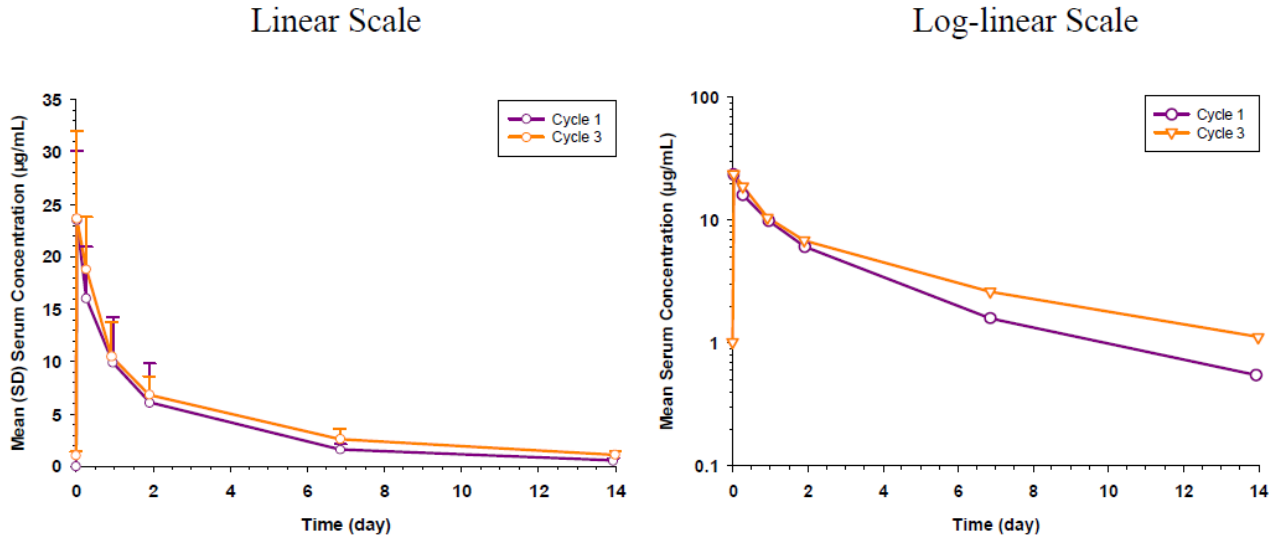


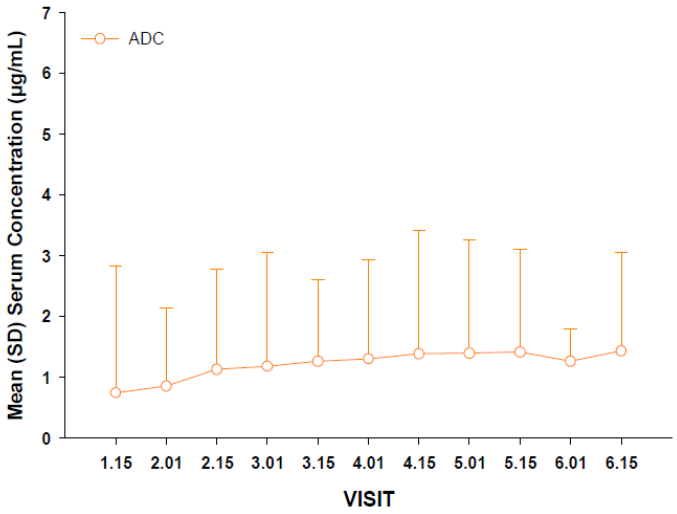
Table 3. Serum PK Parameters of ADC on C1D1 and C3D1 Following IV Administration of 1.2 mg/kg Brentuximab Vedotin Q2W (iPK Patients, A+AVD Arm)

Parameter	Geometric Mean (%CV)			
	C1D1		C3D1	
	N	1.2 mg/kg Q2W	N	1.2 mg/kg Q2W
C_{max} (µg/mL)	55	22.9 (28.1)	52	23.6 (27.8)
t_{max} (day)	55	0.0278 (0.0208, 1.99) (a)	52	0.0403 (0.00347, 1.03) (a)
C_{eoi} (µg/mL)	24	22.2 (25.0)	19	19.9 (35.8)
AUC_{14D} (day*µg/mL)	55	43.2 (28.9)	50	56.1 (23.8)
AUC_{∞} (day*µg/mL)	53	46.0 (25.4)	NR	NR
$t_{1/2z}$ (day)	53	3.70 (19.8)	44	5.00 (16.9)
CL (L/day)	53	1.68 (28.4)	50	1.37 (28.2)
V_z (L)	53	8.96 (29.4)	49	9.96 (27.7)
$R_{ac(AUC14D)}$	NA	NA	46	1.27 (23.9)

(a) Presented as median (minimum, maximum).

Interpatient variability as assessed by % coefficient of variance (CV) of serum ADC exposure in Cmax and the AUC14D was approximately 28.1% and 28.9%, respectively, on C1D1 and 27.8% and 23.8%, respectively, on C3D1. The steady-state geometric mean trough concentration for the ADC was 1.18 µg/mL, as observed on Cycle 6 Day 15 (Figure 3).

Figure 3. Mean (Standard Deviation) Serum Trough Concentrations of ADC (Linear Scale) in Cycles 1 to 6 Following 1.2 mg/kg Brentuximab Vedotin Q2W (iPK and non iPK Patients, A+AVD Arm)



PK Parameters for Total Anti-CD30 Antibody

The PK of the bound and free anti-CD30 antibody (total antibody, TAb) was determined from serum collected from the blood samples of patients who met the study's inclusion criteria, received brentuximab vedotin, and provided evaluable PK data.

Among 59 iPK patients in the A+AVD arm, 4 patients from C1D1 and 7 patients from C3D1 were excluded from the TAb PK analysis using the non-compartmental analysis (NCA) approach because of insufficient concentration data or missing end of infusion concentrations. Two additional implausible predose TAb concentrations on C1D1 were excluded.

Serum concentration-time profiles following IV infusion administration of 1.2 mg/kg brentuximab vedotin Q2W are shown in Figure 4, and PK parameters are summarised in Table 4. Peak serum TAb concentrations occurred at the sampling time point close to the EOI (within 1 hour post EOI) for both C1D1 and C3D1. Geometric mean serum TAb Cmax was 22.6 µg/mL and 26.4 µg/mL for C1D1 and C3D1, respectively. Geometric mean Ceoi was comparable to Cmax. After attaining Cmax, serum Tab concentrations declined in a multi-exponential manner with a geometric mean $t_{1/2z}$ of 4.30 days on C1D1 and 5.35 days for C3D1. Geometric mean AUC14D was 80.7 day*µg/mL on C1D1 and 112 day*µg/mL on C3D1, with an accumulation ratio of 1.36.

Figure 4. Mean (Standard Deviation) Serum Concentration-Time Profiles of TAb (Linear and Log-Linear Scales) on C1D1 and C3D1 Following 1.2 mg/kg Brentuximab Vedotin Q2W (iPK Patients, A+AVD Arm)

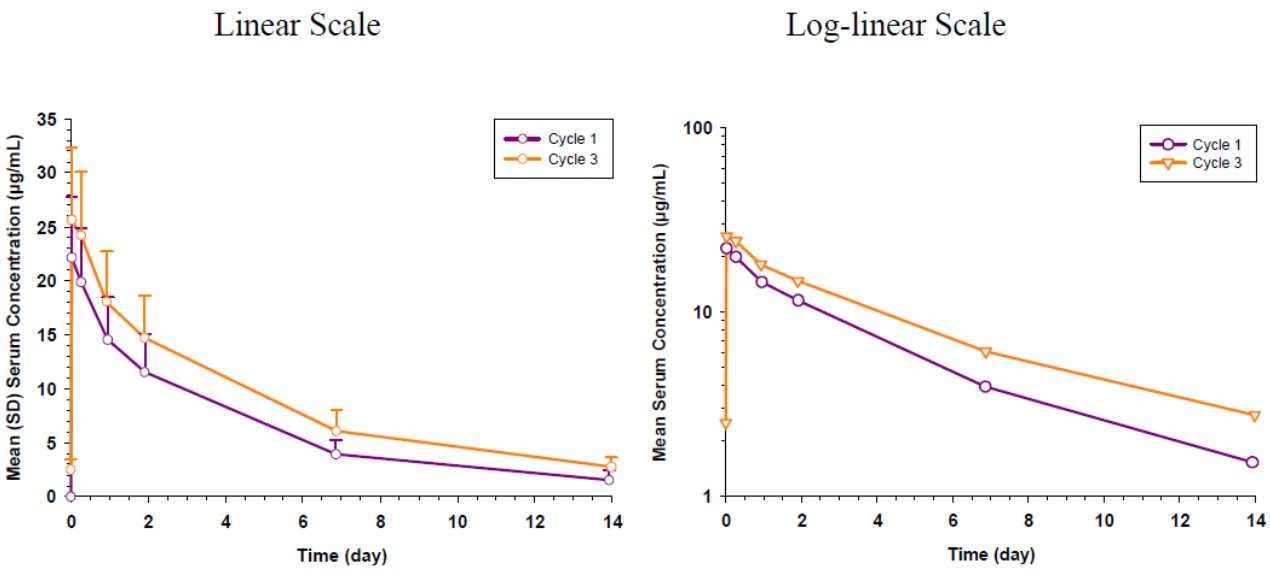
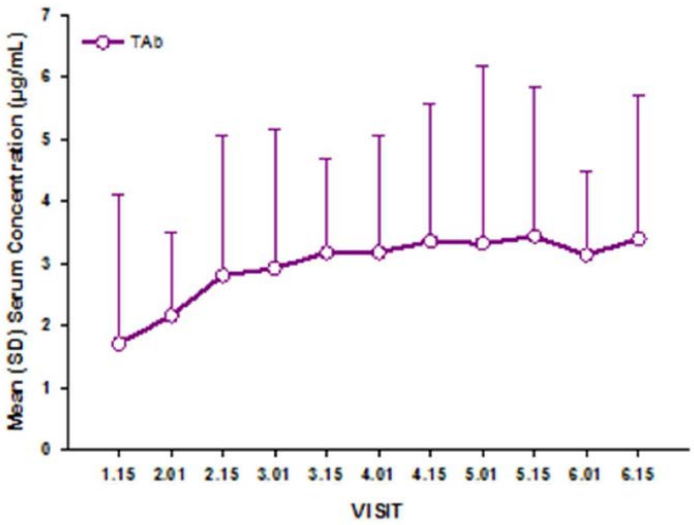


Table 4. Serum PK Parameters of TAb on C1D1 and C3D1 Following IV Administration of 1.2 mg/kg Brentuximab Vedotin Q2W (iPK Patients, A+AVD Arm)

Parameter	Geometric Mean (%CV)			
	C1D1		C3D1	
	N	1.2 mg/kg Q2W	N	1.2 mg/kg Q2W
C_{max} (µg/mL)	55	22.6 (23.6)	52	26.4 (22.5)
t_{max} (day)	55	0.0333 (0.0208, 1.95) (a)	52	0.0514 (0.00347, 1.91) (a)
C_{eoi} (µg/mL)	25	22.2 (25.3)	20	25.2 (25.6)
AUC_{14D} (day*µg/mL)	55	80.7 (25.3)	49	112 (21.9)
AUC_{∞} (day*µg/mL)	51	89.9 (27.6)	NR	NR
$t_{1/2z}$ (day)	51	4.30 (18.0)	47	5.35 (20.7)
$R_{ac(AUC14D)}$	NA	NA	46	1.36 (23.1)

Interpatient variability as assessed by %CV of serum TAb exposure in Cmax and AUC14D were approximately 23.6% and 25.3%, respectively, in C1D1 and 22.5% and 21.9%, respectively, in C3D1. The steady-state geometric mean trough concentration for TAb was 2.88 µg/mL, as observed on Cycle 6 Day 15.

Figure 5. Mean (Standard Deviation) Serum Trough Concentration of TAb (Linear Scale) in Cycles 1 to 6 After 1.2 mg/kg Brentuximab Vedotin Q2W (iPK and non-iPK Patients, A+AVD Arm)



PK Parameters for Monomethyl Auristatin E

The PK of unconjugated drug (MMAE) was determined from plasma collected from the blood samples of patients who met the study's inclusion criteria, received brentuximab vedotin, and provided evaluable PK data.

Among 59 iPK patients in the A+AVD arm, 3 patients from C3D1 were excluded from the MMAE PK analysis using the NCA approach because of insufficient concentration data or missing end of infusion concentrations. One additional implausible predose MMAE concentration on C1D1 was excluded.

Plasma concentration-time profiles following IV infusion administration of 1.2 mg/kg brentuximab vedotin Q2W are shown in Figure 6, and PK parameters are summarised in Table 5. Median peak plasma MMAE concentrations occurred approximately 2 days post EOI for both C1D1 and C3D1. Geometric mean plasma MMAE Cmax was 3.20 ng/mL and 1.36 ng/mL for C1D1 and C3D1, respectively. After attaining Cmax, plasma MMAE concentrations declined in a nearly log-linear manner with a geometric mean $t_{1/2z}$ of 3.11 days on C1D1 and 3.92 days on C3D1. Geometric mean AUC14D was 18.8 day*ng/mL on C1D1 and 9.46 day*ng/mL on C3D1, with an approximately 50% decrease of MMAE exposure following Q2W dosing of brentuximab vedotin.

Figure 6. Mean (Standard Deviation) Plasma Concentration-Time Profiles of MMAE (Linear and Log-Linear Scales) on C1D1 and C3D1 After 1.2 mg/kg Brentuximab Vedotin Q2W (iPK Patients, A+AVD Arm)

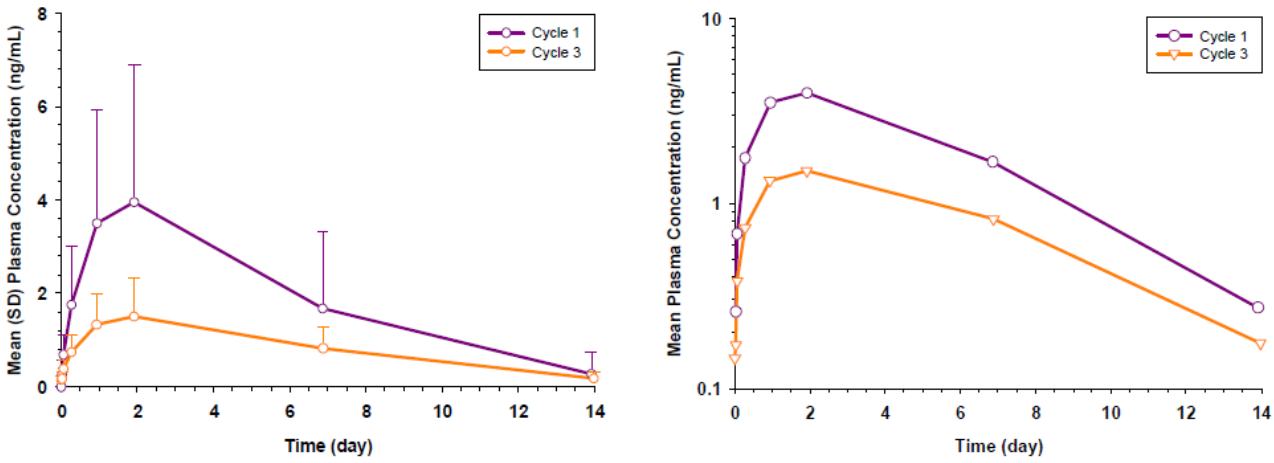
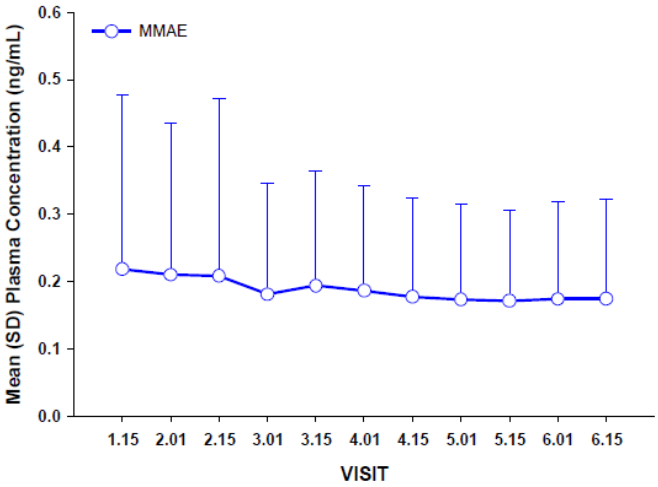


Table 5. Plasma PK Parameters of MMAE on C1D1 and C3D1 After IV Administration of 1.2 mg/kg Brentuximab Vedotin Q2W (iPK Patients, A+AVD Arm)

Parameter	Geometric Mean (%CV)			
	C1D1		C3D1	
	N	1.2 mg/kg Q2W	N	1.2 mg/kg Q2W
C_{max} (ng/mL)	59	3.20 (73.6)	56	1.36 (51.7)
t_{max} (day)	59	1.86 (0.828, 6.94) (a)	56	1.88 (0.188, 7.01) (a)
AUC_{14D} (day*ng/mL)	59	18.8 (74.9)	54	9.46 (50.3)
AUC_{∞} (day*ng/mL)	49	20.1 (75.8)	NR	NR
$t_{1/2z}$ (day)	51	3.11 (35.0)	44	3.92 (21.9)
$R_{ac(AUC14D)}$	NA	NA	54	0.528 (68.6)

Interpatient variability as assessed by %CV of plasma MMAE exposure in Cmax and AUC14D was approximately 73.6% and 74.9%, respectively, in C1D1 and 51.7% and 50.3%, respectively, in C3D1. The steady state geometric mean trough concentration for MMAE was 0.14 ng/mL, as observed on Cycle 6 Day 15 (Figure 7).

Figure 7. Mean (Standard Deviation) Plasma Trough Concentration of MMAE (Linear Scale) in Cycles 1 to 6 After 1.2 mg/kg Brentuximab Vedotin Q2W (iPK and non-iPK Patients, A+AVD Arm)



PK Results for Brentuximab Vedotin as Single Agent (Study C25005) Compared With Combination Therapy (Study C25003)

Study C25005 (Single-Agent Brentuximab Vedotin) was a multicenter, open-label, 1:1, randomized, 2-arm study of brentuximab vedotin (1.8 mg/kg, IV Q3W) with (Arm B) and without (Arm A) concomitant rifampicin. The study evaluated the PK of brentuximab vedotin, MMAE, and 5 MMAE metabolites with and without rifampicin, a cytochrome P450 (CYP) 3A4/5 inducer that could potentially enhance metabolism of free (unconjugated) MMAE. For comparison of the brentuximab vedotin PK results when dosed in combination with AVD, only the PK results from the single-agent treatment (Arm A) from Study C25005 are presented herein. This study was previously submitted as part of procedure EMEA/H/C/002455/II/0033.

For comparison between studies, concentration data for C1D1 on Study C25005 were dose-normalized to an equivalent dose of 1.2 mg/kg for comparison with C1D1 data from Study C25003 in which 1.2 mg/kg was administered.

When administered as either a single agent (1.8 mg/kg 3QW) in Study C25005 or in combination therapy (1.2 mg/kg Q2W) in Study C25003, there were no readily apparent differences observed in the brentuximab vedotin PK profiles on C1D1 for ADC (Figure 8), TAb (Figure 9), and MMAE (Figure 10) when adjusted for differences in the dose administered between the 2 studies. The Cmax for ADC, TAb, and MMAE from Study C25005 were very similar to that reported in Study 25003 (when adjusted for dose differences).

Figure 8. Mean (Standard Deviation) Serum Concentration-Time Profiles of ADC in Studies C25003 and C25005

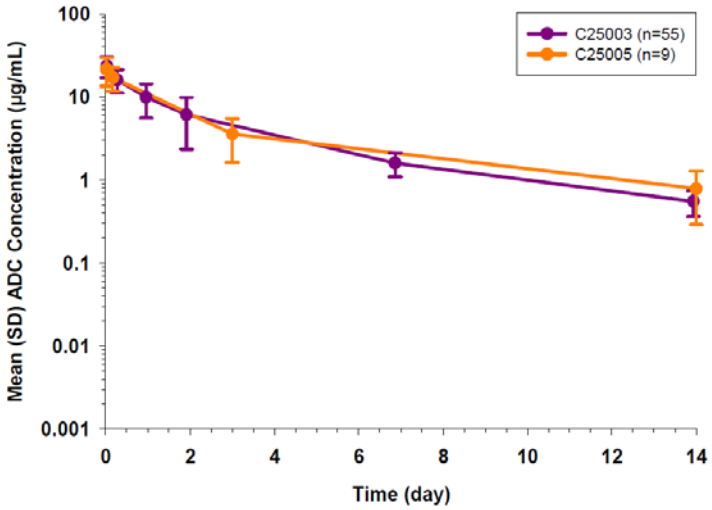


Figure 9. Mean (Standard Deviation) Serum Concentration-Time Profiles of TAb in Studies C25003 and C25005

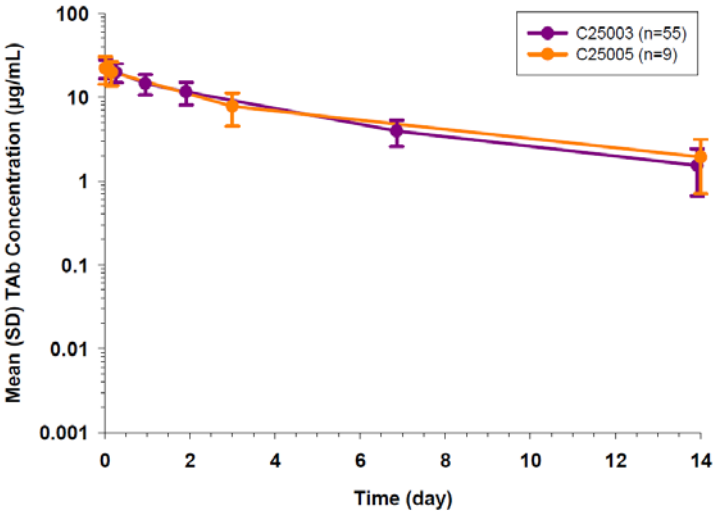
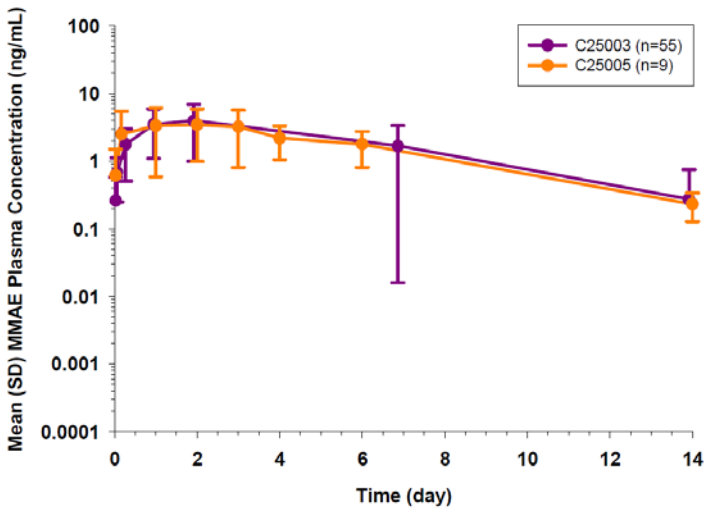


Figure 10. Mean (Standard Deviation) Plasma Concentration-Time Profiles of MMAE in Studies C25003 and C25005



PK Parameters for Doxorubicin, Vinblastine, and Dacarbazine

The PK of doxorubicin, vinblastine, and dacarbazine was determined from the blood samples of iPK patients (59 iPK patients per treatment arm) who met the study's inclusion criteria, received A+AVD or ABVD, and provided evaluable PK data. Two to 16 patients had insufficient concentration data or missing end-of-infusion concentrations so were excluded from non-compartmental analyses of Cycle 1 Day 1 and Cycle 3 Day 1, and 4 to 25 implausible concentrations from these time points were excluded.

Doxorubicin

Following IV infusion of 25 mg/m^2 doxorubicin Q2W, peak plasma doxorubicin concentrations occurred at a median time point close to the EOI for both treatment arms on C1D1 and C3D1, followed by multi-exponential decline. Doxorubicin AUC24h was similar between the 2 arms, with a geometric mean AUC24h ratio of 0.968 (90% CI, 0.832, 1.13) for C1D1 and 0.995 (90% CI, 0.799, 1.24) for C3D1. Similarly, doxorubicin Cmax was comparable between the 2 arms, with a geometric mean Cmax ratio (A+AVD vs ABVD) of 0.958 (90% CI, 0.704, 1.30) for C1D1 and 0.993 (90% CI, 0.677, 1.46) for C3D1.

PK variability as assessed by % CV of plasma doxorubicin exposure ranged from 78.2% to 109% for Cmax and 50.1% to 123% for AUC24h on C1D1 and C3D1 in both the A+AVD and ABVD arms. Geometric mean doxorubicin Ceoi and AUC∞ were close to Cmax and AUC24h, respectively.

Vinblastine

Following IV infusion of 6 mg/m^2 vinblastine Q2W, median peak plasma vinblastine concentrations occurred at a median time point close to the EOI for both treatment arms on C1D1 and C3D1, followed by multi-exponential decline. Vinblastine AUC24h was similar between the 2 arms, with a geometric mean AUC24h ratio of 1.12 (90% CI, 0.951, 1.32) for C1D1 and 1.03 (90% CI, 0.799, 1.34) for C3D1. Similarly, vinblastine Cmax was comparable between the 2 arms, with a geometric mean Cmax ratio (A+AVD vs ABVD) of 1.04 (90% CI, 0.726, 1.49) for C1D1 and 1.07 (90% CI, 0.617, 1.87) for C3D1. PK variability as assessed by % CV of plasma vinblastine exposure ranged from 113% to 193% for Cmax and 50.7% to 165% for AUC24h on C1D1 and C3D1 for both A+AVD and AVBD arms. Geometric mean vinblastine Ceoi and AUC∞ were comparable to Cmax and AUC24h, respectively.

Dacarbazine

Following IV infusion administration of 375 mg/m^2 dacarbazine Q2W, median peak plasma dacarbazine concentrations occurred at a median time point close to the EOI for both treatment arms on C1D1 and C3D1, followed by nearly log-linear decline. Dacarbazine AUC24h was similar between the 2 arms, with a geometric mean AUC24h ratio of 1.10 (90% CI, 0.923, 1.30) for C1D1 and 0.993 (90% CI, 0.842, 1.17) for C3D1. Similarly, dacarbazine Cmax was comparable between the 2 arms, with a geometric mean Cmax ratio (A+AVD vs ABVD) of 0.891 (90% CI, 0.694, 1.14) for C1D1 and 0.933 (90% CI, 0.767, 1.13) for C3D1. PK variability as assessed by %CV of plasma dacarbazine exposure ranged from 36.4% to 102% for Cmax and 44.2% to 61.7% for AUC24h in C1D1 and C3D1 of both A+AVD and AVBD arms. Geometric mean dacarbazine Ceoi and AUC∞ were comparable with the Cmax and AUC24h, respectively.

Special populations

Patients with Hepatic and renal impairment

No studies in patients with severe renal impairment or hepatic impairment have been submitted.

Population Pharmacokinetics

The overall objectives of the population PK analyses were:

1. To build 2 predictive PK models that describe the concentration-time data of ADC and MMAE in patients with cHL in ECHELON-1.

2. To identify and characterize the impact of various intrinsic and extrinsic patient factors (covariates) which influence the PK and PK variability of ADC and MMAE.

3. To estimate the magnitude of unexplained variability in the PK in patients.

4. To evaluate the model performance of the 2 population PK models.

5. To use these models to summarize the systemic exposures of brentuximab vedotin and MMAE estimated in patients with cHL in ECHELON-1.

Two popPK models were developed for this analysis, 1 each for ADC and MMAE. The models were based on a previously developed model for the ALCANZA study (Study C25001) and were built with data from 661 patients with HL from the ECHELON-1 (C25003) study.

The POP PK models for ADC and MMAE were based on the previously reported models and were developed in steps; a base model which included structural components of the model was used to conduct a graphical evaluation of the covariates. Covariates that showed a graphical trend or required further evaluation based on physiological relevance or observation during previous clinical trials of BV were tested as single covariate models ($p<0.01$). A full model including all of the statistically relevant pre- specified covariate effects of interest was then developed. A final model was chosen by retaining only the statistically significant covariate effects ($p<0.001$). The magnitude of the impact of the covariates was also considered, if the magnitude of the impact was small (less than a 20% change over the range of covariate values in the database) or the covariate effect was poorly estimated [e.g., standard error (SE) > 45%] then the covariate may be re-parameterized or discarded. The parameters in the population models were estimated using the NONMEM software program (versions 7.3). The first-order conditional estimation (FOCE) method was used for estimation. A visual predictive check (VPC) was conducted.

Baseline demographic and characteristics data of the patients from Study C25003 included in the PopPK model are summarised in Table 6 and Table 7.

Table 6 Summary of the Categorical Covariates for All Patients in Study C25003

Covariate	Category	N	%
Sex	Male	376	56.9
	Female	285	43.1
Race	White	557	84.3
	Black	20	3.0
	Asian	56	8.5
	Other	18	2.7
	Not Reported	10	1.5
Asian	No	605	91.5
	Yes	56	8.5
Ethnicity	Not Hispanic	568	85.9
	Hispanic	51	7.7
	Not Reported	42	6.4

Table 7 Summary of Baseline Continuous Covariates for All Patients in Study C25003

Covariate	Mean	SD	25th Percentile	50th Percentile	75th Percentile	Range	N
Age (yr)	38.73	15.76	25	35	50	18-82	661
Weight (Kg)	73.49	18.02	61	71	83.09	40.8 -165.5	661
Body Surface Area (m^2)*	1.841	0.283	1.675	1.833	1.999	1.278-2.778	661
Albumin (g/L)	39.08	5.336	36	40	43	17-53	661
Alanine Aminotransferase (U/L)	25.87	28.33	12	18	29	4-457	661
Aspartate Aminotransferase (U/L)	21.92	15.68	15	18	24	6-187	661
Bilirubin (umol/L)	7.138	5.436	4	6	8.55	2-82	661
Creatinine (umol/L)	66.16	16.26	55	65	74	32-222	661
Creatinine Clearance (mL/min)	134.1	45.38	103.1	129.3	155.8	29.2-476.7	661

Brentuximab Vedotin ADC Model Results

PK samples were collected from all patients, including a subset of 59 patients who underwent iPK sampling.

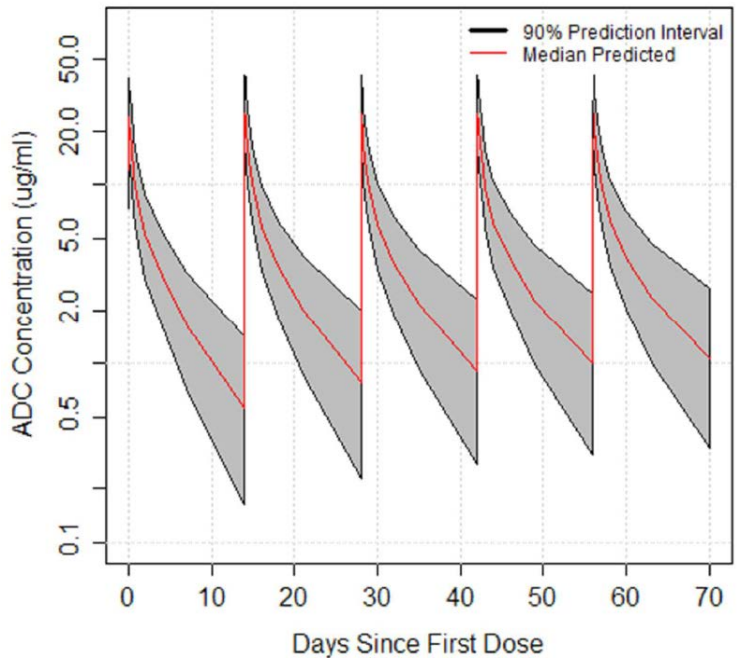
The model for ADC was a linear, 3-compartment model with zero-order input and first-order elimination. The final ADC model included effects of albumin and Body Surface Area (BSA) on clearance, BSA and sex on central volume of distribution, and BSA on peripheral volume 2. Other factors, including age, weight, race, antitherapeutic antibodies (ATA) response, ATA titer, nATA response and International Prognostic Factors Project (IPFP) risk factor were not retained as statistically significant covariates in the model.

Table 8. ADC Final PK Model Parameters

Parameter		Population Mean (SE%)	%CV IIV (shrinkage)
Clearance (L/hr)	Θ_1	0.0615 (1.0%)	19.8 (7.7%)
Central Volume (V_c) (L)	Θ_2	3.58 (0.9%)	14.0 (8.7%)
Inter-compartmental clearance 1 (Q2) (L/hr)	Θ_3	0.113 (3.0%)	-
Peripheral Volume 1 (V2) (L)	Θ_4	3.26 (1.9%)	25.5 (41.2%)
Inter-compartmental clearance 2 (Q3) (L/hr)	Θ_5	0.0239 (2.3%)	41.4 (25.0%)
Peripheral Volume 2 (V3) (L)	Θ_6	15.7 (4.0%)	77.7 (14.5%)
Albumin on Clearance	Θ_8	-0.477 (2.2%)	-
BSA on Clearance	Θ_9	1.1 (4.9%)	-
BSA on Central Volume	Θ_{10}	0.893 (6.3%)	-
Sex on Central Volume	Θ_{11}	0.934 (1.4%)	-
BSA on Peripheral Volume 2	Θ_{12}	1.47 (8.5%)	-
Residual Variability	Θ_7	18.1%CV (0.4%)	-

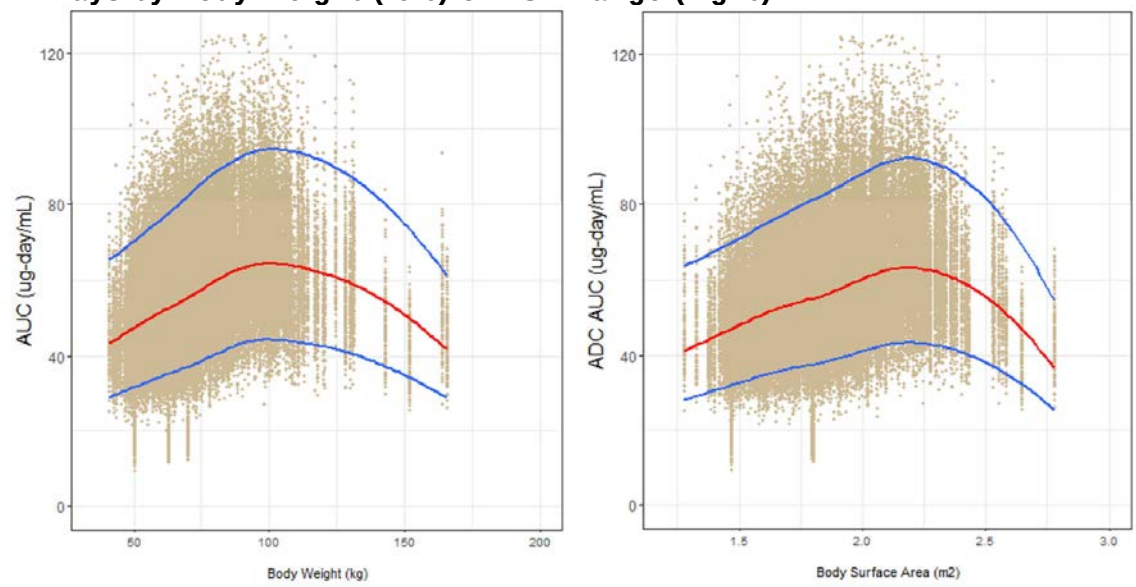
The final PK model for ADC was used to simulate the concentrations produced after a 1.2 mg/kg dose of brentuximab vedotin every 14 days for 5 doses (Cycle 3). All the patients in the dataset were included and their baseline covariate values were used. The doses were capped at 120 mg for patients weighing more than 100 kg, consistent with the dosing strategy used in ECHELON-1. A Monte Carlo simulation approach was used, whereby 150 replicate simulations were performed. Figure 14 is a plot of the ADC 90% prediction interval (black lines with shaded grey area) and median (red line) simulated concentrations. This plot shows some accumulation of ADC with this dosing regimen, in line with the accumulation observed with non-compartmental analysis (NCA).

Figure 11. Simulated ADC Concentration-Time Profile Following 1.2 mg/kg Q2W



With increasing BSA, parameters for ADC clearance (1.10), central volume of distribution (0.893), and volume of distribution 2 (1.47) are predicted to increase by Cycle 3, which results in an increase in AUC14D. The impact of the model estimate of the covariate effects of these parameters on exposure was evaluated by simulating the relationship between BSA/body weight and AUC14D. Consistent with the dosing strategy used in ECHELON-1, doses were capped at 120 mg for patients weighing more than 100 kg. The simulations for BSA/body weight and AUC14D included the 100 kg dose cap (Figure 15). These simulations demonstrate an increase in AUC with higher BSA/body weight that is attenuated by the 100 kg dose cap. Based on the geometric mean AUC, there is an approximately 30% lower AUC for patients weighing less than 61 kg (48.8 µg*day/mL) compared with patients weighing between 88 kg and 100 kg (63.6 µg*day/mL).

Figure 12 Simulated ADC AUC0-14d for Cycle 3 Following a 1.2 mg/kg Dose Every 14 Days by Body weight (left) or BSA Range (right)



The model estimate of the covariate effect of sex on the central volume was 0.934, which indicates an approximate 7% reduction in central volume in female patients relative to that of male patients. The individual model post-hoc clearance parameter estimates (at baseline) for females and males were plotted and indicate significant overlap between the sexes; although the central tendency indicates women had approximately 20% lower central volume than men. This is attributed to the tendency for women to have lower body weight than men, and the combined covariate impact of sex and BSA on central volume. This was further explored by a Monte Carlo simulation that included body weight or BSA stratification. These simulations show that, after accounting for body size differences, the central volume for females is predicted to be 10% to 14% lower than that of males

MMAE Model Results

The model structure for MMAE is characterized as a linear, 2-compartment model with formation from a lag compartment driven by parallel processes from the ADC central compartment and an internalized ADC compartment.

The fraction of MMAE formed directly from ADC decreased after ADC administration, relative to time after dose, and was used to empirically describe the time-dependent PK of MMAE. This model was developed sequentially to the ADC model, whereby the ADC model individual post-hoc parameter estimates were used to drive the input to the MMAE model. The final MMAE model is depicted in Table 9.

Table 9. MMAE Final PK Model Parameters

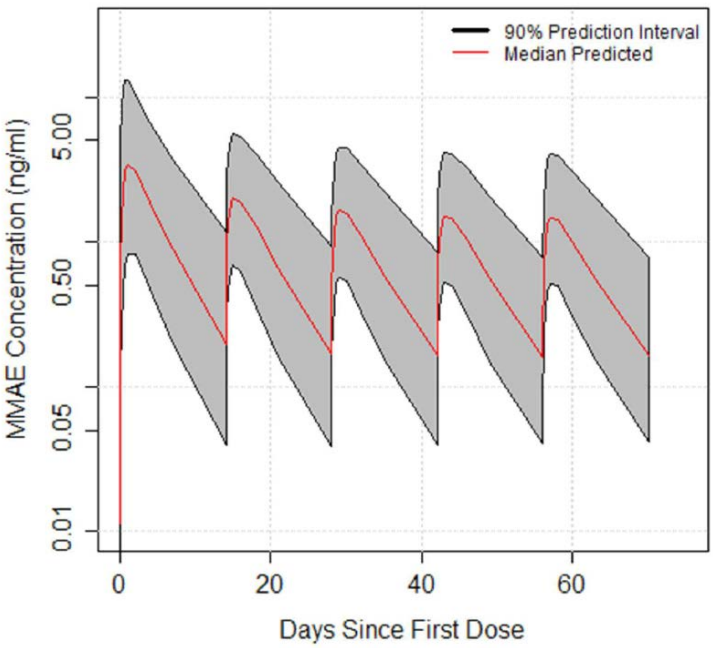
Parameter		Population Mean (SE%)	%CV IIV (Shrinkage)
Clearance (L/hr)	Θ_1	1.45 (0.2%)	38.6 (2.0%)
Central Volume (Vc) (L)	Θ_2	35.5 (0.3%)	68.6 (17.9%)
Binding rate constant (Kd 1/hr)	Θ_3	0.0376 (0.3%)	101.0 (8.8%)
Fraction metabolized	Θ_4	1 FIX	-
ADC to MMAE conversion rate (ALFM 1/hr)	Θ_5	2.35 (0.2%)	-
Lag compartment rate constant (Klag 1/hr)	Θ_6	4.51 (0.3%)	-
Inter-compartmental clearance (Q2) (L/hr)	Θ_7	13.2 (0.3%)	-
Peripheral Volume (V2) (L)	Θ_8	17.7 (0.3%)	-
BSA on Clearance	Θ_{10}	1.04 (1.1%)	-
Glomerular filtration rate on clearance	Θ_{11}	0.125 (3.3%)	-
Albumin concentration on clearance	Θ_{12}	0.0275 (2.8%)	-
Residual Variability	Θ_9	39.5% CV (0.3%)	-

The final MMAE model included effects of BSA, glomerular filtration rate (GFR), and albumin concentration on clearance. Other factors, including age, race, ATA response, ATA titer, nATA response, and IPFP risk factors, were not retained as statistically significant covariates in the model.

The final PK model for MMAE was used to simulate the concentrations produced after a 1.2 mg/kg dose of brentuximab vedotin every 14 days for 5 doses (Cycle 3). Doses were capped at 120 mg for patients weighing more than 100 kg, consistent with the dosing strategy used in ECHELON-1. All the patients in the dataset were included and their baseline covariate values were used. A Monte Carlo simulation approach was used, whereby 150 replicate simulations were performed. Figure 16 is a plot of the

MMAE 90% prediction interval (black lines with shaded grey area) and median (red line) simulated concentrations. This simulation indicated that MMAE AUC and Cmax decreased by approximately 49% and 57%, respectively, between the first and fifth doses, which was consistent with the results observed by NCA.

Figure 13. Simulated MMAE Concentration-Time Profile Following 1.2 mg/kg Brentuximab Vedotin Q2W



The model estimates of the covariate effects on brentuximab vedotin predict a narrow range of MMAE clearance values across albumin concentrations (1.42 L/hr at the low range to 1.46 L/hr at the high range). The covariate effects of the model predict that, with increasing BSA, MMAE clearance increases approximately proportionally, and AUC increases slightly, although these increases were attenuated by inclusion of the 100-kg dose cap. Based on the geometric mean AUC, there is an approximate 13% lower AUC for patients weighing less than 61 kg (10.0 ng*day/mL) compared with patients that weigh between 88 kg and 100 kg (11.3 ng*day/mL).

The model predicts that MMAE clearance increases with increasing GFR. Based on the geometric mean AUC, patients with a GFR <44 mL/min (13.9 ng*day/mL) had an increase in AUC that was approximately 23% higher than for patients with a GFR >90 mL/min (11.3 ng*day/mL).

2.3.3. Pharmacodynamics

Biomarker analysis

Baseline CD30 expression (Study C25003)

CD30 assessment was done by immunohistochemistry and the positivity was determined if CD30 staining was ≥20% on evaluable total lymphocytes. Baseline CD30 expression status in each arm was summarized.

CD30 positivity, when CD30 assessment was available, was comparable between the 2 treatment arms (n=527/528 in the A+AVD arm and n=493/497 in the ABVD arm). CD30 negativity was found in <1%

of patients on both treatment arms. Most of the failures during CD30 assessment (20% in A+AVD arm and 26% in the ABVD arm) were due to poor specimen quality and/or specimen mishandling. Median % positive CD30 staining was comparable between the 2 treatment arms (98% in A+AVD arm and 99% in ABVD arm).

Soluble CD30 concentrations

Soluble CD30 (sCD30) concentration was measured in the serum of patients in both treatment arms at baseline, before administration of study drug on Day 1 of Cycle 2 through Cycle 6, and at EOT.

Mean levels of soluble CD30 at Baseline were highly variable among patients; median levels of soluble CD30 were comparable between the 2 treatment arms at Baseline (207 ng/mL in the A+AVD arm and 209 ng/mL in the ABVD arm).

After brentuximab vedotin treatment, median levels of sCD30 exhibited a trend to be increased at Cycles 2 through 6 in the A+AVD arm relative to the baseline median values (median increase from baseline ranged from 39.3 to 59.6 ng/mL). In the ABVD arm, sCD30 levels exhibited a trend to be decreased at Cycles 2 through 6 relative to the baseline values (median decrease from baseline ranged from 109 to 128 ng/mL).

No consistent changes in mean or median absolute concentrations of sCD30 were observed over time.

Exposure-response analysis

Please refer to section PK/PD modelling.

Antitherapeutic antibodies (ATA) to brentuximab vedotin

Please refer to section clinical efficacy-secondary endpoints.

2.3.4. PK/PD modelling

The population PK model discussed in Section 2.3.2was used to derive an exposure metric for individual patients in ECHELON-1 for brentuximab vedotin ADC and MMAE to examine E-R relationships. Only data from ECHELON-1 were used in this evaluation.

The objectives of this population E-R analysis were:

- To assess relationships between time-averaged ADC exposure (AUC/Time) and mPFS as evaluated by an independent review facility (IRF).
- To assess relationships between AUC/Time of ADC and MMAE and the following AEs:
  - Grade 4 or higher neutropenia (NEU4).
  - Febrile neutropenia (FN).
  - Grade 2 or higher peripheral neuropathy (PN2).
  - Any Grade 3 or higher TEAE (TEAE3).

Exposure-Efficacy Analysis Results

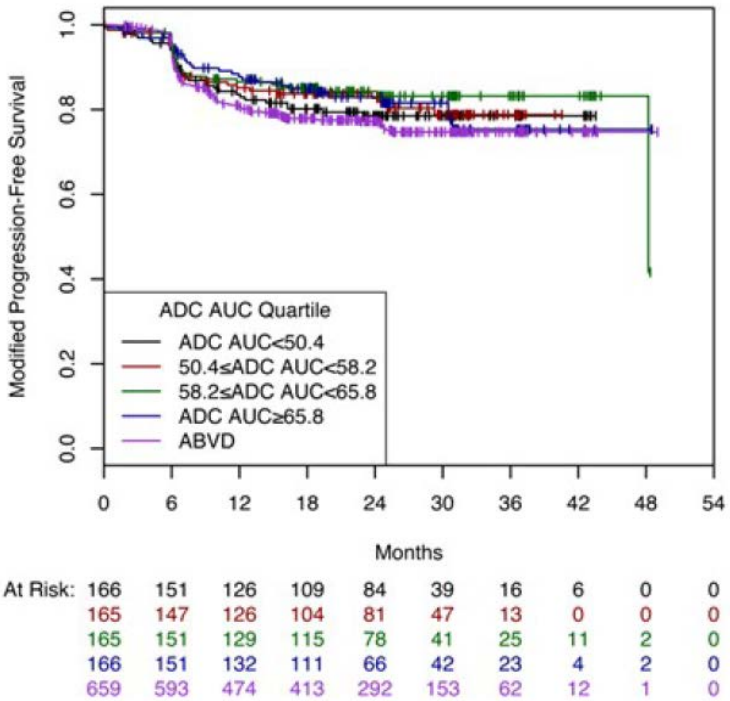
Evaluation of mPFS as a Function of ADC AUC/Time

An assessment of the covariates that could be potentially influential for mPFS was made to ensure these factors were balanced across quartiles of ADC exposure. The covariates factors (region,

extranodal involvement, G-CSF primary prophylaxis, baseline ECOG performance status, and baseline CD30) appeared evenly balanced across all ADC AUC/Time quartiles, whereas International Prognostic Factors Project (IPFP) score suggested some imbalance in the data across ADC AUC/Time quartile.

Figure 17 shows Kaplan-Meier curves for mPFS per IRF. The ADC AUC/Time values were grouped by quartiles and a separate curve for the ABVD arm is provided as reference. There was a large degree of overlap among the 4 AUC/Time bins (log-rank test p=0.86). Visually, on average, patients treated with brentuximab vedotin had longer mPFS times across all quartiles of exposure compared with patients in the ABVD arm.

Figure 14. Kaplan-Meier Curves for mPFS by Quartiles of the ADC AUC/Time With ABVD Overlaid



A Cox proportional hazards regression analysis was performed on mPFS and AUC/Time as a continuous predictor. The proportional hazards regression model was stratified by region and IPFP score, with AUC/Time included as a continuous variable. The ABVD arm was not included. ADC AUC/Time as a continuous variable was not a significant predictor of mPFS (p=0.70105), suggesting that there was a consistent treatment benefit across the range of exposures achieved (HR=1.00; 95% CI=0.987, 1.02). The parameters for Cox regression are presented in Table 10.

Table 10. Cox Proportional Hazard Analysis of mPFS as a Function of ADC AUC/Time

Test	Likelihood Ratio χ^2	DF	p-value
AUC/Time	0.14738	1	0.70105

Additional Subgroup Analyses for mPFS were performed for 2 subgroups (patients with extranodal involvement and categorized by disease stage). Kaplan-Meier curves for mPFS per IRF were plotted by ADC AUC/Time quartile. A separate curve for the ABVD arm was overlaid on the same plot as a reference. In addition, Cox proportional hazards regression analysis was also performed for the same subgroups. Analyses for the results for the subgroup of patients with stage IV disease or with extranodal involvement indicated that also in these situations ADC AUC/Time was not a statistically significant predictor of mPFS as a continuous covariate for patients.

Exposure-AE Analyses Results

Peripheral Neuropathy Grade ≥2 as a Function of Time Averaged ADC AUC/Time

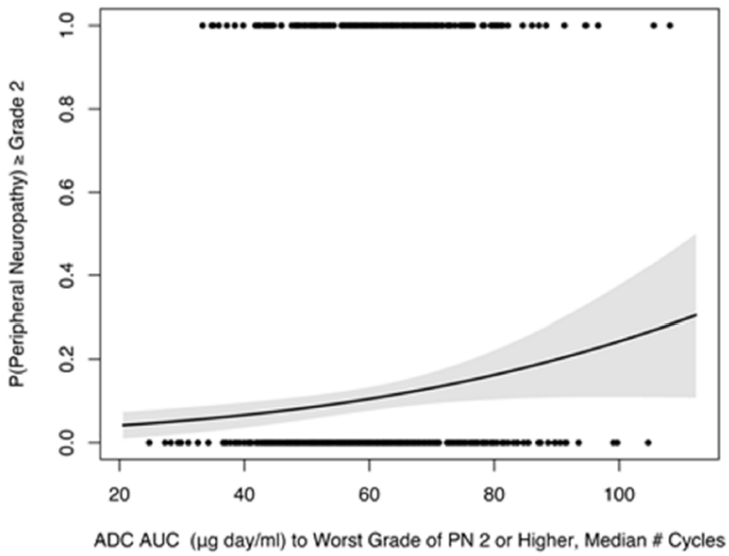
A logistic regression analysis was performed to assess whether AUC/Time was predictive of a Grade ≥2 peripheral neuropathy. The addition of a parameter to the model based on ADC AUC/Time resulted in a likelihood ratio of 8.337 with 1 additional parameter, an additional degree of freedom (DF), which corresponds to a p-value <0.01, which was statistically significant. The parameters for the final logistic regression function are provided in Table 11.

Table 11. Coefficients of the Logistic Regression of Grade ≥2 Peripheral Neuropathy as a Function of ADC AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
Intercept	1.688	0.5973		
PN2 ADC AUC/Time	0.02513	0.008754	1.025	(1.008, 1.043)
PN2CYCLE	-0.8896	0.06659	0.4108	(0.359, 0.4662)

Figure 18 presents the model results. The observed values of ADC AUC/Time are shown by the dots for patients who did (P=1) and did not (P=0) experience Grade ≥2 PN. Increasing ADC AUC/Time resulted in greater probability of Grade ≥2 PN.

Figure 15. Probability of Grade ≥2 PN AE as a Function of ADC AUC/Time



PN Grade ≥2 as a Function of Time Averaged MMAE AUC/Time

A logistic regression analysis was performed to assess whether MMAE AUC/Time at the worst event was predictive of a patient experiencing a Grade ≥2 PN event. The addition of a parameter to the model based on MMAE AUC/Time resulted in a 1.643 likelihood ratio with 1 additional parameter (1 additional DF), which corresponds to p=0.1999, which was not statistically significant at the 0.05 level. This indicated that MMAE AUC/Time was not predictive of the probability of experiencing a Grade ≥2 PN event. A summary of the coefficients in the model are shown in Table 12. MMAE AUC/Time was not identified as being predictive of Grade ≥2 PN.

Table 12. Coefficients of the Logistic Regression of Grade ≥2 PN as a Function of MMAE AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	5.907	0.8266		
PN2 MMAE AUC/Time	-0.1898	0.05049	0.8271	(0.7462,0.9111)
PN2CYCLE	-1.457	0.1733	0.233	(0.1639,0.324)
PN2 MMAE AUC:PN2CYCLE	0.04092	0.0112	1.042	(1.019,1.065)

Grade ≥4 Neutropenia as a Function of Time Average ADC AUC/Time

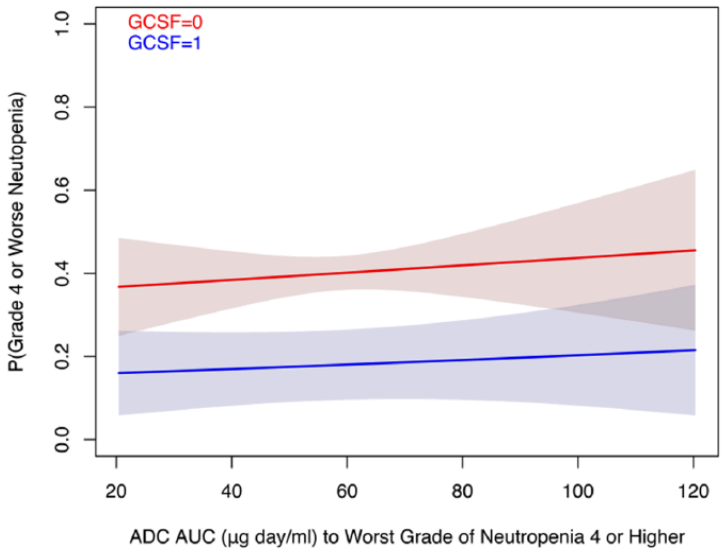
A logistic regression analysis was performed to assess whether ADC AUC/Time was predictive of a patient experiencing Grade ≥4 neutropenia. G-CSF primary prophylaxis was also included in the model. The addition of a parameter to the model based on ADC AUC/Time was not considered statistically significant (p>0.05). The addition of G-CSF primary prophylaxis resulted in a likelihood ratio of 16.7 (p<0.01). The parameters for the final logistic regression function are provided in Table 13.

Table 13. Coefficients of the Logistic Regression of Grade ≥4 Neutropenia as a Function of ADC AUC/Time and G-CSF Primary Prophylaxis

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	-0.6173	0.3749		
G-CSF primary prophylaxis=Yes	-1.116	0.2979	0.3277	(0.1766,0.5721)
ADC AUC/Time	0.003647	0.006197	1.004	(0.9915,1.016)

A plot of the probability of Grade ≥4 neutropenia versus ADC AUC/Time overlaid by G-CSF primary prophylaxis is provided in Figure 19. The solid lines represent the expected probability of an event and the shaded areas are the associated 95% CI of the probability. No relationship was observed between ADC AUC/Time and Grade ≥4 neutropenia, although G-CSF primary prophylaxis was found to reduce Grade ≥4 neutropenia.

Figure 16. Probability of Grade ≥4 Neutropenia as a Function of ADC AUC/Time Overlaid by G-CSF Primary Prophylaxis Status



Grade ≥4 Neutropenia as a Function of Time-Averaged MMAE AUC/Time

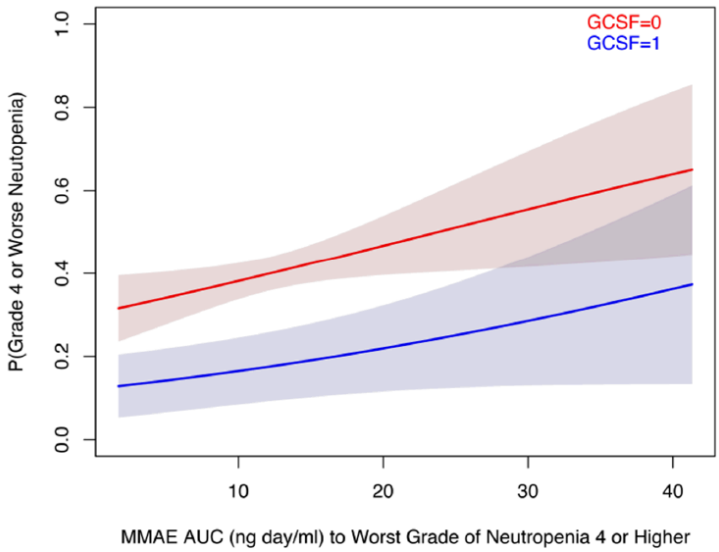
A logistic regression analysis was performed to assess whether MMAE AUC/Time was predictive of a patient experiencing Grade ≥4 neutropenia. Because administration of G-CSF can reduce the likelihood of neutropenia, G-CSF primary prophylaxis was also included in the model. The addition of a parameter to the model based on MMAE AUC/Time was considered statistically significant ($p<0.05$). The parameters for the final logistic regression function are provided in Table 14.

Table 14. Coefficients of the Logistic Regression of Grade ≥4 Neutropenia as a Function of MMAE AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	-0.8356	0.2081		
G-CSF primary prophylaxis=yes	-1.141	0.2993	0.3196	(0.1717,0.5594)
MMAE AUC/Time	0.03526	0.01528	1.036	(1.005,1.068)

A plot of the probability of Grade ≥4 neutropenia versus MMAE AUC/Time overlaid by G-CSF primary prophylaxis is provided in Figure 20. The solid lines represent the average expected probability; the shaded regions are the 95% CI of the probability. MMAE AUC/Time was found to be predictive of Grade ≥4 neutropenia and G-CSF primary prophylaxis was found to reduce Grade 4 neutropenia.

Figure 17. Probability of Grade ≥4 Neutropenia as a Function of MMAE AUC/Time Overlaid by G-CSF Primary Prophylaxis Status



Febrile Neutropenia as a Function of Time Averaged ADC AUC/Time

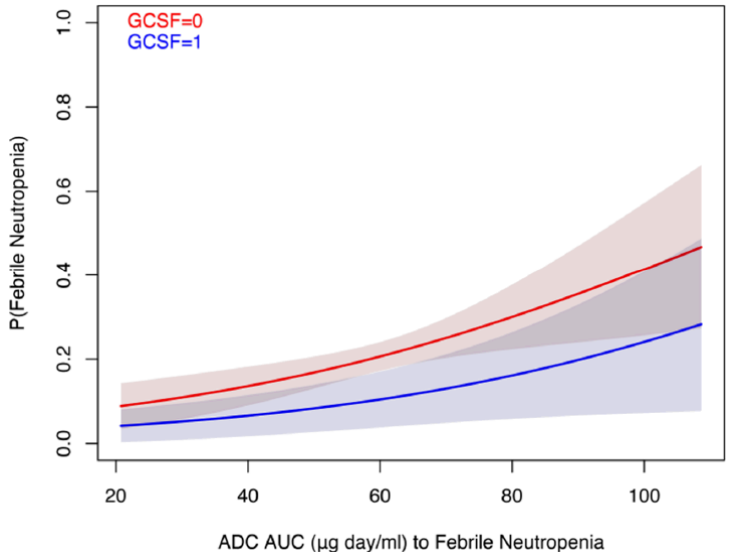
A logistic regression analysis was performed to assess whether AUC/Time was predictive of a patient experiencing febrile neutropenia. G-CSF primary prophylaxis was also included in the model. The addition of a parameter to the model based on ADC AUC/Time resulted in a likelihood ratio of 10.1 with 1 additional parameter (1 additional DF), which corresponds to a $p<0.01$, which is considered statistically significant. The addition of G-CSF primary prophylaxis resulted in a likelihood ratio of 5.577 ($p<0.05$), which is statistically significant. The parameters for the final logistic regression function are provided in Table 15.

Table 15. Coefficients of the Logistic Regression of Febrile Neutropenia as a Function of ADC AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	-2.85	0.4922		
G-CSF primary prophylaxis=yes	-0.8021	0.3692	0.4484	(0.2036,0.8799)
ADC AUC/Time	0.02504	0.007894	1.025	(1.01,1.041)

Plots of the probability of febrile neutropenia versus ADC AUC/Time are provided in Figure 21, overlaid by G-CSF primary prophylaxis. The solid lines represent the average expected probability, the shaded regions represent the 95% CI of the probability. ADC AUC/Time was found to be predictors of febrile neutropenia, with the probability of febrile neutropenia increasing with increasing ADC AUC/Time. G-CSF primary prophylaxis was found to reduce febrile neutropenia.

Figure 18. Probability of Febrile Neutropenia as a Function of ADC AUC/Time Overlaid by G-CSF Primary Prophylaxis Status



Febrile Neutropenia as a Function of Time Averaged MMAE AUC/Time

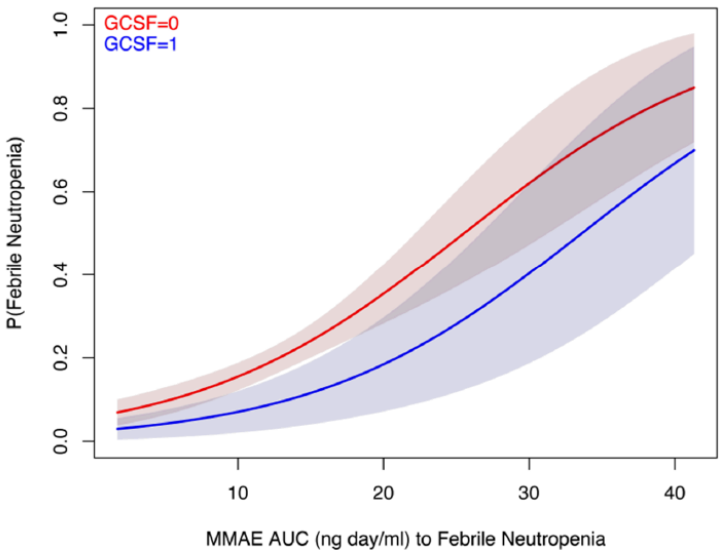
A logistic regression analysis was performed to assess whether MMAE AUC/Time was predictive of a patient experiencing febrile neutropenia. G-CSF primary prophylaxis was also included in the model. The addition of a parameter to the model based on MMAE AUC/Time resulted in a likelihood ratio of 37.98 with 1 additional parameter (1 additional DF) ($p<0.01$). The addition of G-CSF primary prophylaxis resulted in a likelihood ratio of 6.306 ($p<0.05$). The parameters for the final logistic regression function are provided in Table 16.

Table 16. Coefficients of the Logistic Regression of Febrile Neutropenia as a Function of MMAE AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	-2.792	0.2706		
G-CSF primary prophylaxis=yes	-0.8855	0.3842	0.4125	(0.1819,0.8331)
MMAE AUC/Time	0.1094	0.01815	1.116	(1.077,1.157)

Plots of the probability of febrile neutropenia versus MMAE AUC/Time are provided in Figure 22, overlaid by G-CSF primary prophylaxis. The solid lines represent the average expected probability, the shaded regions represent the 95% CI of the probability. MMAE AUC/Time was found to be predictors of febrile neutropenia, with the probability of febrile neutropenia increasing with increasing MMAE AUC/Time. G-CSF primary prophylaxis was found to reduce febrile neutropenia.

Figure 19. Probability of Febrile Neutropenia as a Function of MMAE AUC/Time Overlaid by G-CSF Primary Prophylaxis Status



Treatment-Emergent Adverse Events Grade ≥3 as a Function of Time Averaged ADC AUC/Time

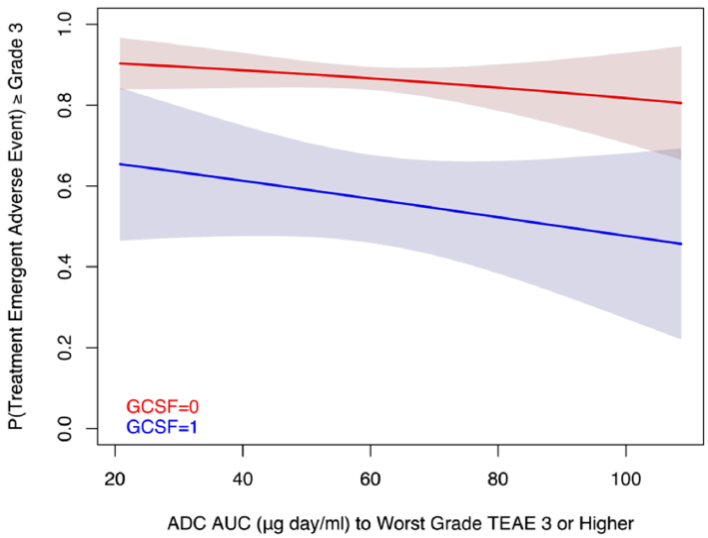
A logistic regression analysis was performed on Grade ≥3 TEAEs and ADC AUC/Time at the time of TEAE of highest severity. For patients who did not experience a Grade ≥3 TEAE, AUC/Time was calculated over the treatment duration. Because TEAEs also captured neutropenia, G-CSF primary prophylaxis was included as a covariate. The addition of a parameter to the model based on ADC AUC/Time was not statistically significant ($p>0.05$). However, G-CSF primary prophylaxis had a likelihood ratio of 36.71 with an associated $p<0.01$. The parameters for this logistic regression evaluation are presented in Table 17.

Table 17. Coefficients of the Logistic Regression of Grade ≥3 TEAEs as a Function of ADC AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	2.421	0.5407		
G-CSF primary prophylaxis=Yes	-1.593	0.2535	0.2032	(0.1237,0.335)
ADC AUC/Time	-0.009221	0.008811	0.9908	(0.9739,1.008)

Plots of the probability of a Grade ≥3 TEAE versus ADC AUC/Time, overlaid by G-CSF primary prophylaxis are provided in Figure 23. The solid lines represent the average expected probability, the shaded regions represent the 95% CI of the probability. ADC AUC/Time was not found to be a statistically significant predictor of a Grade ≥3 TEAE event. Concomitant G-CSF primary prophylaxis was found to reduce the probability of a Grade ≥3 TEAE.

Figure 20 Logistic Regression of Grade ≥3 TEAEs as a Function of ADC AUC/Time Overlaid by G-CSF Primary Prophylaxis Status



TEAEs Grade ≥3 as a Function of Time Averaged MMAE AUC/Time

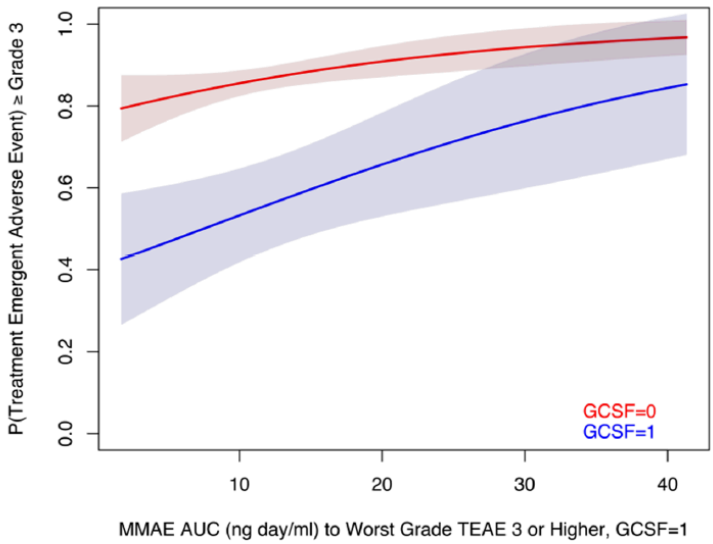
A logistic regression analysis was performed on Grade ≥3 TEAE and MMAE AUC/Time at the time of the event with the worst severity. Because neutropenia was included in these events, and G-CSF can reduce the likelihood of neutropenia, G-CSF primary prophylaxis was included as a covariate. The addition of a parameter to the model based on MMAE AUC/Time resulted in a likelihood of 5.829 with 1 additional parameter (1 additional DF) ($p<0.05$.) The addition of G-CSF primary prophylaxis resulted in a likelihood of 38.63 ($p<0.01$). The parameter values for the logistic regression are provided in Table 18.

Table 18. Coefficients of the Logistic Regression of Grade ≥3 TEAEs as a Function of MMAE AUC/Time

Covariate	Estimate	Standard Error	OR	95% CI for OR
(Intercept)	1.259	0.283		
G-CSF primary prophylaxis=yes	-1.648	0.2563	0.1924	(0.1164,0.3187)
MMAE AUC/Time	0.05196	0.02246	1.053	(1.01,1.103)

Plots of the probability of a Grade ≥3 TEAE versus MMAE AUC/Time are provided overlaid by G-CSF primary prophylaxis.

Figure 21. Logistic Regression of the Grade ≥3 TEAEs as a Function of MMAE AUC/Time Overlaid by G-CSF Primary Prophylaxis Status



2.3.5. Discussion on clinical pharmacology

The clinical pharmacology characteristics of brentuximab vedotin as monotherapy was already assessed as part of the initial marketing authorisation application. In this variation, additional data were provided on the clinical pharmacology of brentuximab vedotin in combination with doxorubicin, vinblastine, and/or dacarbazine (AVD), in the treatment of Hodgkin lymphoma (HL).

The pharmacokinetics of brentuximab vedotin in combination with AVD were evaluated in a single phase 3 study in 661 patients. Population pharmacokinetic analysis indicated that the pharmacokinetics of brentuximab vedotin in combination with AVD were consistent to that in monotherapy.

After multiple-dose, IV infusion of 1.2 mg/kg brentuximab vedotin every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a multi-exponential decline with a $t_{1/2z}$ of approximately 4 to 5 days. Maximal plasma concentrations of MMAE were observed approximately 2 days after the end of infusion, and exhibited a mono-exponential decline with a $t_{1/2z}$ of approximately 3 to 4 days.

After multiple-dose, IV infusion of 1.2 mg/kg brentuximab vedotin every two weeks, steady-state trough concentrations of ADC and MMAE were achieved by Cycle 3. Once steady-state was achieved, the PK of ADC did not appear to change with time. ADC accumulation (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) was 1.27-fold. The exposure of MMAE (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) appeared to decrease with time by approximately 50% (see SmPC section 5.2).

As measured by Cmax, AUC24h, Ceoi, and AUCinf, no apparent differences were observed in the PK of each component of AVD between the 2 treatment arms (A-AVD vs doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD). Co-administration of brentuximab vedotin did not affect the plasma exposure of doxorubicin, vinblastine, or dacarbazine as compared to the situation when given in a ABVD regimen. Doxorubicin, vinblastine and dacarbazine were analysed using sufficiently validated assays.

Two popPK models were developed for this analysis, 1 each for ADC and MMAE. The models were based on a previously developed model for the ALCANZA study (Study C25001) and were built with

data from 661 patients with HL from the ECHELON-1 (C25003) study. Based on pop-PK simulations, ADC AUC increased with increasing body size, although this increase was attenuated with the 100-kg dose cap. Likewise, MMAE CL increased with increasing body size. With body weight-based dosing and the 100-kg dose cap, only small changes in MMAE AUC were observed across body sizes. The increases are unlikely to be clinically meaningful given the significant overlap in exposure between the body size ranges.

Further, the pop-PK model predicts that, with increasing albumin concentration, ADC clearance decreases and AUC slightly increases. Based on the geometric mean AUC, the AUC for patients with albumin concentrations < 37 g/L (49.5 µg*day/mL) is approximately 20% lower than for patients with albumin concentrations ≥43 g/L (59.6 µg*day/mL). The covariate effects of the model predict that, with increasing BSA, MMAE clearance increases approximately proportionally, and AUC increases slightly, although these increases were attenuated by inclusion of the 100-kg dose cap. Based on the geometric mean AUC, there is an approximate 13% lower AUC for patients weighing less than 61 kg (10.0 ng*day/mL) compared with patients that weigh between 88 kg and 100 kg (11.3 ng*day/mL). These differences are unlikely to be clinically meaningful given the significant overlap in exposure across the albumin concentration ranges.

Simulations for ADC show that, after accounting for body size differences, the central volume for females is predicted to be 10% to 14% lower than that of males. These differences are unlikely to be clinically meaningful given the overall variability in ADC PK. The influence of age, race (Asian and non-Asian), ATA (nATA and ATA titer), and IPFP score were not identified as significant covariates impacting the PK of ADC or MMAE. No dosing adjustment based on these intrinsic or extrinsic patient factors evaluated is recommended for brentuximab vedotin in adult patients. The model predicts that MMAE clearance increases with increasing GFR. Based on the geometric mean AUC, patients with a GFR <44 mL/min (13.9 ng*day/mL) had an increase in AUC that was approximately 23% higher than for patients with a GFR >90 mL/min (11.3 ng*day/mL). However, given the substantial overlap in exposures across the range of GFRs, these differences are not expected to be clinically meaningful.

Overall, the results of this analysis showed that the PK models for ADC and MMAE adequately describe their concentration-versus-time profiles.

With regards to elderly, the population pharmacokinetics of brentuximab vedotin in combination with AVD were examined including data from 661 patients up to 82 years old (42 patients ≥65-<75 and 17 patients ≥75 years of age). The influence of age on pharmacokinetics was investigated in each analysis and it was not a significant covariate (see SmPC section 5.2). The dosing recommendations for patients aged 65 and older are the same as for adults (see section 4.2).

There is no clinical trial experience using brentuximab vedotin in combination with chemotherapy in patients with renal impairment, where serum creatinine is ≥ 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance is ≤ 40 mL/minute. Use of brentuximab vedotin in combination with chemotherapy should be avoided in patients with severe renal impairment. Patients with renal impairment should be closely monitored for adverse events.

There is no clinical trial experience using brentuximab vedotin in combination with chemotherapy in patients with hepatic impairment, where total bilirubin is > 1.5 times the upper limit of normal (ULN) (unless due to Gilbert syndrome), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are > 3 times the ULN, or > 5 times the ULN if their elevation may be reasonably ascribed to the presence of HL in the liver. Use of brentuximab vedotin in combination with chemotherapy should be avoided in patients with moderate and severe hepatic impairment. The recommended starting dose in patients with mild hepatic impairment is 0.9 mg/kg administered as an intravenous infusion over

30 minutes every 3 weeks. Patients with hepatic impairment should be closely monitored for adverse events.

In terms of pharmacodynamics no statistically significant correlations between sCD30 or other biomarkers and disease pathway/drug mechanism have been described.

For patients experiencing treatment-related toxicities upon treatment at the starting dose, protocol-specified dose reductions for brentuximab vedotin are recommended as supported by exposure-safety analyses that revealed relationships between ADC and/or MMAE exposure and the incidence of all evaluated AE outcomes of clinical interest (Grade ≥2 PN, Grade ≥4 neutropenia, febrile neutropenia, and Grade ≥3 TEAE). G-CSF primary prophylaxis reduced the occurrence of neutropenia, febrile neutropenia, and Grade ≥3 TEAE (as these are mostly neutropenia-related).

Collectively, these results support the findings that the safety profile of brentuximab vedotin can be adequately managed by the dose modification/dose reduction for neuropathy and G-CSF primary prophylaxis for neutropenia(-related) AEs, as established in ECHELON-1.

Regarding neuropathy, in the case of grade 2 the dose should be reduced to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks; if grade 3 neuropathy develops treatment with ADCETRIS should be withheld until toxicity is ≤ Grade 2, then treatment can be restarted at a reduced dose to 0.9 mg/kg every 2 weeks; in case of a grade IV neuropathy treatment should be discontinued.

In patients who develop Grade 3 or Grade 4 neutropenia, G-CSF or GM-CSF should be considered in subsequent cycles.

2.3.6. Conclusions on clinical pharmacology

Overall it is concluded that the clinical pharmacology has been adequately investigated. Relevant dosing recommendations and warnings have been included in the SmPC sections 4.4, 4.5 and 5.2.

2.4. Clinical efficacy

2.4.1. Dose response study

Dose escalation Study SGN35-009

This Phase 1 dose escalation study investigated the safety and maximum tolerated dose (MTD) of brentuximab vedotin in combination with a standard of care multi-chemotherapy ABVD (n=25) or in combination with a modified standard of care therapy AVD (n=26). Adult (18-60 years) treatment–naïve HL patients with histologically confirmed Stage IIa bulky disease or Stage IIb-IV disease were eligible for this study.

The tested dose levels of brentuximab vedotin in combination with ABVD were 0.6, 0.9, and 1.2 mg/kg and the planned dose level of brentuximab vedotin in combination with AVD was 1.2 mg/kg.

No protocol-defined dose-limiting toxicities (DLTs) were observed with doses of brentuximab vedotin up to 1.2 mg/kg every 2 weeks (the maximum planned dose). However, unacceptable pulmonary toxicity (44%, including 2 fatal events) was noted in patients treated with brentuximab vedotin plus ABVD. In contrast, no pulmonary toxicity was observed in patients treated with brentuximab vedotin plus AVD. Furthermore, 24 of 25 (96%) response evaluable patients treated with brentuximab vedotin plus AVD achieved a complete response at the end of frontline therapy and the 5-year failure-free survival for this cohort was 92%.

Safety signal

In the brentuximab vedotin with ABVD regimen, 11 of 25 patients (44%) experienced an AE associated with pulmonary toxicity; events resolved in 9 of 11 patient. One event of pulmonary toxicity was Grade 5 (fatal) and another event was not recovered/resolved at the time of the patient's death due to hospitalization-related complications and resultant cerebral haemorrhage. Six of the 11 patients who discontinued bleomycin prior to Cycle 5 Day 1 were able to complete frontline therapy with a combination of brentuximab vedotin and AVD.

This pulmonary toxicity signal emerged after the DLT evaluation period (Cycle 2 Day 1) and events primarily occurred between Cycles 4 and 6. After the brentuximab vedotin with ABVD regimen had established the MTD at 1.2 mg/kg, and with pulmonary toxicity observed in later treatment cycles, the additional regimen combining brentuximab vedotin with AVD was added to the protocol study design to assess safety and efficacy in a regimen omitting bleomycin. No patients in the brentuximab vedotin with AVD regimen experienced pulmonary toxicity.

Efficacy results

Per investigator assessment, the complete remission (CR) rate for all 51 patients at EOT was 80%: 68% in the brentuximab vedotin with ABVD regimen and 92% in the brentuximab vedotin with AVD regimen. Response assessments at EOT were missing for 7 patients (14%): 6 patients (24%) in the brentuximab vedotin with ABVD regimen and 1 patient (4%) in the brentuximab vedotin with AVD regimen.

Progression-free survival rate was 85% for patients in the brentuximab vedotin with ABVD regimen at 12 months, and 95% for patients in the brentuximab vedotin with AVD regimen.

2.4.2. Main study

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 (test arm)

A+AVD consists of 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 (control arm)

ABVD consists of 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 19.

Table 19 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. The use of prophylactic CSFs for neutropenia was recommended for patients in the A+AVD treatment arm starting with the first treatment cycle.

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.

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 was for OS 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.

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.

Last observation carried forward method and multiple imputation method may be considered for some clinical outcomes as deemed appropriate.

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; Figure 25). The study was conducted in 218 investigative sites located in 21 countries across 4 regions: Asia Pacific, Europe, Latin America and North America.

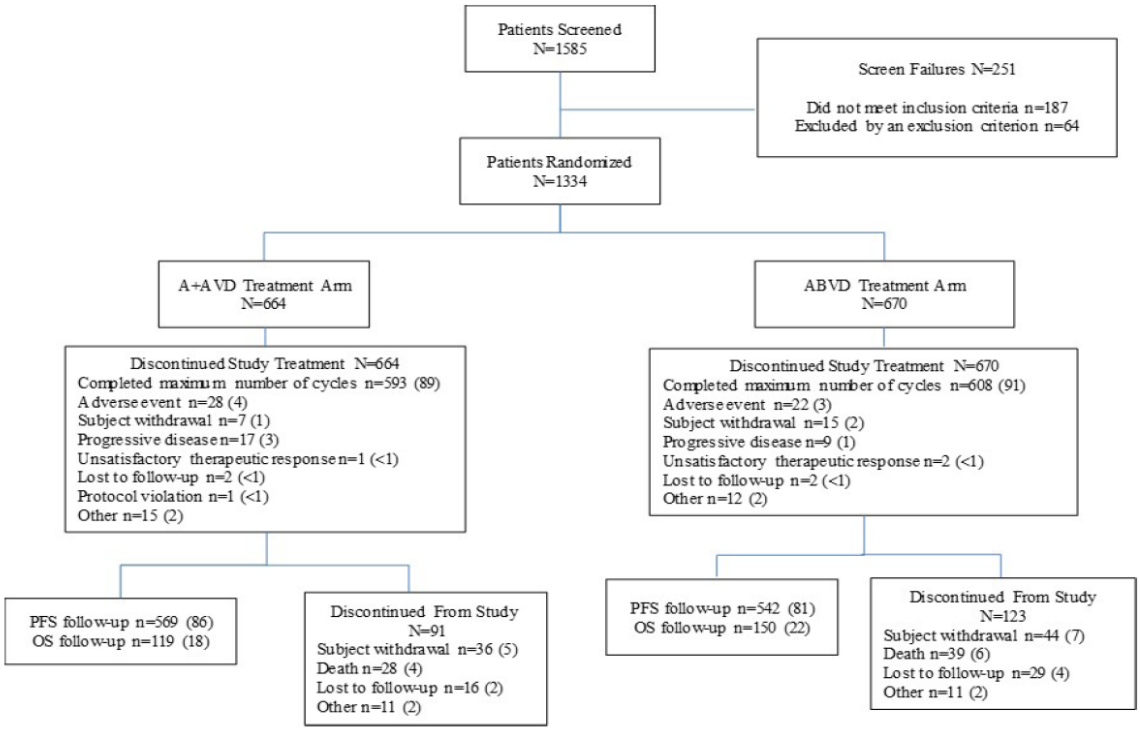


Figure 22 Study C25003: Subject Disposition as of 20 April 2017 Data Cut-off

A total of 91 A+AVD patients (14%) and 123 ABVD patients (18%) are off study; for 28 A+AVD patients (4%) and 39 ABVD patients (6%), the off study reason was death. A small percentage of patients on the A+AVD arm and ABVD arm (14 patients [2%] and 9 patients [1%], respectively, Table 24) completed frontline treatment with an AFM.

Recruitment

First patient enrolled: 9 November 2012

Last patient assessed for primary analysis: 20 April 2017

Clinical database lock: 12 June 2017

Conduct of the study

Study protocol amendments

The original protocol was dated 29 March 2012, and subsequently amended 7 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 enrolment period.
- Increase enrolment 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.

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 analysis

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 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 21). Most patients were male (~58% in both arms), white (~83%) and not Hispanic or Latino (86%). The median age was ~36 years.

Table 20: 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

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

Baseline disease characteristics were also generally balanced between the 2 treatment arms in the ITT population (Table 22). 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 21 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)

The baseline disease characteristics for the subgroup of the ITT population with Stage IV disease were well balanced between treatment arms, and generally similar with the ITT population. Fewer patients with stage IV disease had 0-1 IPFP risk factors (13% and 10% in the A+AVD and ABVD arms, respectively, compared with 21% in both arms in the ITT population), and more patients with Stage IV disease had 4-7 IPFP risk factors (34% and 36%, compared with 25% and 27%). Patients with Stage IV disease also had more bone marrow involvement and more evidence of extranodal involvement.

Table 22: Study C25003: Baseline Disease Characteristics (ITT subgroup with Baseline Stage IV Disease)

	A+AVD N=425	ABVD N=421
Time since initial diagnosis, months (a)		
n	424	413
Mean (std dev)	1.05 (1.268)	1.22 (4.163)
Median	0.85	0.85
Min, max	0.1, 21.4	0.0, 81.4
Missing	1	8
Disease type, n (%)		
HL	424 (100)	420 (100)
Nodular lymphocyte predominant HL	0	0
cHL (b)	98 (23)	96 (23)
Nodular sclerosis cHL	273 (64)	240 (57)
Lymphocyte-rich cHL	5 (1)	13 (3)
Mixed-cellularity cHL	46 (11)	66 (16)
Lymphocyte-depleted cHL	2 (<1)	5 (1)
Other (c)	1 (<1)	1 (<1)
Ann Arbor stage at initial diagnosis, n (%)		
Stage IV	425 (100)	421 (100)
Number of IPFP risk factors, n (%)		
0-1	55 (13)	43 (10)
2-3	225 (53)	227 (54)
4-7	145 (34)	151 (36)

ECOG performance status, n (%)		
0	221 (52)	217 (52)
1	184 (43)	181 (43)
2	20 (5)	22 (5)
Bone marrow involvement at initial diagnosis or study entry, n (%)		
Yes	142 (33)	140 (33)
No	271 (64)	276 (66)
Unknown	12 (3)	5 (1)
Evidence of extranodal involvement at initial diagnosis, n (%)		
Yes	363 (85)	359 (85)
1 extranodal site	178 (42)	181 (43)
>1 extranodal sites	185 (44)	178 (42)
B symptoms (d)		
Number of patients with any B symptom, n (%)	276 (65)	256 (61)
Unexplained weight loss of >10% of the body weight, n (%)		
Yes	146 (34)	124 (29)
No	278 (65)	296 (70)
Not done/missing	1 (<1)	1 (<1)
Unexplained, persistent, or recurrent fever, temperature >38°C, n (%)		
Yes	123 (29)	128 (30)
No	301 (71)	292 (69)
Not done/missing	1 (<1)	1 (<1)
Recurrent drenching night sweats, n (%)		
Yes	237 (56)	208 (49)
No	187 (44)	212 (50)
Not done/missing	1 (<1)	1 (<1)
Clinical evaluation		
Palpable liver, n (%)		
Yes	28 (7)	25 (6)
No	390 (92)	392 (93)
Indeterminate	4 (<1)	2 (<1)
Not done	3 (<1)	2 (<1)
Palpable spleen, n (%)		
Yes	41 (10)	38 (9)
No	377 (89)	375 (89)
Indeterminate	4 (<1)	6 (1)
Not done	3 (<1)	2 (<1)

Table 23 ECHELON-1: Demographics (ITT Population, Subset of Patients with Stage III HL)

	A+AVD N=237	ABVD N=246
Sex n (%)		
Male	133 (56)	154 (63)
Female	104 (44)	92 (37)
Ethnicity n (%)		
Hispanic or Latino	23 (10)	20 (8)
Not Hispanic or Latino	194 (82)	209 (85)
Not Reported	20 (8)	17 (7)
Race n (%)		
White	194 (82)	204 (83)
Asian	19 (8)	21 (9)
Korean	9 (4)	8 (3)
Japanese	4 (2)	4 (2)
Chinese	4 (2)	3 (1)
Asian Indian	0	4 (2)
Other	2 (<1)	1 (<1)
Not Reported	0	1 (<1)
Black or African American	10 (4)	6 (2)

	A+AVD N=237	ABVD N=246
Not Reported	5 (2)	10 (4)
Other	9 (4)	5 (2)
American Indian or Alaskan Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Age (years)a		
n	237	246
Mean (std dev)	38.5 (16.76)	39.0 (15.87)
Median	33.0	35.0
Min, Max	18, 79	18, 80
Age Categories (years)[a], n (%)		
<45	159 (67)	162 (66)
45-59	47 (20)	50 (20)
60-64	8 (3)	14 (6)
≥65	23 (10)	20 (8)
Height (cm)		
n	235	246
Mean (std dev)	171.9 (10.05)	172.4 (10.05)
Median	172.0	172.7
Min, Max	140, 197	140, 193
Missing	2	0
Weight (kg)		
n	237	246
Mean (std dev)	75.21 (17.798)	80.29 (22.084)
Median	73.90	75.90
Min, Max	41.0, 160.5	44.6, 181.2
Body Surface Area[b] (m^2)		
n	235	246
Mean (std dev)	1.886 (0.2539)	1.947 (0.2838)
Median	1.894	1.936
Min, Max	1.28, 2.85	1.32, 2.97
Missing	2	0

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 analyses were based on the ITT analysis set, defined as all 1334 randomized patients. A summary of all study populations is provided below.

Table 24: 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

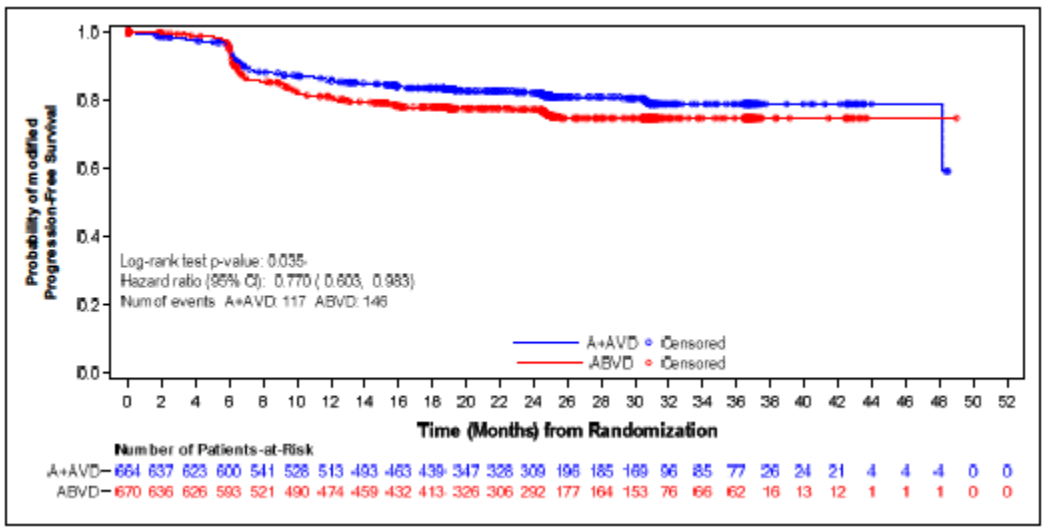
Primary endpoint – modified Progression-Free Survival per IRF

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 25).

Table 25 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)

Figure 23 Study C25003: KM Plot of mPFS per IRF Assessment (ITT)_

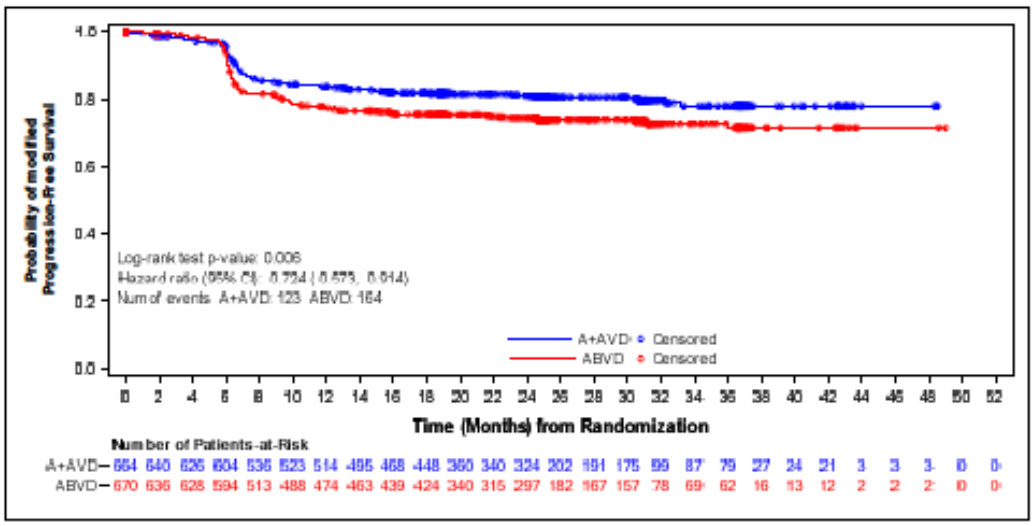


Secondary analysis of mPFS

mPFS per INV

The results for mPFS per investigator (INV, sensitivity analysis 2a: see also forest plot of sensitivity analysis) for the ITT population support the primary efficacy analysis. The stratified hazard ratio was 0.724 (95% CI, 0.573-0.914) indicating a 27.6% reduction in the risk of mPFS with A+AVD compared with ABVD (p=0.006). The mPFS rate per INV was 81.0% for the A+AVD patients vs 74.4% for ABVD patients at 2 years.

Figure 24 Study C25003: KM Plot of mPFS per INV Assessment (ITT)



A concordance analysis between IRF and INV assessments of mPFS events showed that of 1334 cases assessed for mPFS events, 1214 (91%) were concordant. The concordance was the same in both arms.

mPFS for PP population

A supplementary analysis of mPFS per IRF using the PP population is consistent with those obtained for the primary endpoint using the ITT population. The stratified HR was 0.769 (95% CI 0.600, 0.986; p=0.037).

Sensitivity analyses of mPFS

A sensitivity analysis of mPFS per IRF was performed in which the following events each were considered mPFS events:

1) treatment discontinuation for undocumented disease progression after the last adequate assessment, and
2) an event after more than 1 missed visit.

Results of this analysis were consistent with results of the primary analysis. The stratified hazard ratio was 0.765 (95% CI, 0.603-0.970, p=0.026). At 2 years, the rate of patients alive without progression or a modified progression event (modified progression-free) was 81% in the A+AVD arm vs 76% in the ABVD arm.

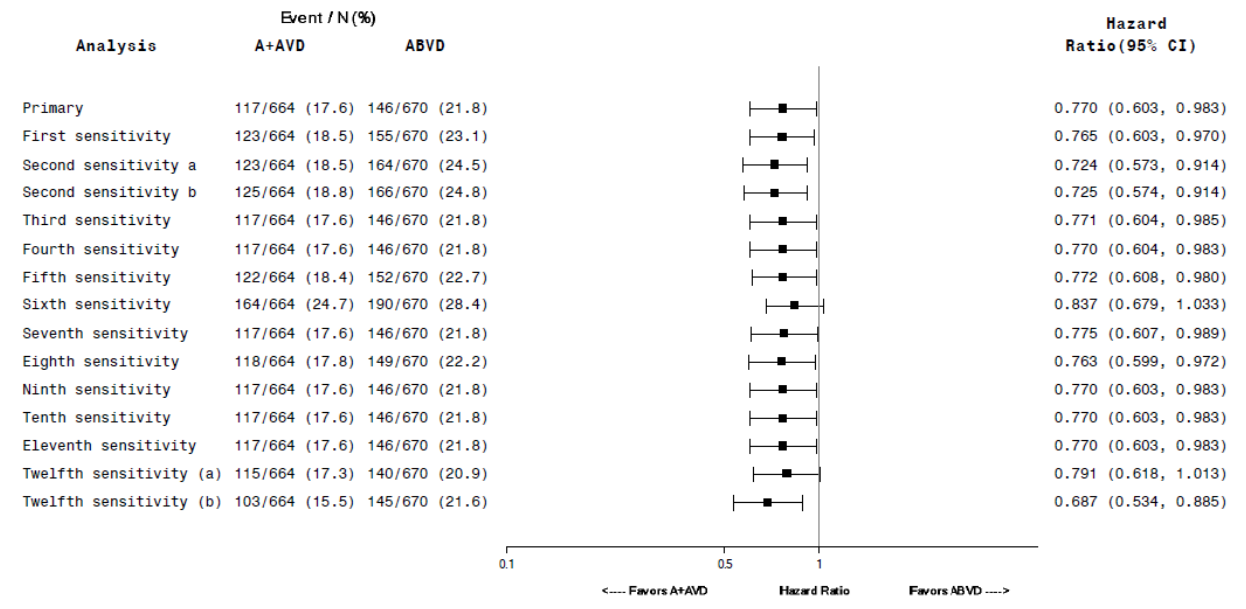
Another analysis was performed for mPFS per INV, showing similar results.

Additional sensitivity analyses of mPFS

In the ITT population, sensitivity analyses were performed for mPFS to evaluate the robustness of treatment effects. Included among the analyses were alterations of the handling of missing

assessments and censoring, on the basis of 1 alteration per analysis (for exact definitions see section *statistical methods* above). The sensitivity analyses of mPFS were generally consistent with the primary analysis. For the ITT population, a forest plot of mPFS sensitivity analyses.

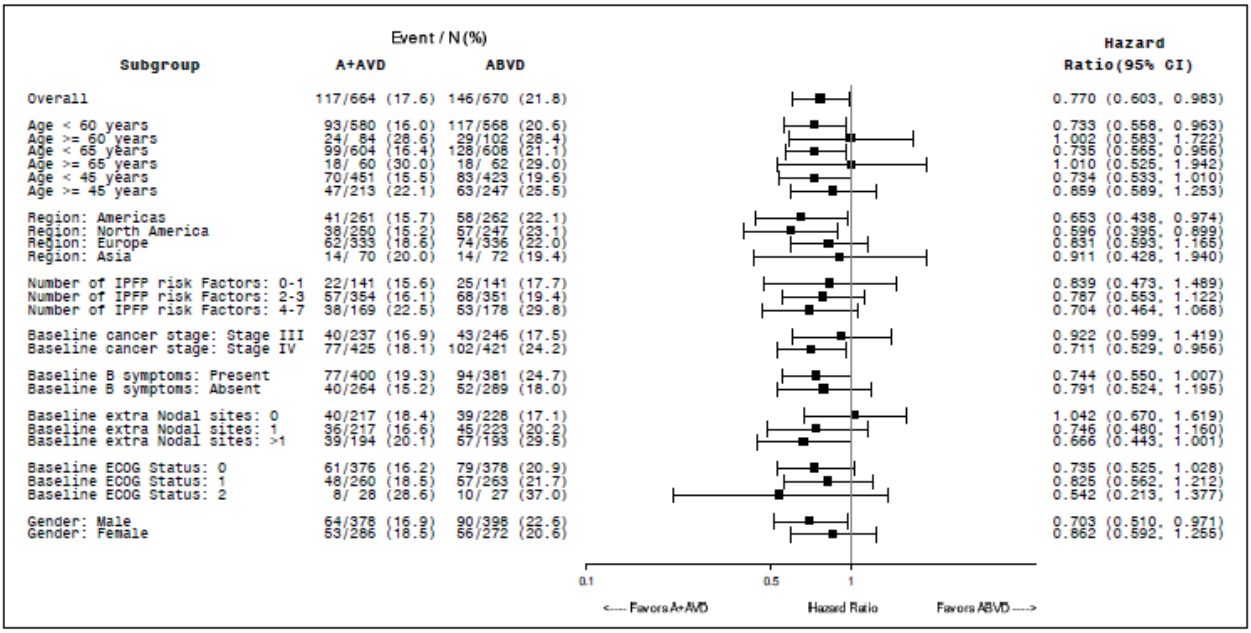
Figure 25 Study C25003: Forest Plot of HRs: Sensitivity Analyses of mPFS (ITT)



Subgroup analysis of mPFS

A treatment benefit was observed with A+AVD in some baseline disease factor-defined subgroups (Figure 29 and additional subgroups in Table 26). Subgroups that did not show a treatment benefit with A+AVD were 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 with no extranodal disease at baseline (N=445; HR=1.042; 95% CI: 0.670, 1.619).

A substantial number of subgroups demonstrated a HR <1 but confidence intervals crossing 1. These subgroups were: patients <45 years (n=874), patients ≥45 years (n=460), female patients (n=558), patients with a Cycle 2 PET Deauville Score of 5 (n=51), patients from Europe (n=669) or Asia (n=142), patients with baseline cancer stage III (n=483), patients with present (n=781) or absent (n=553) B symptoms, patients with Cycle 2 PET results positive (n=105) or negative (n=1165), patients that received alternative frontline therapy (n=24), and patients in all three categories of ECOG performance status/baseline extranodal sites(1,>1) / and number of IPFP sites.



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 26 Study C25003: Forest Plot of mPFS per IRF Assessment HR by Baseline Risk Factor Subgroups (ITT)

Table 26 Study C25003: Subgroup Analysis of mPFS per IRF Assessment

Subgroup Analysis on the Basis of IRF Response Assessment	Estimated hazard ratio (95% CI)	P-value
Age		
<60 years (N=1148)	0.733 (0.558, 0.963) vs	0.025
≥60 years (N=186)	1.002 (0.583, 1.722)	0.993
<65 years (N=1212)	0.735 (0.565, 0.956) vs	0.021
≥65 years (N=122)	1.010 (0.525, 1.942)	0.977
<45 years (N=874)	0.734 (0.533, 1.010) vs	0.056
≥45 years (N=460)	0.859 (0.589, 1.253)	0.429
Gender		
Male (N=776)	0.703 (0.510, 0.971)	0.031
Female (N=558)	0.862 (0.592, 1.255)	0.438
Cycle 2 PET Deauville Score		
<5 (N=1219)	0.763 (0.584, 0.997)	0.047
5 (N=51)	0.697 (0.337, 1.440)	0.320
Region		
Americas (N=523)	0.653 (0.438, 0.974)	0.035
North America (N=497)	0.596 (0.395, 0.899)	0.012
Europe (N=669)	0.831 (0.593, 1.165)	0.281
Asia (N=142)	0.911 (0.428, 1.940)	0.810
Baseline cancer stage		
Stage III (N=483)	0.922 (0.599, 1.419)	0.712
Stage IV (N=846)	0.711 (0.529, 0.956)	0.023
Baseline B symptoms		
Present (N=781)	0.744 (0.550, 1.007)	0.054
Absent (N=553)	0.791 (0.524, 1.195)	0.264
Cycle 2 PET results		
Positive (N=105)	0.609 (0.341, 1.088)	0.089
Negative (N=1165)	0.774 (0.586, 1.022)	0.070
Receipt of Alternative Frontline Therapy		
Yes (N=24)	0.577 (0.128, 2.601)	0.469
No (N=1310)	0.767 (0.599, 0.982)	0.035
Baseline ECOG performance status		
0 (N=754)	0.735 (0.525, 1.028)	0.070
1 (N=523)	0.825 (0.562, 1.212)	0.326
2 (N=55)	0.542 (0.213, 1.377)	0.190
Baseline extranodal sites		
0 (N=445)	1.042 (0.670, 1.619)	0.856
1 (N=440)	0.746 (0.480, 1.160)	0.191
>1 (N=387)	0.666 (0.443, 1.001)	0.049
Number of IPFP risk factors		
0-1 (N=282)	0.839 (0.473, 1.489)	0.548
2-3 (N=705)	0.787 (0.553, 1.122)	0.183
4-7 (N=347)	0.704 (0.464, 1.068)	0.097

Subgroup: mPFS for patients in the ITT with Stage III and IV disease

For these patients, the unstratified HR was 0.711 (95% CI: 0.529, 0.956), indicating a 28.9% reduction in the risk of an mPFS event for A+AVD patients with Stage IV disease compared with ABVD patients (p=0.023). At 2 years, the rate of patients with Stage IV disease without mPFS events was 82.0% (95% CI: 77.8, 85.5) for A+AVD patients (No. of patients at risk=205) vs 75.3% (95% CI: 70.6, 79.3) for ABVD patients (No. of patients at risk=186).

For patients with less advanced disease (Stage III) the unstratified HR was 0.922 (95% CI: 0.599, 1.419), indicating an 7.8% improvement in the risk of an mPFS event for A+AVD patients compared with ABVD patients (p=0.712). At 2 years, the rate of patients with Stage III disease without mPFS events was 82.1% (95% CI: 76.0, 86.8) for A+AVD patients (No. of patients at risk=104) vs 81.0% (95% CI: 75.1, 85.6) for ABVD patients (No. of patients at risk=106).

Figure 27 Study C25003: KM Plot of mPFS per IRF by Cancer Stage (ITT Patients with Baseline Cancer Stage III or IV)

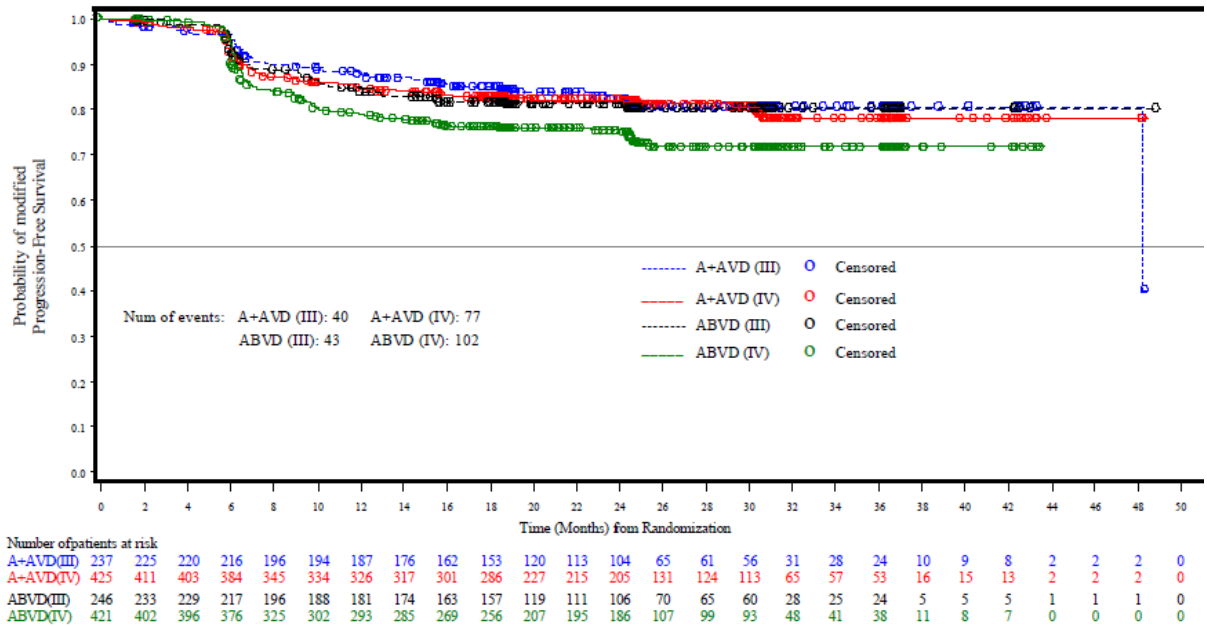


Table 27 ECHELON-1: Summary of mPFS per IRF (ITT Population Patients with Stage III HL)

	A+AVD N=237	ABVD N=246
mPFS (months)		
Number with Events (%)	40 (17)	43 (17)
Number Censored (%)	197 (83)	203 (83)
25th Percentile (95% CI)	48.2 (24.5, NE)	NE (24.5, NE)
Median (95% CI)	48.2 (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[a] (95% CI)	0.922 (0.599, 1.419)	
P-value	0.712	
Kaplan-Meier Estimates[b] % (95% CI)		
1 Year	87.9 (82.8, 91.5) [n=187]	84.5 (79.0, 88.6) [n=181]
2 Years	82.1 (76.0, 86.8) [n=104]	81.0 (75.1, 85.6) [n=106]
2.5 Years	80.4 (73.9, 85.4) [n=56]	80.2 (74.1, 84.9) [n=60]
3 Years	80.4 (73.9, 85.4) [n=24]	80.2 (74.1, 84.9) [n=24]

	A+AVD N=237	ABVD N=246
Median mPFS follow-up[c] (months) (95% CI)	24.5 (21.85, 24.87)	24.5 (20.96, 24.74)
Reason Leading to mPFS Event		
Progressive disease	29 (12)	33 (13)
Death due to any cause	9 (4)	8 (3)
Receipt of additional therapy after non-CR[d]	2 (<1)	2 (<1)
Reason for Censoring		
No baseline and/or no post-baseline assessment	5 (2)	7 (3)
mPFS event after more than one missed visit	1 (<1)	2 (<1)
Treatment discontinuation for undocumented disease progression	2 (<1)	2 (<1)
Loss to follow-up	5 (2)	13 (5)
Withdrawal by subject	10 (4)	10 (4)
No documented mPFS event	174 (73)	169 (69)

Table 28 ECHELON-1: Summary of mPFS per IRF (European Subset of ITT Population With Stage IV HL)

	A+AVD N=233	ABVD N=237
mPFS (months)		
Number with Events (%)	44 (19)	60 (25)
Number Censored (%)	189 (81)	177 (75)
25th Percentile (95% CI)	NE (25.0, NE)	24.6 (9.7, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th Percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 43.5*	0.0*, 43.6*
Hazard Ratio[a] (95% CI)	0.745 (0.505, 1.099)	
P-value	0.136	
Kaplan-Meier Estimates[b] % (95% CI)		
1 Year	82.8 (77.1, 87.2) [n=175]	77.8 (71.8, 82.7) [n=169]
2 Years	81.8 (76.0, 86.3) [n=104]	76.4 (70.3, 81.4) [n=110]
2.5 Years	80.0 (73.7, 84.9) [n=59]	70.6 (63.4, 76.7) [n=54]
3 Years	77.1 (69.5, 83.0) [n=25]	70.6 (63.4, 76.7) [n=22]
Median mPFS follow-up[c] (months) (95% CI)	24.5 (22.74, 24.67)	24.8 (24.61, 25.20)
Reason Leading to mPFS Event		
Progressive disease	32 (14)	43 (18)
Death due to any cause	8 (3)	9 (4)
Receipt of additional therapy after non-CR[d]	4 (2)	8 (3)
Reason for Censoring		
No baseline and/or no post-baseline assessment	5 (2)	4 (2)
mPFS event after more than one missed visit	0	0
Treatment discontinuation for undocumented disease progression	0	1 (<1)
Loss to follow-up	2 (<1)	3 (1)
Withdrawal by subject	8 (3)	5 (2)
No documented mPFS event	174 (75)	164 (69)

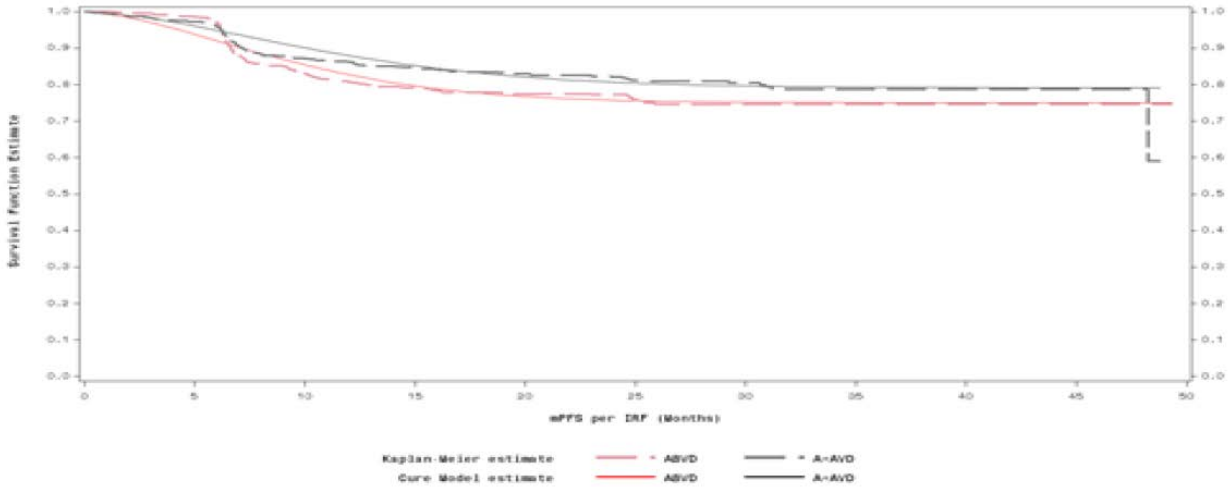
Subgroup: mPFS for patients in the ITT with extranodal disease

For ITT patients, the unstratified HR was 0.699 (95% CI: 0.518, 0.943). This indicates a 30.1% reduction in the risk of an mPFS event for A+AVD patients with extranodal involvement (p=0.018). At 2 years, the rate of patients with extranodal involvement without mPFS events was 82.4% (95% CI: 78.2, 85.9) for A+AVD patients (No. of patients at risk=193) vs 74.9% (95% CI: 70.2, 79.0) for ABVD patients (No. of patients at risk=182).

Survival model of mixed cure analysis on mPFS

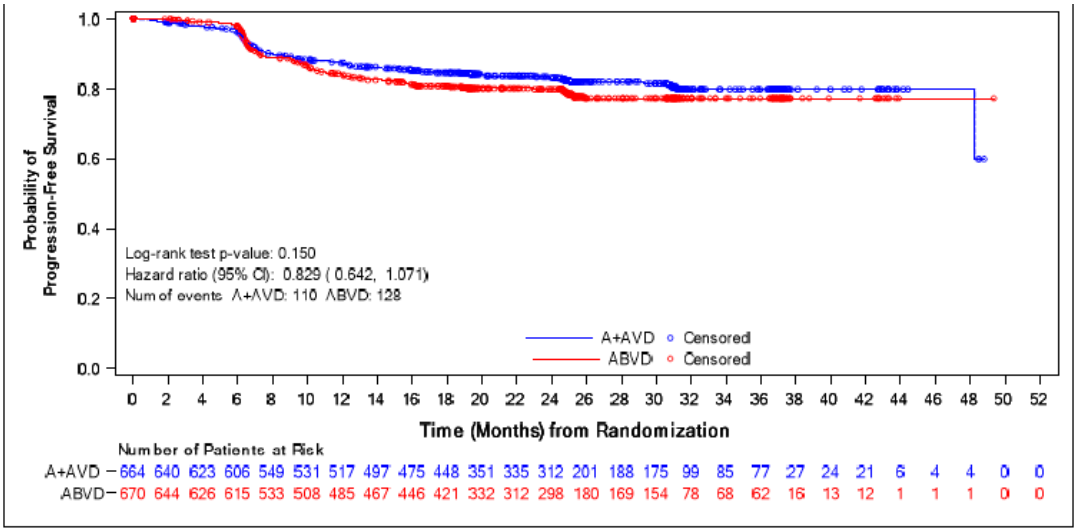
Based on a prespecified mixed cure analysis with a Weibull survival model on mPFS per IRF with treatment as a factor, the estimated cure rates were 79.1% and 75.0% for the A+AVD patients and the ABVD patients, respectively. The odds ratio of not cured was 0.791 (95% CI, 0.592; 1.056), indicating that patients in the A+AVD arm had a 20.9% reduction in the odds of not being cured (equivalently, a 26.4% increase in the odds of being cured) compared with patients in the ABVD arm, and the RR of 0.741 (95% CI, 0.538; 1.022) indicated that patients who were not cured had a 25.9% reduction in the risk of having an mPFS event for patients on the A+AVD arm compared with patients on the ABVD arm.

Figure 28 Study C25003: KM Plot of Survival Function Estimates of mPFS and the Estimates from the Weibull Mixture Cure Model Per IRF (ITT)



PFS

This analysis of PFS included only death and progressive disease as events. After a median follow-up of approximately 25 months, a total of 238 PFS events and 241 PFS events were observed in the ITT population by IRF and investigator assessment, respectively. The median PFS was not estimable for either treatment arm by either IRF or investigator assessment, with censored PFS of 0 to 49 months. The stratified HR for PFS per IRF was 0.830 (95% CI: 0.642, 1.071; p=0.150). An estimated 83.1% (95% CI: 79.8%, 85.9%) of A+AVD patients vs 79.8% (95% CI: 76.3%, 82.8%) of ABVD patients were alive without progression at 2 years. The stratified HR for PFS per investigator was 0.701 (95% CI: 0.542, 0.905; p=0.006). An estimated 84.2% (95% CI: 81.1%, 86.9%) of A+AVD patients vs 78.0% (95% CI: 74.4%, 81.1%) of ABVD patients were alive without progression at 2 years.



Source: Table 15.2.5.1

Figure 29 Study C25003: KM Plot of PFS per IRF-ITT population

Table 15.2.5.1
Summary of Progression-Free Survival (PFS) per IRF
ITT Population

	A+AVD N=664	ABVD N=670	Total N=1334	Hazard Ratio[a] (95% CI)	P-value
				0.829 (0.642, 1.071)	0.150
PFS (months)					
Number with Events (%)	110 (17)	128 (19)	238 (18)		
Number Censored (%)	554 (83)	542 (81)	1096 (82)		
25th Percentile (95% CI)	48.2 (48.2, NE)	NE (24.9, NE)	48.2 (48.2, NE)		
Median (95% CI)	NE (48.2, NE)	NE (NE, NE)	NE (48.2, NE)		
75th Percentile (95% CI)	NE (48.2, NE)	NE (NE, NE)	NE (NE, NE)		
Min, Max	0.0*, 48.8*	0.0*, 49.3*	0.0*, 49.3*		

* indicates a censored observation

Table 15.2.5.1
Summary of Progression-Free Survival (PFS) per IRF
ITT Population

	A+AVD N=664	ABVD N=670	Total N=1334	Hazard Ratio[a] (95% CI)	P-value
Kaplan-Meier Estimates[b] % (95% CI)					
6 Months	95.9 (94.1, 97.2) [n=606]	97.8 (96.3, 98.7) [n=615]	96.9 (95.8, 97.7) [n=1221]		
12 Months	87.3 (84.5, 89.7) [n=517]	83.9 (80.7, 86.6) [n=485]	85.6 (83.5, 87.5) [n=1002]		
18 Months	84.5 (81.4, 87.2) [n=448]	80.7 (77.3, 83.6) [n=421]	82.6 (80.4, 84.7) [n=869]		
24 Months	83.1 (79.8, 85.9) [n=312]	79.8 (76.3, 82.8) [n=298]	81.5 (79.1, 83.6) [n=610]		
30 Months	81.5 (77.9, 84.6) [n=175]	77.2 (73.3, 80.6) [n=154]	79.4 (76.8, 81.7) [n=329]		
36 Months	79.8 (75.7, 83.3) [n=77]	77.2 (73.3, 80.6) [n=62]	78.5 (75.7, 81.0) [n=139]		
42 Months	79.8 (75.7, 83.3) [n=21]	77.2 (73.3, 80.6) [n=12]	78.5 (75.7, 81.0) [n=33]		
48 Months	79.8 (75.7, 83.3) [n=4]	77.2 (73.3, 80.6) [n=1]	78.5 (75.7, 81.0) [n=5]		

* indicates a censored observation

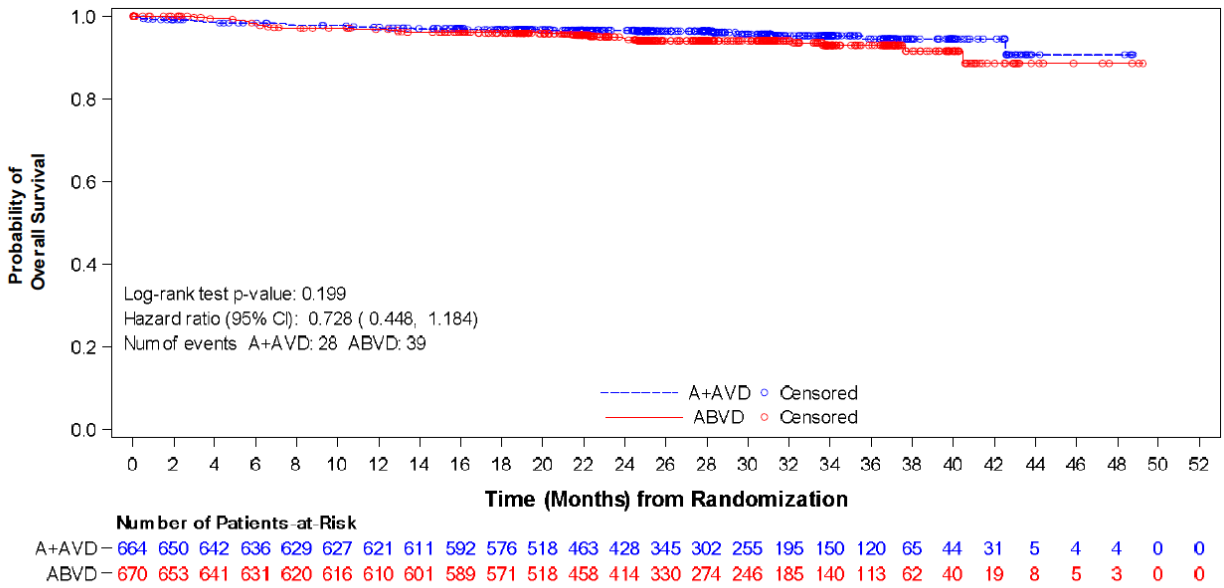
Key secondary endpoint

Overall survival – interim analysis

This interim analysis of OS was performed coincident with the final mPFS analysis at 20 April 2017 data cutoff, at which time 67 deaths had occurred in the ITT population (5% of the ITT population). A final OS analysis is planned when 112 deaths have been reported in the study, to be approximately 4 years after randomization of the last patient.

The median OS was not reached (Figure 33). 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. 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.

Figure 30 Study C25003: KM Plot of OS (ITT)



Other secondary endpoints

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. 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.

A by-patient listing of CR, PR, stable disease, progressive disease and overall response is presented for the ITT population per IRF and per investigator in Table 30 and Table 31.

Table 29 Study C25003: 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 30 Study C25003: CR Rate, 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)

Table 31 ECHELON-1: CR Rate, ORR, PET Negativity Rate, and Deauville Score at Cycle 2, Rate of Deauville Score At End of Frontline Therapy per IRF Assessment (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 32 ECHELON-1: CR Rate, ORR, PET Negativity Rate, and Deauville Score by IRF (ITT Population -- Baseline Stage IV Disease)

	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)

Source: m2.7.3 – ECHELON-1, Table 3.e

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; Table 30).

Concordance between IRF and INV assessments of CR and ORR

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.

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]; Table 30).

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]).

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.

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%).

Subsequent anticancer therapy

Slightly fewer A+AVD arm patients (121 patients, 18%) received at least 1 subsequent anticancer therapy compared with ABVD patients (144 patients, 22%).

Subsequent chemotherapy was received by 10% in the A+AVD arm (n=66) vs. 15% in the ABVD arm (n=99), and high-dose chemotherapy + transplant in 5% (n=36) vs. 8% (n=54). Consolidative radiation was received by 8% of patients on each treatment arms.

Time to subsequent systemic therapy was defined as the time from first dose to the date of the first documentation of subsequent therapy which excludes radiation only treatment or to the time of censoring. Patients without subsequent systemic therapy were censored at last contact date or date of death. The stratified HR was 0.690 (95% CI: 0.517, 0.921; p=0.011).

In the ITT population, 33% fewer patients treated with ADCETRIS + AVD in the ITT population received subsequent salvage chemotherapy (n=66) and high-dose chemotherapy and transplant (n=36) compared with those treated with ABVD (n=99 and n=54, respectively). In the Stage IV population, 35% fewer patients treated with ADCETRIS + AVD received subsequent salvage chemotherapy (n=45) compared with those treated with ABVD (n=69) and 22% fewer patients treated with ADCETRIS + AVD received high-dose chemotherapy and transplant (n=29) compared with those treated with ABVD (n=37).

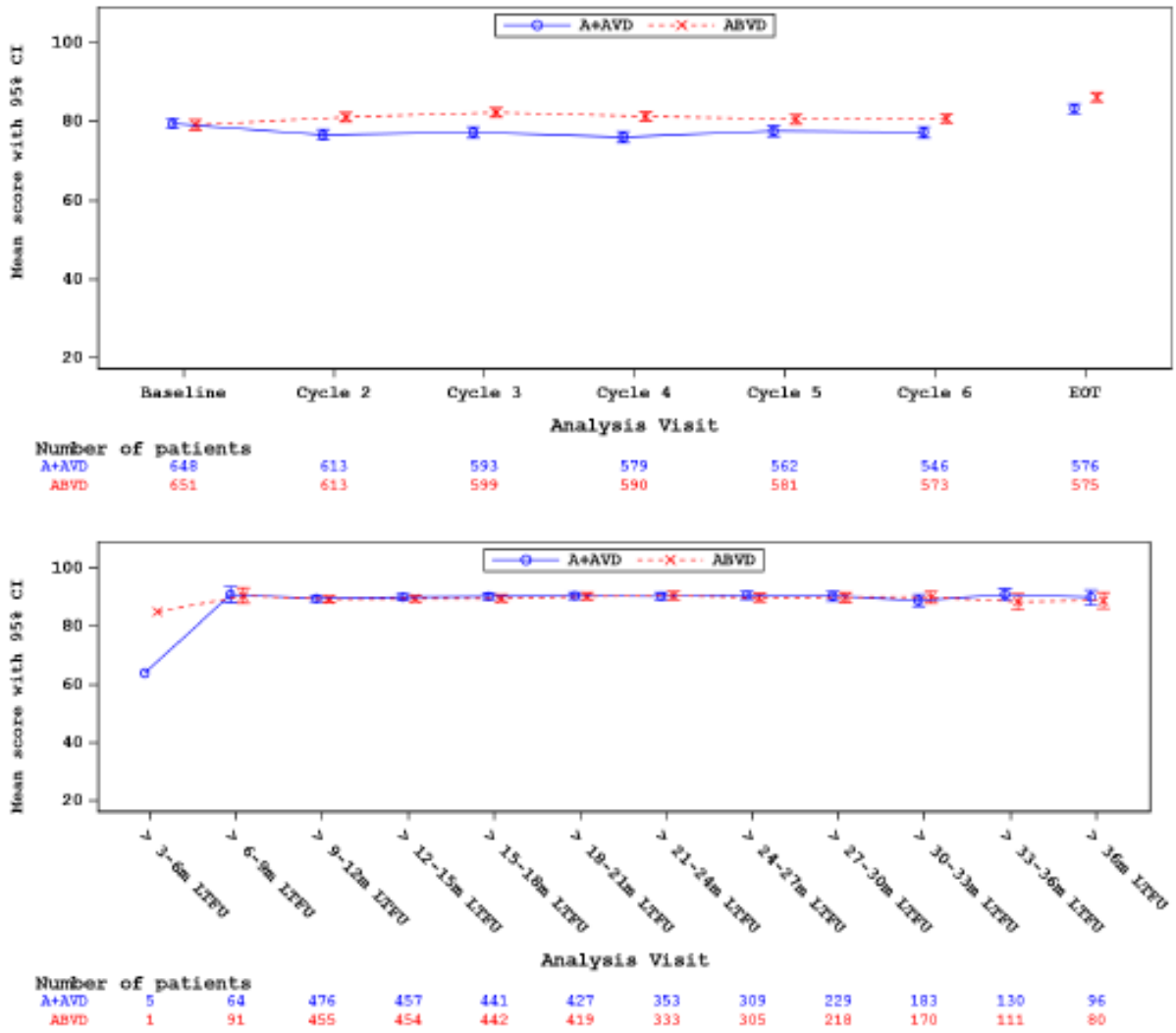
Patient-reported outcomes (PRO) per European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30.

Compliance (ITT)

Compliance was defined as the number of forms actually completed as a proportion of those anticipated. Over time, compliance was generally high in both the A+AVD and ABVD groups, ranging from 86% to 98% across the treatment arms.

Mean EORTC QLQ-C30 summary scores (ITT)

Figure 31 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)

Compliance ranged from 86% to 98% across treatment arms.

PRO per Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group- Neurotoxicity (FACT/GOG-Ntx) subscale questionnaire (ITT)

Compliance ranged from 85% to 98% across treatment arms.

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

Compliance ranged from 87% to 99% across treatment arms.

Overall, mean scores over time were not different between the 2 treatment arms on the basis of the MID of 0.07 established for the UK TTO score. During PTFU, mean scores returned to Baseline levels or better. Trends observed for the US-based value set were consistent with those observed for the UK-based value set.

Utilization of medical resources

Medical resource utilization was assessed from Screening through PTFU. 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.

MRU among patients in the ITT population with Stage IV were similar that of the ITT population.

Percent of patients alive without HL at 3 and 5 years

As of the 20 April 2017 data cut-off 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 the 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

Post hoc subgroup analyses for patients with Stage IV:

Post-hoc subgroup analyses of modified PFS per IRF for patients with Stage IV disease were performed including age, region, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, baseline ECOG status and gender. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD in most subgroups. Patients with Stage IV disease for whom extranodal disease was reported ([n=722] [HR=0.69, 95% CI (0.50, 0.94)]) showed an mPFS (per IRF) benefit. In patients with Stage IV disease for whom no extranodal disease was reported, no benefit has been shown at time of analysis ([n=85] [HR=1.49, 95% CI (0.51, 4.31)]). The significance of this finding in stage IV HL patients with no extranodal disease is not established due to small patient numbers and low event rates (14 events). The efficacy in elderly patients with Stage IV disease in the A + AVD arm (patients ≥ 60 years of age [n=118] [HR=0.80, 95% CI (0.42, 1.53)] and ≥ 65 years of age [n=78] [HR=0.78, 95% CI (0.36, 1.67)]) showed better benefit compared with elderly patients in ITT population.

Subgroup analysis on OS

Subgroup: OS for Patients in the ITT with Baseline Stage IV Disease

The median OS was not reached for the subgroup with Stage IV disease (Figure 34). The unstratified HR was 0.507 (95% CI, 0.265; 0.971, p=0.037), suggesting a larger benefit in this subgroup compared to the overall ITT population. At 2 years, the OS rate was 97.4% (95% CI: 95.3, 98.5) for A+AVD patients (No. of patients at risk=280) vs 93.4% (95% CI: 90.3, 95.6) for ABVD patients (No. of patients at risk=258); at 3 years it was 95.8% (95% CI: 91.8, 97.9) for A+AVD patients (No. of patients at risk=79) vs 93.1% (95% CI: 89.9, 95.3) for ABVD patients (No. of patients at risk=66).

Figure 32 Study C25003: KM Plot of OS (ITT Subgroup with Baseline Stage IV Disease)

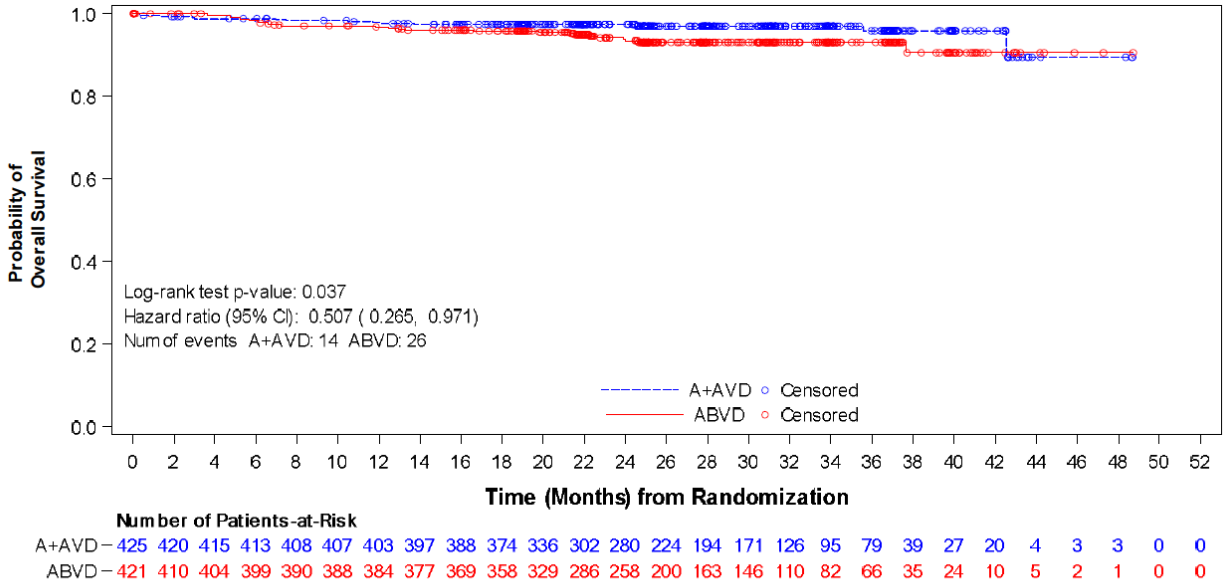


Table 33 ECHELON-1: OS (ITT Population With Stage III HL)

	A+AVD N=237	ABVD N=246
Number with events (%)	14 (6)	12 (5)
Number censored (%)	223 (94)	234 (95)
Reason for censoring		
End of study	23 (10)	35 (14)
Loss to follow up	6 (3)	15 (6)
Withdrawal by patient	13 (5)	17 (7)
Other	4 (2)	3 (1)
Still alive at date of last contact	200 (84)	199 (81)
25th percentile (95% CI)	NE (NE, NE)	NE (40.5, 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*	0.1*, 49.2*
Hazard Ratio (95% CI)(a)	1.216 (0.563, 2.630)	
P-value	0.618	
K-M estimates (95% CI) (b)		
1 Year	96.1 (92.7, 98.0) [n=218]	96.6 (93.4, 98.3) [n=225]
2 Years	95.1 (91.4, 97.3) [n=148]	95.6 (91.9, 97.6) [n=155]
2.5 Years	93.1 (88.0, 96.1) [n=84]	95.6 (91.9, 97.6) [n=99]
3 Years	91.9 (86.0, 95.4) [n=41]	94.1 (88.8, 97.0) [n=47]
Median OS follow-up (months) (95% CI) (c)	27.8 (25.40, 28.32)	27.8 (25.46, 28.55)

Source: /bdm/tbos/SGN-035/C25003/CSR2/Adhoc/more_subgrp_apr2018/Tables/T98.2.9.1.C-

Subgroup: OS for Patients in the ITT with Extranodal Involvement

The median OS was not reached in the subgroup of patients with extranodal involvement (≥1 extranodal sites) either. The unstratified hazard ratio was 0.431 (95% CI, 0.218; 0.852, p=0.013), suggesting a greater OS benefit than the overall ITT population in this subgroup as well. At 2 years, the OS rate was 97.5% (95% CI: 95.4, 98.6) for A+AVD patients (No. of patients at risk=268) vs 93.4% (95% CI: 90.3, 95.6) for ABVD patients (No. of patients at risk=257); at 3 years it was 97.1% (95% CI: 94.8, 98.4) for A+AVD patients (No. of patients at risk=72) vs 92.2% (95% CI: 88.3, 94.8) for ABVD patients (No. of patients at risk=69).

Summary of main study

The following table summarized the efficacy results from the main studies 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 34: Summary of Efficacy for trial C25003: ECHELON-1

Title: ECHELON-1			
Study identifier	C25003		
Design	Randomized, Open-label, Phase 3 Trial of A+AVD Versus ABVD as Frontline Therapy in Patients With Advanced Classical Hodgkin Lymphoma		
	Study Initiation Date: Primary Completion Date Estimated Study Completion Date		9 Nov 2012 20 Apr 2017
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.
	Key secondary endpoints	OS	Time from randomization to date of death.
	Other Important Secondary Endpoint	CR rate	Proportion of patients with CR at the end of randomized treatment.
		ORR	Proportion of patients with CR or PR at the end of randomized treatment.
		PET neg at cycle 2	Proportion of patients that were PET negative at the end of cycle 2.
		EFS	Time from randomization to any cause of treatment failure.
		DFS	Time from CR to disease progression or death from lymphoma or acute toxicity from treatment.
		PRO	Changes from baseline in EORTC QLQ-C30 questionnaire.
Database lock	12 Jun 2017		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**ITT population** Data cut off: 20 April 2017		
Descriptive statistics and estimate variability	Treatment group	A+AVD	ABVD
	Number of subject	664	670
	Median mPFS (IRF)	NE	NE
	95% CI	(48.2, NE)	(NE, NE)
	Median OS	NE	NE
	95% CI	(NE, NE)	(NE, NE)
	CR Rate	73%	70%
	ORR	86%	83%
	PET negativity at cycle 2	89%	86%
	Median EFS	NE (43.8, NE)	NE (NE, NE)
	DFS	NE (42.1, NE)	NE (NE, NE)
	PRO – EORTC QLQ-C30	Mean summary scores over time were lower in A+AVD arm vs. ABVD arm across treatment cycles and at EOT. During PTFU, scores returned to baseline levels or better.	
Effect estimate per comparison	Primary endpoint mPFS	Comparison groups	A+AVD vs. ABVD
		Hazard ratio (HR)	0.77
		95% CI	(0.603-0.983)
		P-value	0.035
	Key Secondary endpoint OS	Comparison groups	A+AVD vs. ABVD
		Hazard ratio (HR)	0.728
		95% CI	(0.448, 1.184)
		P-value	0.199
	Secondary endpoint EFS	Comparison groups	A+AVD vs. ABVD
		Hazard ratio (HR)	0.900
		95% CI	(0.726, 1.117)
		P-value	0.339
	Secondary endpoint DFS	Comparison groups	A+AVD vs. ABVD
		Hazard ratio (HR)	0.701
		95% CI	(0.504, 0.976)
		P-value	0.034
Analysis description	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.		
Abbreviations	*CI: Confidence Interval, CR: complete remission, DFS: disease free survival, DOR: Duration of Response, EFS: event free survival, IRF: independent review facility, ITT: intent to treat, MID: minimal important difference, NE: not estimable, ORR: Objective Response Rate, OS: Overall Survival, PET: positron emission tomography, mPFS: modified Progression Free Survival, PR: partial remission, PRO: patient reported outcome.*		
Analysis description	**Prespecified Subgroup analysis**		

Analysis population and time point description	*Stage IV HL* *Data cut off: 20 April 2017*		
Descriptive statistics and estimate variability	Treatment group	A+AVD	ABVD
	Number of subject	425	421
	Median mPFS (IRF)	NE	NE
	95% CI	-	-
	Median OS	NE	NE
	95% CI	(NE, NE)	(NE, NE)
	CR Rate	70%	69%
	ORR	85%	83%
	PET negativity at cycle 2	89%	85%
Effect estimate per comparison	Primary endpoint mPFS	Comparison groups	A+AVD vs. ABVD
		Hazard ratio (HR)	unstratified HR 0.711
		95% CI	(0.529-0.956)
		P-value	0.023
	Key Secondary endpoint OS	Comparison groups	A+AVD vs. ABVD
		Hazard ratio (HR)	unstratified HR 0.507;
		95% CI	0.265-0.971
		P-value	0.037
Abbreviations	*CI: Confidence Interval, CR: complete remission, DFS: disease free survival, DOR: Duration of Response, EFS: event free survival, IRF: independent review facility, ITT: intent to treat, MID: minimal important difference, NE: not estimable, ORR: Objective Response Rate, OS: Overall Survival, PET: positron emission tomography, mPFS: modified Progression Free Survival, PR: partial remission, PRO: patient reported outcome.*		

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

No pooled analysis 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.

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]). 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

Table 35 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 36 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_apr2018/Tables/T97.2.10.3-Summary_OS_StageIV_Elder, run date

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy of brentuximab vedotin in frontline HL patients has been investigated in Study ECHELON-1. This is a Phase 3, 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.

The proposed dose of brentuximab vedotin is 1.2 mg/kg as an intravenous infusion in combination with AVD. This is a lower starting dose compared to the existing 1.8 mg/kg monotherapy dose, but with a more frequent dosing schedule (every 2 weeks, instead of every 3 weeks) to maintain similar exposure. In line with scientific advice by the CHMP, outcomes of the Phase 1 study and PK from ECHELON-1 were used to substantiate the proposed dosing regimen, which is acceptable.

In Phase-1 study SGN35-009, brentuximab vedotin in combination with the standard frontline chemotherapy combination ABVD resulted in an increased incidence of pulmonary adverse events, likely due to the combination of bleomycin and brentuximab vedotin. A combination chemotherapy omitting bleomycin (AVD instead of ABVD) was therefore selected for pivotal study ECHELON-1. The comparator arm ABVD was accepted by the CHMP during scientific advice in 2011. Although the alternative treatment option BEACOPP-escalated (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone escalated dose regime) could also be used in fit patients <60 years of age according to the ESMO clinical practice guideline, it was agreed with the applicant that ABVD is the preferred regimen for advanced HL in Europe. The more pronounced toxicity has prevented widespread utilization of BEACOPP and some randomized clinical studies indicate that the long-term clinical outcome for ABVD and standard BEACOPP is similar.

The primary endpoint mPFS is also in line with CHMP scientific advice and considered acceptable, as any effort has been made to limit the risk of investigator subjectivity with the decision to use subsequent anticancer chemotherapy. All patients were to be assessed for response post study drug treatment using Cheson criteria, the PET-CT scans were read independently and centrally, and the decision to start subsequent therapy was to be proposed according to judgement of the readers. This endpoint was chosen because the primary goal of frontline therapy in advanced stage HL is curative, and it is agreed that the modified PFS endpoint better reflects whether the goal of initial therapy has been achieved (CR). The sample size was increased during the study based on external information along with timing of interim OS analysis. Because this was based on external information, this is considered acceptable. After the Cycle 2 PET assessment, patients could be switched to alternative frontline medication (AFM) of the physician's choice for the remainder of planned frontline therapy without the switch being considered an mPFS event. It is reassuring that, while this was permitted, in practice, very few patients were switched to an AFM (≤2% in both arms). Therefore, the estimate from this trial (where alternative frontline therapy was part of the treatment policy) would not be expected to differ substantially from that from a treatment policy where this would not have been allowed.

The key secondary endpoint OS was not expected to demonstrate large differences in treatment arms, due to the very long survival and number of treatment options in relapsed setting, including SCT. Moreover, the secondary and exploratory QoL endpoints are considered difficult to interpret, because of the open-label design of the trial.

Despite a higher use of myeloid growth factor in the A+AVD group concomitant medications were comparable between the treatment arms.

The ECHELON-1 clinical database was reopened and revised after the initial database lock based on the 20 April 2017 cut-off for data analysis to correct a data mapping error at the dataset level that substituted the screening date for randomization date in a high proportion (95%) of patients in the intent-to-treat (ITT) population.

Efficacy data and additional analyses

Brentuximab vedotin +AVD treatment resulted in a statistically significant improvement in IRF-based mPFS compared to ABVD treatment in the ITT, with a HR of 0.770 (95% CI, 0.603-0.983, p=0.035). At the 20 April 2017 data cut-off date, the median mPFS was not reached in either treatment arm and the KM plot of mPFS showed treatment curves in very close proximity of each other. From the PFS analysis, it is clear that the modified component (subsequent therapy for HL after completion of frontline therapy in patients who failed to achieve CR per IRF) is for a large part responsible for this result (difference in mPFS event free at 2 year: ~5% (p=0.035) vs ~3% (p=0.15) in favour of A+AVD). The proportion of patients free from a mPFS event at 2 years after randomization was 82.1% in the A+AVD arm versus 77.2% in the ABVD arm. Results from an INV-based mPFS analyses, as well as several sensitivity analyses were consistent with those obtained for the primary endpoint. The sensitivity analyses which were performed to further investigate the potential influence of the additional PFS event of 'receipt of additional therapy' in the mPFS definition produced point estimates for the hazard ratio which were generally consistent with those from the primary analysis.

A higher proportion of patients who did not have a complete response in the ABVD arm received subsequent therapy compared with the A+AVD arm. Of the patients without CR at the end of frontline therapy, 58% (38/65) in the A+AVD arm received subsequent therapy, compared with 73% (58/79) in the ABVD arm. This discrepancy between the study arms in receiving subsequent therapy could be due to a variety of factors, among which the open label design of the study or persisting AEs after A+AVD. Additional sensitivity analysis provided for mPFS in which all patients who were non-complete

responders and still at risk of a PFS event at the time of post-frontline assessment were considered to have had an mPFS event showed consistency with the results from the primary PFS analysis. Thus, it is unlikely that the observed PFS results were overly influenced by the option to provide subsequent therapy to patients who did not demonstrate a complete response. Unfortunately, it is currently unknown whether the decision to provide a patient with subsequent therapy is associated with disease, treatment and patient factors at the time of the decision to provide subsequent therapy (after end of frontline therapy). Further analysis pursuing this issue were not requested as further assessment will be hampered by methodological concerns (non-randomized comparison after frontline therapy) and the outcome will not change the B/R of Adcetris for the requested indication.

Several secondary endpoints supported the primary endpoint, showing similar efficacy, or slight differences in favour of A+AVD were observed (i.e. in CR rate, ORR, PET negativity rate at Cycle 2, DFS, EFS, and use of subsequent anticancer therapy). It is reassuring that overall survival data suggest similar results between A+ AVD and ABVD at the interim analysis as well. The concordance rates for ORR per IRF and Investigator was high (91%) whereas a lower concordance rate was observed for the CR rates per IRF and investigator at the end of randomized and frontline treatment, respectively. This pattern was however in line with what was observed for pivotal relapsed or refractory HL Study SG035-0003.

Although a statistically significant efficacy benefit of A+AVD over ABVD has been observed in the ITT population, treatment effects were not consistent among all subgroups. Based on the forest plot analyses, A+AVD seems more effective in younger patients and patients with more advanced disease (lower HR with more IPFP risk factors, higher Cycle 2 PET Deauville score; and extranodal sites, B-symptoms present or higher stage disease at baseline). The subgroup analyses showed that patients with stage IV disease (HR mPFS: 0.711 (95% CI 0.529, 0.956) or 1 or more extranodal sites (mPFS HR 0.699 (95% CI 0.518, 0.943) seem to experience more benefit of A+AVD when compared with the ITT population (HR=0.770 [95% CI 0.603, 0.983]; p=0.035). A+AVD patients with Stage III HL (HR=0.922, [95% CI 0.599-1.419]) or no sites of extranodal HL (HR=1.042, [95% CI 0.670- 1.619]) seemed to have no significant efficacy outcomes relative to ABVD than seen in the ITT and in stage IV patients. This may well be explained by an apparently higher efficacy of the control arm in patients with less advanced disease. It must be noted that the results of these subgroup analyses should be interpreted with caution due to the low number of events, wide confidence intervals and high censoring rates.

Post-hoc subgroup analyses of modified PFS per IRF for patients with Stage IV disease were also provided. Patients with Stage IV disease for whom extranodal disease was reported ([n=722] [HR=0.69, 95% CI (0.50, 0.94)]) showed an mPFS (per IRF) benefit. In patients with Stage IV disease for whom no extranodal disease was reported, no benefit has been shown at time of analysis ([n=85] [HR=1.49, 95% CI (0.51, 4.31)]). The significance of this finding in stage IV HL patients with no extranodal disease is not established due to small patient numbers and low event rates (14 events). The observed differences in the effect size between stage IV patients with extranodal vs no extranodal disease is of clinical relevance. (see SmPC section 5.1).

Regarding elderly patients, the risk of a mPFS event in the elderly ITT Population patients (stage III and IV) seems higher in the A+AVD arm as compared to ABVD (patients ≥ 60 years of age [n=186] [HR=1.00, 95% CI (0.58, 1.72)] and ≥ 65 years of age [n=122] [HR=1.01, 95% CI (0.53, 1.94)]). Elderly patients with stage IV HL had a trend towards a slightly favourable mPFS treated with A+AVD versus ABVD: patients aged ≥60, n=118, mPFS per IRF: HR = 0.804 (95% CI: 0.42 to 1.53), p = 0.506 and patients aged ≥65, n=78, HR = 0.777 (95% CI: 0.36 to 1.67), p = 0.515. A favourable effect was also noticed in the Kaplan-Meier estimates from 1, 2, 2.5 and 3 years both for patients aged > 60 and >65 years. The same trend in favour of A+AVD was observed for OS events up to 3 years.

However, the number of patients within the elderly stage IV subgroup is relatively small and the number of events is low with a high censoring rate (82% elderly stage IV). This leads to uncertainty in the HR point estimates of these subgroups, as illustrated by the wide confidence intervals. The data have been reflected in the SmPC section 5.1.

PRO data did not indicate a clinically meaningful difference between treatment arms, but a trend of unfavourable scores on various subscales and symptom measures of EORTC-QLQ C30/ FACIT-Dyspnea 10 was observed in the A+AVD arm compared with the ABVD arm during the treatment period. Medical resource utilization was slightly higher in the A+AVD arm (36% vs. 28% in the ABVD arm). These data are consistent with the higher frequency of AEs and SAEs observed in A+AVD patients. However, PTFU, scores on EORTC-QLQ C30 were observed to return to at least baseline levels.

Immunogenicity data indicated that the presence of ATA or nATA was not associated with a reduction in efficacy response.

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). Due to the short follow up, limited data on retreatment after frontline therapy with brentuximab vedotin is currently available. The amendment of the ECHELON-1 study to include an extension of 10 year may provide some data on next line treatment although a thorough assessment of the efficacy of retreatment will likely not be feasible.

2.4.4. Conclusions on the clinical efficacy

In the ECHELON-1 comparing A+AVD vs ABVD in the first line HL treatment, a mPFS HR of 0.770 (95% CI, 0.603-0.983, p=0.035) was in favour of the A+AVD arm.

The mPFS effect was consistent across several sensitivity analyses. However, the point estimate of mPFS is compatible with a smaller effect in patients with less advanced disease, e.g. Stage III HL and patients with no extranodal disease at baseline, which may well be explained by an apparently higher efficacy of the control arm in patients with less advanced disease. The mPFS point estimate in the stage IV population is compatible with a higher effect of A+AVD over ABVD.

The MAH is conducting a 10-year extension of the pivotal Phase 3 study C25003 (ECHELON-1). The extension study will follow-up on subsequent therapy and OS. Response data on retreatment and salvage therapy will be collected, as well as additional data with respect to next line treatment, such as the reason for the next therapy and the time period during which symptoms leading to next therapy have existed (e.g. in case there was delay of therapy for any reason).

The CHMP considers the following measures necessary to address issues related to efficacy:

- Results from the 10-year extension of the ECHELON-1 trial should be provided when available.

2.5. Clinical safety

Introduction

The existing safety profile of brentuximab vedotin administered as monotherapy is based on two single arm phase II studies in 160 patients diagnosed with relapsed or refractory HL or sALCL, one placebo

controlled Phase III trial (AETHERA) in 165 HL patients at increased risk for relapse after ASCT, and one Phase III open-label trial in patients with CD30-positive cutaneous T-cell lymphoma (ALCANZA).

The safety and tolerability of brentuximab vedotin plus chemotherapy for the frontline treatment of patients with advanced stage HL was analysed in the pivotal Phase 3 study C25003 (ECHELON-1) with 1321 patients (662 in the A+AVD arm and 659 In the ABVD arm) as well as in a Phase 1 study (SGN35-009) with 51 patients (26 in the A+AVD arm and 25 in the A+ABVD arm).

A brief comparison of the safety profiles including the results from the pivotal Phase 3 trial (C25003) as well as the Phase 1 trial is provided below (Table 37). More detailed information regarding the C25003 trial is provided in the subsequent sections.

Table 37 Comparison of safety profiles for different indications/studies (table by Assessor)

	ECHELON-1 (Phase 3, frontline HL)		SGN35-009 (Phase 1, frontline HL)		Pivotal Ph. 2 (r/r HL and r/r sALCL)	AETHERA (Ph 3, risk of relapse HL)	ALCANZA (Ph 3, CTCL)
	A+AVD N=662	ABVD N=659	A+AVD N=26	A+ABVD N=25	N=160	N= 167	N= 66
Any TEAE	99% (653)	98% (646)	100% (26)	96% (24)	99% (158)	98% (163)	95% (63)
Any ≥ Grade 3 TEAE	83% (549)	66% (434)	81% (21)	88% (22)	58% (92)	56% (93)	41% (27)
Treatment related TEAE	97% (641)	94% (617)	100% (26)	88% (22)	92% (147)	88% (147)	86% (57)
Treatment related ≥ Grade 3 TEAE	79% (525)	59% (389)	NR	NR	NR	46% (76)	29% (19)
Serious TEAE	43% (284)	27% (178)	27% (7)	56% (14)	31% (50)	25% (41)	29% (19)
Treatment related SAE	36% (240)	19% (125)	12% (3)	40% (10)	16% (25)	11% (19)	14% (9)
TEAE resulting treatment discontinuation	13% (88)	16% (105)	12% (3)	24% (6)	23% (36)	32% (54)	24% (16)
Deaths	1% (9) Related: N=8	2% (13) Related: N=7	0% (0)	4% (1)	4% (6)	1% (1)	6% (4)

Patient exposure

Safety data was presented for ECHELON-1, a randomized, Open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced cHL. Patients in the Safety population were analysed according to the actual treatment received. The Safety population consisted of 662 A+AVD patients and 659 ABVD patients who received at least 1 dose of any study drug in the study treatment regimen. The randomized treatment regimen was administered IV to patients in both treatment arms on day 1 and 15 of each 28-day treatment cycle.

The A+AVD patients received a median of 6 treatment cycles (range 1 to 6 cycles) over a median of 24.2 weeks (range 2.0 to 35.0 weeks) for brentuximab vedotin, 24.5 weeks for doxorubicin and dacarbazine, and 24.4 weeks for vinblastine (range 2.0 to 48.9 weeks for AVD). The median relative dose intensity (RDI (%) (defined as 100 × (total dose received)/(total dose intended) was 99.5% (range 16.7% to 114.3%) for brentuximab vedotin, 100% (range 4.1% to 109.2%) for doxorubicin, 99.1% (range 15.4% to 115.2%) for vinblastine, and 100% (range 66.0% to 111.9%) for dacarbazine.

ABVD patients received a median of 6 treatment cycles (range 1 to 6 cycles) over a median of 24.0 weeks for all 4 study drugs (range 2.0 to 39.1 weeks for bleomycin, and 2.0 to 45.4 weeks for AVD). A median RDI of 99.8% was reported for bleomycin (range 8.1% to 119.4%), a median RDI of 100% for doxorubicin (range 59.6% to 111.1%), a median RDI of 99.3% for vinblastine (range 9.3% to 116.2%), and a median RDI of 100% (range 13.9% to 114.0%) for dacarbazine.

Discontinuations, Dose Delays and Modifications

The permanent discontinuation of study drug was attributed to brentuximab vedotin for 71 A+AVD patients (11%) and to bleomycin for 106 ABVD patients (16%) (Table 39). An adverse event led to the study drug discontinuation for A+AVD vs ABVD in 13% vs 16%. of patients. For the A+AVD patients, a slightly higher proportion of interventions were reported for brentuximab vedotin than for the other 3 agents in the randomized regimen. Over the treatment duration, at least 1 action was reported for brentuximab vedotin in 66% of patients, 54% of patients who received doxorubicin, 57% of patients who received vinblastine, and 53% of patients who received dacarbazine. A study drug dose delay was the most frequently reported modification for the A+AVD patients (48% to 49% of patients for each drug) (Table 38). For the ABVD treatment arm, the highest proportion of interventions were reported for bleomycin. Over the treatment duration, at least 1 action was reported for 48% of patients who received bleomycin, 43% of patients who received vinblastine, 39% of patients who received dacarbazine, and 38% of patients who received doxorubicin (Table 38). A dose delay was the most frequently reported modification for ABVD patients (32% to 33% of patients for each drug), followed by premature and permanent study drug discontinuation and dose reduction.

Table 38 Study C25003: Action on Study Drugs (Safety Population)

	A+AVD N=662			
	Brentuximab Vedotin (mg/kg)	Doxorubicin (mg/m^2)	Vinblastine (mg/m^2)	Dacarbazine (mg/m^2)
All Cycles				
Number of patients treated	662	656	661	661
No action taken, n (%)	228 (34)	307 (46)	284 (43)	312 (47)
Action on study drug, n (%) (a)	434 (66)	355 (54)	378 (57)	350 (53)
Dose reduced prescribed	170 (26)	25 (4)	58 (9)	29 (4)
Dose reduced nonprescribed	3 (<1)	2 (<1)	1 (<1)	2 (<1)
Dose held	41 (6)	2 (<1)	12 (2)	1 (<1)
Dose missed	0	0	1 (<1)	0
Dose interrupted	12 (2)	8 (1)	1 (<1)	11 (2)
Dose delayed	315 (48)	323 (49)	319 (48)	317 (48)
Dose discontinued permanently	71 (11)	38 (6)	52 (8)	38 (6)
	ABVD N=659			
	Bleomycin (IU/m^2)	Doxorubicin (mg/m^2)	Vinblastine (mg/m^2)	Dacarbazine (mg/m^2)
All Cycles				
Number of patients treated	659	649	659	659
No action taken, n (%)	344 (52)	409 (62)	378 (57)	403 (61)
Action on study drug, n (%) (a)	315 (48)	250 (38)	281 (43)	256 (39)
Dose reduced prescribed	17 (3)	24 (4)	61 (9)	19 (3)
Dose reduced nonprescribed	1 (<1)	1 (<1)	2 (<1)	3 (<1)
Dose increased prescribed	0	0	1 (<1)	0
Dose increased nonprescribed	1 (<1)	1 (<1)	0	1 (<1)
Dose held	32 (5)	1 (<1)	9 (1)	1 (<1)
Dose missed	2 (<1)	2 (<1)	3 (<1)	2 (<1)
Dose interrupted	6 (<1)	11 (2)	3 (<1)	28 (4)
Dose delayed	211 (32)	218 (33)	219 (33)	215 (33)
Dose discontinued permanently	106 (16)	22 (3)	34 (5)	22 (3)

Impact of G-CSF Primary Prophylaxis

The use of G-CSFs according to institutional guidelines was allowed per protocol for the management of neutropenia. After enrolment of approximately 70% of the ECHELON-1 study population, the independent data monitoring committee recommended that patients randomized to the A+AVD treatment arm be given prophylactic growth factor support beginning with Cycle 1. For the purpose of assessing the impact of the G-CSF use on the safety profile, the sponsor defined G-CSF primary prophylaxis as G-CSF given by Day 5 of study treatment, where Day 1 is the treatment start date. By this definition, 83 patients in the A+AVD treatment arm and 43 patients in the ABVD treatment arm received G-CSF primary prophylaxis.

For the A+AVD arm, no action pertaining to brentuximab vedotin was reported for 43% of patients who received G-CSF primary prophylaxis compared with 33% of patients who received no G-CSF primary prophylaxis. Fewer dose reductions (20% with prophylaxis vs 26% without prophylaxis) and dose delays (35% with prophylaxis vs 49% without prophylaxis) were reported across treatment arms for the subset of patients who received G-CSF primary prophylaxis (Table 39).

Table 39 Action on Study Drugs by G-CSF Primary Prophylaxis (Safety Population; A+AVD Treatment Arm)

	A+AVD (N=662)							
	G-CSF Primary Prophylaxis (N=83)				No G-CSF Primary Prophylaxis (N=579)			
All Cycles	Brentuximab Vedotin n (%)	Doxorubicin n (%)	Vinblastine n (%)	Dacarbazine n (%)	Brentuximab Vedotin n (%)	Doxorubicin n (%)	Vinblastine n (%)	Dacarbazine n (%)
Number of patients	83 (100)	83 (100)	83 (100)	83 (100)	579 (100)	573 (99)	578 (100)	578 (100)
No action taken	36 (43)	50 (60)	49 (59)	50 (60)	192 (33)	257 (44)	235 (41)	262 (45)
Action on study drug (a)	47 (57)	33 (40)	34 (41)	33 (40)	387 (67)	322 (56)	344 (59)	317 (55)
Dose reduced prescribed	17 (20)	0	4 (5)	0	153 (26)	25 (4)	54 (9)	29 (5)
Dose reduced nonprescribed	0	0	0	0	3 (<1)	2 (<1)	1 (<1)	2 (<1)
Dose increased prescribed	0	0	0	0	0	0	0	0
Dose held	5 (6)	0	0	0	36 (6)	2 (<1)	12 (2)	1 (<1)
Dose missed	0	0	0	0	0	0	1 (<1)	0
Dose interrupted	1 (1)	2 (2)	0	1 (1)	11 (2)	6 (1)	1 (<1)	10 (2)
Dose delayed	29 (35)	31 (37)	29 (35)	31 (37)	286 (49)	292 (50)	290 (50)	286 (49)
Dose discontinued permanently	8 (10)	4 (5)	6 (7)	4 (5)	63 (11)	34 (6)	46 (8)	34 (6)

Exposure-Response Analysis Results and Relationship to Safety

An exposure-response analysis was performed to evaluate the impact of overall time-averaged ADC and MMAE exposure on the incidence of Grade 2 or higher peripheral neuropathy (PN), Grade 4 or higher neutropenia, febrile neutropenia of any grade, and Grade 3 or higher treatment-emergent adverse events (TEAEs) reported in the ECHELON-1 study.

Concomitant medication

At least 1 concomitant medication was reported for 659 patients (100%) in the A+AVD treatment arm and for 653 patients (99%) in the ABVD treatment arm. The most commonly reported concomitant medications (>25% of patients) for the A+AVD patients were ondansetron (73% of patients), filgrastim (61%), dexamethasone (58%), paracetamol (50%), allopurinol (42%), metoclopramide (29%), lorazepam (28%), and sodium chloride (26%).

The most commonly reported concomitant medications (>25% of patients) for ABVD patients were ondansetron (75% of patients), dexamethasone (59%), paracetamol (50%), filgrastim (43%), allopurinol (42%), lorazepam (27%), palonosetron and metoclopramide (26% each), and Bactrim (trimethoprim/sulfamethoxazole) (25%).

Myeloid growth factor usage was reported for a higher proportion of the A+AVD patients either as a concomitant medication or as secondary prophylaxis for neutropenia. At least 1 myeloid growth factor (immunostimulant) was reported for 536 A+AVD patients (81%) and 373 ABVD patients (57%) in the Safety population. Filgrastim was the most frequently reported growth factor for patients across treatment arms. Filgrastim usage was reported for 405 A+AVD patients (61%) and 286 ABVD patients (43%).

Adverse events

Table 40 Study C25003: Overview of Safety Profile (Safety Population)

	A+AVD N=662 n (%)	ABVD N=659 n (%)
Any AE	653 (99)	646 (98)
Treatment-related AE	641 (97)	617 (94)
Grade 3 or higher AE	549 (83)	434 (66)
Treatment-related Grade 3 or higher AE	525 (79)	389 (59)
SAE	284 (43)	178 (27)
Treatment-related SAE	240 (36)	125 (19)
AEs resulting in study drug discontinuation	88 (13)	105 (16)
AE resulting in dose modification	423 (64)	293 (44)
Dose held	44 (7)	32 (5)
Dose interrupted	22 (3)	33 (5)
Dose reduced	191 (29)	65 (10)
Dose delayed	318 (48)	217 (33)
On-study deaths	9 (1)	13 (2)
Deaths due to study treatment-related AEs	8 (1)	7 (1)

Treatment-Emergent Adverse Events: Any Grade

Table 41 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)

Treatment-Related TEAEs: Any Grade

Table 42 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

Grade 3 or Higher Treatment-Emergent Adverse Events

Table 43 Study C25003: Grade 3 or Higher TEAEs Reported for at Least 1% of Patients in Either Treatment Arm by PT and CTC Grade (Safety Population)

	A+AVD N=662			ABVD N=659		
Preferred Term	Grade 3 or Higher n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 or Higher n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least 1 TEAE (a)	549 (83)	193 (29)	347 (52)	434 (66)	224 (34)	197 (30)
Neutropenia	357 (54)	111 (17)	246 (37)	260 (39)	116 (18)	144 (22)
Febrile neutropenia	128 (19)	89 (13)	39 (6)	52 (8)	39 (6)	13 (2)
Neutrophil count decreased	83 (13)	12 (2)	71 (11)	67 (10)	30 (5)	37 (6)
Anaemia	54 (8)	51 (8)	3 (<1)	25 (4)	24 (4)	1 (<1)
Peripheral sensory neuropathy	31 (5)	31 (5)	0	3 (<1)	3 (<1)	0
Neuropathy peripheral	27 (4)	27 (4)	0	6 (<1)	6 (<1)	0
White blood cell count decreased	26 (4)	18 (3)	8 (1)	18 (3)	15 (2)	3 (<1)
Leukopenia	25 (4)	16 (2)	9 (1)	18 (3)	11 (2)	7 (1)
Vomiting	23 (3)	23 (3)	0	9 (1)	9 (1)	0
Alanine aminotransferase increased	22 (3)	22 (3)	0	1 (<1)	1 (<1)	0
Abdominal pain	21 (3)	21 (3)	0	4 (<1)	4 (<1)	0
Nausea	20 (3)	20 (3)	0	7 (1)	7 (1)	0
Diarrhoea	19 (3)	17 (3)	2 (<1)	5 (<1)	5 (<1)	0
Fatigue	19 (3)	19 (3)	0	7 (1)	7 (1)	0
Pyrexia	19 (3)	17 (3)	2 (<1)	13 (2)	13 (2)	0
Pneumonia	18 (3)	15 (2)	3 (<1)	17 (3)	11 (2)	3 (<1)
Sepsis	18 (3)	6 (<1)	12 (2)	6 (1)	0 (<1)	6 (<1)
Pulmonary embolism	15 (2)	14 (2)	1 (<1)	11 (2)	11 (2)	0
Gamma-glutamyltransferase increased	13 (2)	13 (2)	0	3 (<1)	3 (<1)	0

Preferred Term	A+AVD N=662			ABVD N=659		
	Grade 3 or Higher n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 or Higher n (%)	Grade 3 n (%)	Grade 4 n (%)
Dehydration	12 (2)	12 (2)	0	4 (<1)	4 (<1)	0
Peripheral motor neuropathy	13 (2)	13 (2)	0	0	0	0
Constipation	11 (2)	11 (2)	0	4 (<1)	3 (<1)	1 (<1)
Syncope	11 (2)	11 (2)	0	7 (1)	7 (1)	0
Hyperglycaemia	10 (2)	9 (1)	1 (<1)	5 (<1)	5 (<1)	0
Stomatitis	10 (2)	10 (2)	0	3 (<1)	3 (<1)	0
Dyspnoea	9 (1)	9 (1)	0	11 (2)	11 (2)	0
Thrombocytopenia	9 (1)	5 (<1)	4 (<1)	3 (<1)	3 (<1)	0
Hypokalaemia	8 (1)	6 (<1)	2 (<1)	8 (1)	6 (<1)	2 (<1)
Neutropenic sepsis	8 (1)	2 (<1)	5 (<1)	2 (<1)	1 (<1)	1 (<1)
Deep vein thrombosis	7 (1)	7 (1)	0	1 (<1)	1 (<1)	0
Device related infection	7 (1)	7 (1)	0	2 (<1)	2 (<1)	0
Hyponatraemia	7 (1)	5 (<1)	2 (<1)	6 (<1)	4 (<1)	2 (<1)
Pneumonitis	2 (<1)	2 (<1)	0	9 (1)	5 (<1)	3 (<1)
Pulmonary toxicity	0	0	0	7 (1)	5 (<1)	1 (<1)

Source: C25003 Table 15.3.1.27.
A+AVD=brentuximab vedotin (Adcetris) plus doxorubicin (Adriamycin), vinblastine, dacarbazine, ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, AE=adverse event, CTC=Common Terminology Criteria, PT=Preferred Term, TEAE=treatment-emergent adverse event.
(a) A patient was counted once for each Grade 3 or higher preferred term. Percentages were determined using the number of patients in the treatment arm as denominator.

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

Table 44 Study C25003: Drug-Related Grade 3 or Higher TEAEs Reported for at Least 5% 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 Grade 3 or higher drug-related TEAE	525 (79)	389 (59)
Neutropenia	344 (52)	242 (37)
Febrile neutropenia	120 (18)	46 (7)
Neutrophil count decreased	81 (12)	64 (10)
Anaemia	46 (7)	18 (3)

Deaths

On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy. Post treatment follow-up (PTFU) deaths were defined as deaths that occurred after 30 days of the last dose of frontline therapy.

As of the 20 April 2017 cut-off for data analysis, 67 deaths were reported in the study. A total of 9 on-study deaths were reported for the A+AVD patients and 13 on-study deaths for ABVD patients, and 19 deaths for the A+AVD patients and 26 deaths for ABVD during PTFU.

On-Study Deaths

On-study death was reported for 9 A+AVD patients. All 9 patients who died on study received the randomized regimen only without a switch to an alternative frontline medication (AFM). The cause of death for these 9 patients was reported as myocardial infarction (2 patients), cardiorespiratory arrest, haematophagic histiocytosis, respiratory failure, death of unknown cause, multiple organ dysfunction syndrome, neutropenic sepsis, and septic shock (1 patient each). The investigator considered the on-study death of 8 A+AVD patients to be treatment related, and 7 deaths were associated with neutropenia and its complications, including neutropenic sepsis and septic shock. None of the A+AVD patients for whom on-study death was reported received G-CSF primary prophylaxis.

Thirteen ABVD patients died on study. One of the 13 patients received an AFM after the Cycle 2 PET assessment. The cause of death for the 13 ABVD patients was reported as pneumonia (3 patients),

cardiac arrest (2 patients), and *Pneumocystis* pneumonia, pulmonary toxicity, cardiopulmonary failure, pneumonitis, acute respiratory distress syndrome (ARDS), acute respiratory disorder, cerebrovascular accident (CVA), and an unknown cause (1 patient each). The investigator considered the on-study death of 7 ABVD patients to be treatment related, and the majority were associated with pulmonary-related toxicity.

Deaths during Post treatment Follow-Up

The death of 19 A+AVD patients was reported between 31 days to 1186 days of the last dose of frontline therapy. None of these patients had switched to an AFM. Thirteen of these 19 patients completed 6 cycles of frontline therapy. The primary cause of death for 10 patients was reported as related to disease under study or associated complications.

The 19 A+AVD patients who died during PTFU included 5 A+AVD patients who died within 120 days of the last dose of frontline therapy. The primary cause of death for these 5 A+AVD patients was reported as related to disease under study or complications thereof (reported as exacerbation of chronic obstructive pulmonary disease in the CIOMS report), intracerebral haemorrhage, intracranial haemorrhage, completed suicide, and AE (reported as soft tissue infection and sepsis in the CIOMS reports). According to the CIOMS reports, the investigator assessed the death of 2 A+AVD patients within 120 days of the last dose of frontline therapy to be related to SAEs reported during frontline therapy

The death of 26 ABVD patients was reported between 40 days to 1075 days of the last dose of frontline therapy. Three patients had been switched to an AFM and died more than 300 days after their last dose of randomized therapy (309, 332, and 930 days, respectively). Seventeen of the 26 patients completed 6 cycles of frontline therapy. The primary cause of death was reported as related to primary disease or associated complications for 16 patients. The 26 ABVD patients included 6 ABVD patients who died within 120 days of the last dose of frontline therapy. The primary cause of death for these 6 ABVD patients was reported as related to disease under study or associated complications (3 patients), *Pneumocystis* pneumonia, T-cell lymphoma, and bile duct cancer (pneumonia, *Pneumocystis* pneumonia, T-cell lymphoma, HL, pneumonitis, and bile duct cancer in the CIOMS reports). The investigator assessed the death of 4 ABVD patients within 120 days of the last dose of frontline therapy to be related to SAEs reported during frontline therapy.

Other Serious Adverse Events

Table 45 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)

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).

The most frequently reported drug-related SAEs for ABVD patients were febrile neutropenia (6% of patients), pyrexia (3%), and pneumonitis (2%). Grade 4 neutropenia and Grade 2 anaemia were reported as SAEs in error in the clinical database for 1 A+AVD patient each. The inclusion of these 2 AEs in the overall SAE count was considered to have minimal impact on the reporting frequency of SAEs for the A+AVD treatment arm.

Other Significant Adverse Events

Other significant AEs included the AEs that resulted in premature study drug discontinuation or a dose modification, defined as a dose delay or dose hold, dose reduction, and/or infusion interruption. A dose hold or dose delay was instituted according to institutional guidelines and /or investigator judgement.

Table 46 Study C25003: TEAEs Resulting in Study Drug Discontinuation for at Least 2 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 TEAE resulting in study drug or dose discontinuation	88 (13)	105 (16)
Peripheral sensory neuropathy	23 (3)	6 (<1)
Neuropathy peripheral	16 (2)	3 (<1)
Peripheral motor neuropathy	10 (2)	1 (<1)
Febrile neutropenia	9 (1)	4 (<1)
Sepsis	4 (<1)	0
Neutropenia	3 (<1)	1 (<1)
Dyspnoea	2 (<1)	25 (4)
Hypoaesthesia	2 (<1)	0
Lung infiltration	2 (<1)	0
Myocardial infarction	2 (<1)	1 (<1)
Polyneuropathy	2 (<1)	1 (<1)
Rash macular	2 (<1)	0
Septic shock	2 (<1)	0
Pneumonia	1 (<1)	2 (<1)
Pneumonitis	1 (<1)	9 (1)
Carbon monoxide diffusing capacity decreased	0	10 (2)
Cough	0	12 (2)
Dyspnoea exertional	0	2 (<1)
Interstitial lung disease	0	3 (<1)
Painful respiration	0	2 (<1)
Pulmonary toxicity	0	12 (2)
Pyrexia	0	3 (<1)

TEAEs That Resulted in Study Drug Modification

A dose modification was defined as a dose reduction, dose delay or dose hold of any drug in the randomized regimens, or an infusion interruption. A dose delay occurred when the scheduled dose of any drug in either regimen was given but not within the time frame specified by the protocol for that particular scheduled dosing day/cycle. A dose hold occurred when a planned or scheduled dose of any drug in either regimen was not given because of an intentional physician intervention as a result of a TEAE.

A higher incidence of dose modifications was reported for the A+AVD treatment arm. At least 1 TEAE that resulted in a dose modification was reported for 423 patients (64%) in the A+AVD treatment arm and 293 patients (44%) in the ABVD treatment arm. The most frequently reported TEAEs that resulted in a dose modification for the A+AVD patients were neutropenia (22% of patients); febrile neutropenia; peripheral sensory neuropathy and PN (9% each); pyrexia (5%); and decreased neutrophil count, increased alanine aminotransferase (ALT), decreased weight, and PMN (3% each). The most frequently reported TEAEs that resulted in a dose modification for ABVD patients were neutropenia (15% of patients); febrile neutropenia (4%); peripheral sensory neuropathy; and decreased neutrophil count and pyrexia (3% each). A dose delay was the most frequently reported dose modification for patients across treatment arms. A higher percentage of dose reductions and dose delays was reported for the A+AVD patients, whereas a slightly higher proportion of dose interruptions was reported for ABVD patients. An AE resulted in dose reduction for 191 A+AVD patients (29%) and 65 ABVD patients (10%), a dose delay for 318 A+AVD patients (48%) and 217 ABVD patients (33%), and a dose interruption for 22 A+AVD patients (3%) and 33 ABVD patients (5%).

Table 47 Study C25003: TEAEs Resulting in Study Drug or Dose Modification for at Least 2% 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 TEAE resulting in dose modification	423 (64)	293 (44)
Dose held	44 (7)	32 (5)
Dose interrupted	22 (3)	33 (5)
Dose reduced	191 (29)	65 (10)
Dose delayed	318 (48)	217 (33)
Neutropenia	145 (22)	102 (15)
Peripheral sensory neuropathy	62 (9)	17 (3)
Febrile neutropenia	60 (9)	25 (4)
Neuropathy peripheral	60 (9)	11 (2)
Pyrexia	30 (5)	17 (3)
Neutrophil count decreased	23 (3)	22 (3)
Alanine aminotransferase increased	18 (3)	3 (<1)
Weight decreased	18 (3)	1 (<1)
Peripheral motor neuropathy	17 (3)	2 (<1)
Pneumonia	14 (2)	13 (2)
Leukopenia	13 (2)	8 (1)
Upper respiratory tract infection	10 (2)	13 (2)
Vomiting	5 (<1)	11 (2)
Cough	3 (<1)	14 (2)
Dyspnoea	1 (<1)	15 (2)

Other Selected Adverse Events of Clinical Importance

Neutropenia

Table 48 Study C25003: Neutropenia (Safety Population)

HLT PT	A+AVD N=662 n (%)	ABVD N=659 n (%)
Neutropenias	435 (66)	328 (50)
Neutropenia	382 (58)	295 (45)
Febrile neutropenia	128 (19)	52 (8)
Agranulocytosis	3 (<1)	1 (<1)
Granulocytopenia	0	1 (<1)
Treatment-emergent, any grade, n (%)	454 (69)	361 (55)
Grade 3 neutropenia	117 (18)	139 (21)
Grade 4 neutropenia	313 (47)	178 (27)
Treatment-emergent drug related, n (%)	438 (66)	334 (51)
Grade 3 neutropenia	110 (17)	132 (20)
Grade 4 neutropenia	306 (46)	164 (25)
SAE, n (%)	22 (3)	5 (<1)
Grade 3 neutropenia	2 (<1)	1 (<1)
Grade 4 neutropenia	19 (3)	4 (<1)

Dose Modifications For Neutropenia

Neutropenia resulted in at least 1 dose modification for 167 patients (25%) in the A+AVD treatment arm and 121 patients (18%) in the ABVD treatment arm. A dose delay was the most frequently reported modification instituted for neutropenia. Neutropenia resulted in at least 1 dose delay for 158 A+AVD patients (24%) and 117 ABVD patients (18%), and at least 1 dose reduction for 14 A+AVD patients (2%) and 8 ABVD patients (1%).

Infection Associated With Grade 3 or Grade 4 Neutropenia

Grade 3 or Grade 4 neutropenia was reported for 430 A+AVD patients (65%) and 317 ABVD patients (48%). At least 1 TEAE of any grade in the SOC Infections and infestations was reported for 145

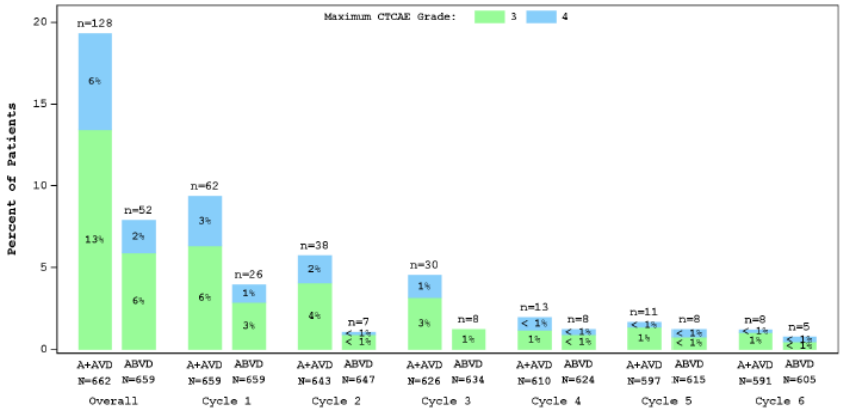
A+AVD patients (22%) and 92 ABVD patients (14%) within 7 days of Grade 3 or Grade 4 neutropenia. Upper respiratory tract infection (URTI) was the most frequently reported infection-related PT within 7 days of Grade 3/4 neutropenia across treatment arms. URTI was reported for 28 A+AVD patients (4%); nasopharyngitis and pneumonia for 13 patients each, oral candidiasis for 12 patients, and pharyngitis for 11 patients (2% each). URTI was reported for 23 ABVD patients (3%) and nasopharyngitis for 12 ABVD patients (2%).

Febrile Neutropenia

Treatment-emergent febrile neutropenia of any grade was reported for 128 patients (19%) in the A+AVD treatment arm and 52 patients (8%) in the ABVD treatment arm. Grade 3 febrile neutropenia was reported for 89 A+AVD patients (13%) and 39 ABVD patients (6%), and Grade 4 febrile neutropenia for 39 A+AVD patients (6%) and 13 ABVD patients (2%). Febrile neutropenia was reported as an SAE for 114 A+AVD patients (17%) and 43 ABVD patients (7%). Grade 5 febrile neutropenia was not reported for either treatment arm. Febrile neutropenia resulted in at least 1 dose modification for 60 patients (9%) in the A+AVD treatment arm and 25 patients (4%) in the ABVD treatment arm. This included at least 1 dose delay for 56 A+AVD patients (8%) and 23 ABVD patients (3%), and a dose reduction for 8 A+AVD patients (1%) and 5 ABVD patients (<1%).

The highest frequency of febrile neutropenia was reported during Cycle 1 for both treatment arms (Figure 36). During Cycle 1, treatment-emergent febrile neutropenia was reported for 62 A+AVD patients (9%) and 26 ABVD patients (4%). Thereafter, the frequency of febrile neutropenia declined for patients in both treatment arms, and ranged from 9% during Cycle 1 to 1% during Cycle 6 for the A+AVD patients and from 4% during Cycle 1 to <1% during Cycle 6 for ABVD patients.

Figure 33 Study C25003: Febrile Neutropenia by Cycle and Grade (Safety Population)



Potential Risk Factors for Febrile Neutropenia

An assessment was performed of the role of selected potential risk factors for febrile neutropenia. Assessed risk factors included age groups (<60 years and ≥60 years), sex, disease stage (Ann Arbor Stage III or Stage IV), bone marrow involvement, extranodal involvement at initial diagnosis, and haemoglobin value at baseline. Among the potential risk factors evaluated, advanced age was the only risk factor identified for febrile neutropenia.

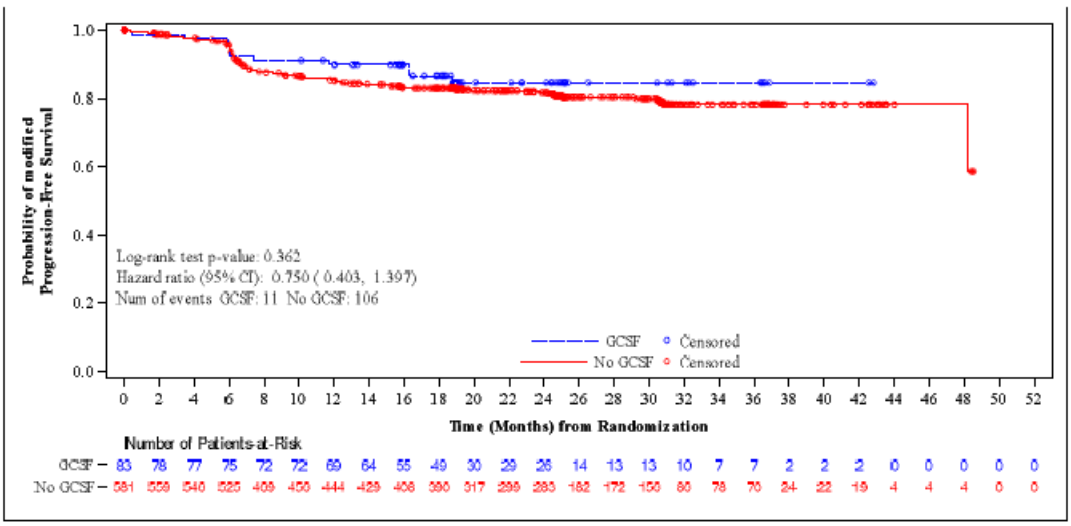
Impact of G-CSF Primary Prophylaxis on Febrile Neutropenia and Other Safety Endpoints

The IDMC recommended the use of growth factor as prophylaxis after 70% of patients were enrolled in the study. G-CSF primary prophylaxis was defined as G-CSF given by Day 5 of study treatment. By this definition, 83 A+AVD patients and 43 ABVD patients received G CSF primary prophylaxis. Febrile neutropenia at any time during treatment was reported for 9 A+AVD patients (11%) who received G-CSF primary prophylaxis compared with 119 patients (21%) who received no G-CSF primary

prophylaxis. Febrile neutropenia during Cycle 1 was reported for 1 A+AVD patient (1%) who received G-CSF primary prophylaxis compared with 61 A+AVD patients (11%) who received no G-CSF primary prophylaxis. Grade 3 or higher Infections and infestations (SOC) were reported for 9 A+AVD patients (11%) who received G-CSF primary prophylaxis compared with 107 A+AVD patients (18%) who received no G-CSF primary prophylaxis. Neutropenia of any grade was reported for 29 A+AVD patients (35%) who received G-CSF primary prophylaxis and 425 A+AVD patients (73%) who received no G-CSF primary prophylaxis. Grade 3 or higher neutropenia was reported for 24 A+AVD patients (29%) who received G-CSF primary prophylaxis compared with 406 A+AVD patients (70%) who received no G-CSF primary prophylaxis. SAEs of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, and infection-related TEAEs were reported for 20 A+AVD patients (24%) who received G-CSF primary prophylaxis compared with 190 A+AVD patients (33%) who received no G-CSF primary prophylaxis. The frequency of Grade 3 or higher neutropenia, infections, Grade 3 or higher TEAEs, and SAEs was also lower for the subgroup of 43 ABVD patients who received G-CSF primary prophylaxis than the subgroup who received no G-CSF primary prophylaxis.

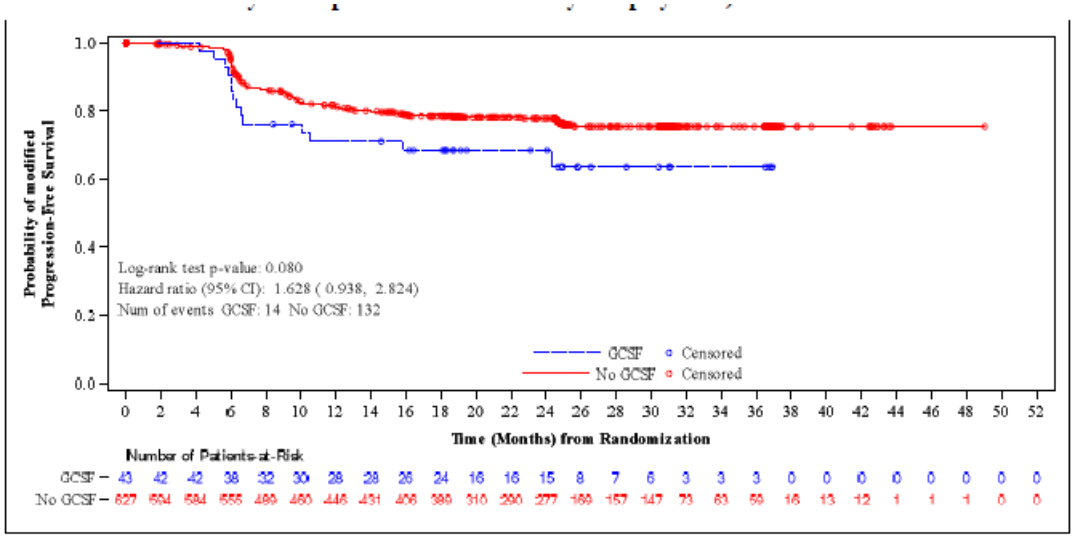
Kaplan-Meier plots of mPFS by treatment arm and G-CSF use were produced to assess the impact of G-CSF prophylaxis on mPFS.

Figure 34 ECHELON-1: Kaplan-Meier Plot of mPFS per IRF (ITT Population, A+AVD Arm by Receipt of G-CSF Primary Prophylaxis)



Hazard ratio (G-CSF/No G-CSF) and 95% CI are based on an unstratified Cox's proportional hazard regression model with Primary G-CSF as the explanatory variable in the model. Hazard ratio <1 favors G-CSF arm.
Source: /bdm/tbos/SGN-035/C25003/CSR2/rsi_apr2018/Figures/F97.2.3.1-Summary_mPFS_IRF_KM_Plot_GCSF, Run date 01 June 2018, 16:26.

Figure 35 ECHELON-1: Kaplan-Meier Plot of mPFS per IRF (ITT Population, ABVD Arm by Receipt of G-CSF Primary Prophylaxis)



As assessed by Cox regression analysis, the unstratified hazard ratio was 0.308 (95% CI, 0.210; 0.453), showing a 69% risk reduction in treatment-emergent neutropenia for patients who received G-CSF primary prophylaxis compared with the patients who received no G-CSF primary prophylaxis. Treatment-emergent neutropenia was reported for an estimated 34% of the A+AVD patients who received G-CSF primary prophylaxis compared with 73% of patients in the same treatment arm who received no G-CSF primary prophylaxis. At 1 month, an estimated 83% of patients who received G-CSF primary prophylaxis (95% CI,73.0, 89.5; [No of patients at risk=68]) were free of treatment-emergent neutropenia compared with 38% of patients who received no G-CSF primary prophylaxis (95% CI, 34.1; 42.0; [No. of patients at risk=219]).

Peripheral Neuropathy

At least 1 PN event of any grade within the PN (SMQ) was reported for 442 patients (67%) in the A+AVD treatment arm and 286 patients (43%) in the ABVD treatment arm. At least 1 PN event within the Peripheral Sensory Neuropathy (SSQ) was reported for 429 patients (65%) in the A+AVD treatment arm and 273 patients (41%) 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%). PN (SMQ) events included at least 1 Grade 3 PN event reported for 69 patients (10%) in the A+AVD treatment arm and 11 patients (2%) in the ABVD treatment arm. The most frequently reported Grade 3 PN events for the A+AVD patients were peripheral sensory neuropathy (5% of patients), PN (4%), and PMN (2%). The most frequently reported Grade 3 PN events for ABVD patients were peripheral sensory neuropathy and PN (<1% each).

Only 1 Grade 4 PN (SMQ) event was reported in the study. Grade 4 polyneuropathy, Grade 4 neurological infection, and Grade 5 respiratory failure were reported for 1 A+AVD patient at Cycle 3 Day 15. This patient was 1 of the 9 on-study deaths reported for the A+AVD treatment arm. Autonomic neuropathy was reported for 1 A+AVD patient and for 2 ABVD patients (<1%). Grade 2 autonomic neuropathy was reported for the A+AVD patient and Grade 2 and Grade 3 autonomic neuropathy were reported for 1 ABVD patient each. At least 1 drug-related PN (SMQ) event of any grade was reported for 417 A+AVD patients (63%) and 251 ABVD patients (38%), and at least 1 Grade 3 drug-related PN event was reported for 64 A+AVD patients (10%) and 10 ABVD patients (2%).

A dose reduction was the most frequently reported modification for a PN (SMQ) event across treatment arms. Among the patients with at least 1 treatment-emergent PN (SMQ) event, at least 1 dose reduction was reported for 138 A+AVD patients (31%) and 32 ABVD patients (11%), and at least 1 dose delay for 7 A+AVD patients (2%) and 3 ABVD patients (1%).

Among the patients with at least 1 treatment-emergent PN (SMQ) event, premature study drug discontinuation was reported for 44 A+AVD patients (10%) and 11 ABVD patients (4%). The A+AVD patients received a median of 8 doses (range 2 to 12 doses) and ABVD patients, a median of 5 doses (range 1 to 11 doses) of study treatment before PN resulted in premature study drug discontinuation.

Among patients with at least 1 treatment-emergent PN (SMQ) event of any grade, first onset was reported at a median of 8.0 weeks (range 0 to 29 weeks) for the A+AVD patients and at a median of 7.0 weeks (range 0 to 32 weeks) for ABVD patients. First onset of the highest grade PN event was reported at a median of 12.0 weeks (range 0 to 29 weeks) for the A+AVD patients and at a median of 8.0 weeks (range 0 to 32 weeks) for ABVD patients.

Among patients who experienced peripheral neuropathy in the pivotal phase 2 studies and randomized phase 3 studies 82-85% had resolution or improvement of their peripheral neuropathy symptoms at the time of last evaluation with the median follow up time ranging from 48.9 to 98 weeks (approximately 13 to 25 months). In the phase 3 AETHERA study, 85% of patients who experienced PN had resolution or improvement of the PN at last follow-up with a median follow-up of 98 weeks (approximately 25 months).

In ECHELON-1, 76% of patients reported improvement or resolution of PN at the slightly longer follow-up of 31 months with the vast majority of remaining peripheral neuropathy events Grade 1 or Grade 2 in severity. Time to PN onset differences were observed between ECHELON-1 and AETHERA. In the AETHERA study, for the patients in the brentuximab vedotin arm who had at least 1 event of PN, the median time to first onset of any grade was 13.7 weeks (range 0.1 to 47.4)). In ECHELON-1, among patients with at least 1 treatment emergent PN (SMQ) event of any grade, first onset was reported at a median of 8.0 weeks (range 0 to 29 weeks) for the A+AVD patients.

Resolution or Improvement of PMN

Among patients with at least 1 treatment-emergent PMN (SSQ) event, resolution or improvement was reported for 30 A+AVD patients (41%) and 21 ABVD patients (72%) at EOT, and for 45 A+AVD patients (61%) and 23 ABVD patients (79%) at the time of last follow-up. At EOT, PMN was reported to be ongoing for 48 A+AVD patients (65%) and 8 ABVD patients (28%). Among the 48 A+AVD patients with ongoing PMN at EOT, Grade 3 was reported for 11 patients (15%), Grade 2 for 20 patients (27%), and Grade 1 for 17 patients (23%). For the8 ABVD patients with ongoing PMN at EOT, Grade 2 was reported for 1 patient (3%) and Grade 1 for 7 patients (24%).

At the time of last follow-up, PMN was reported to be ongoing for 39 A+AVD patients (53%) and 6 ABVD patients (21%). Among the 39 A+AVD patients with ongoing PMN at the time of last follow-up, Grade 3 was reported for 7 patients (9%), Grade 2 for 13 patients (18%), and Grade 1 for 19 patients (26%). For the 6 ABVD patients with ongoing PMN at the time of last follow-up, Grade 2 was reported for 1 patient (3%) and Grade 1 for 5 patients (17%). At the time of last follow-up, PMN was reported to be resolved for 10 A+AVD patients (14%)and 2 ABVD patients (7%) who had ongoing PMN at EOT. For these patients, resolution of PMN was reported at a median of 24.5 weeks (range 0 to 65 weeks) from EOT for the A+AVD patients and at a median of 13.0 weeks (range 4 to 22 weeks) from EOT for ABVD patients. Among patients with at least 1 PMN (SSQ) event of any grade, resolution was reported at a median of 7.0 weeks (range 0 to 123 weeks) from time of first onset for the A+AVD patients and at a median of 2.0 weeks (range 0 to 36 weeks) from the time of first onset for ABVD patients.

Pulmonary Toxicity

A comprehensive review was performed of MedDRA PTs under the interstitial lung disease (ILD). The PTs identified from the ILD SMQ broad review were lung infiltration, pneumonitis, ILD, ARDS, organizing pneumonia, pulmonary fibrosis, and pulmonary toxicity. At least 1 treatment-emergent ILD (SMQ) event of any grade was reported for 12 patients (2%) in the A+AVD treatment arm and 44 patients (7%) in the ABVD treatment arm. The ILD events of any grade reported for the A+AVD patients were lung infiltration and pneumonitis, reported for 6 patients each and ILD, reported for 1 patient (<1% each). The most frequently reported ILD events of any grade for ABVD patients were pneumonitis, reported for 18 patients (3%), pulmonary toxicity for 16 patients (2%), and ILD for 6 patients (<1%). At least 1 Grade 3 or higher ILD event was reported for 5 A+AVD patients (<1%) and 21 ABVD patients (3%), including 3 ABVD patients with a Grade 5 (fatal) ILD event. Grade 4 lung infiltration and Grade 3 pneumonitis were reported for 2 A+AVD patients each (<1%). No Grade 5 ILD event was reported for the A+AVD patients. Grade 3 or higher pneumonitis was reported for 9 ABVD patients and Grade 3 or higher pulmonary toxicity for 7 ABVD patients (1% each). Grade 5 pneumonitis, ARDS, and pulmonary toxicity were reported for 1 ABVD patient each. An ILD event was reported as an SAE for 5 A+AVD patients (<1%) and 21 ABVD patients (3%). Lung infiltration and pneumonitis were reported as an SAE for 2 A+AVD patients each and ILD was reported as an SAE for 1 A+AVD patient. Pneumonitis was reported as an SAE for 12 ABVD patients (2%) and pulmonary toxicity was reported as an SAE for 5 ABVD patients (<1%).

A higher frequency of ILD (SMQ) events was reported for the ABVD treatment (44 (7%) versus 12 (2%)) and ILD events were associated with severe clinical outcomes including on-study death and premature study drug discontinuation. An ILD event resulted in the premature study drug discontinuation for 3 A+AVD patients (<1%) and 24 ABVD patients (4%), a dose delay for 7 A+AVD patients and 9 ABVD patients (1% each), and a dose hold for 1 A+AVD patient and 3 ABVD patients (<1% each).

Among patients with at least 1 treatment-emergent ILD (SMQ) event, first onset was reported at a median of 16.0 weeks (range 1 to 21 weeks) for the A+AVD patients and 17.5 weeks (range 0 to 38 weeks) for ABVD patients. First onset of the highest grade ILD event was reported at a median of 16.5 weeks (range 1 to 21 weeks) for the A+AVD patients and 19.5 weeks (range 0 to 38 weeks) for ABVD patients.

Comparison of Pulmonary Toxicity in ECHELON-1 Versus Historical Reports for ABVD

In ECHELON-1, pulmonary-related toxicity, including more severe and fatal events, was reported for a higher proportion of ABVD patients than A+AVD patients. Among other studies that included patients with HL who received ABVD as frontline therapy, the incidence of pulmonary toxicity varied considerably, ranging from 0%, 10%, and 15%, respectively (Jalali. et al., Ann. Hemtology 2016; Gobbi et al., JCO 2005; Huskin et al., JCO 2009). The incidence of Grade 3 or higher pulmonary toxicity ranged from <1% to 24.5% in 6 other studies that included patients with HL who received ABVD as frontline therapy.

Hepatotoxicity

Hepatotoxicity was assessed using the following 4 MedDRA SMQs, identical to those used in the ADCETRIS European Risk Management plan:

- Cholestasis and jaundice of hepatic origin SMQ, Broad.

- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ, Broad.

- Hepatitis, non-infectious SMQ, Broad.

- Liver related investigations, signs and symptoms SMQ, Broad.

Table 49 ECHELON-1: Treatment-Emergent Hepatotoxicity Events (Safety Population)

		All	Drug Related	≥Grade 3	Serious Adverse Event	Rslt. in Study Drug Disc.	Fatal
Subjects with at Least One Treatment-Emergent Hepatotoxicity[a]	A+AVD	123 (19)	81 (12)	44 (7)	4 (<1)	0	0
	ABVD	61 (9)	33 (5)	11 (2)	1 (<1)	1 (<1)	0
Liver related investigations, signs and symptoms (SMQ)	A+AVD	116 (18)	76 (11)	42 (6)	2 (<1)	0	0
	ABVD	58 (9)	32 (5)	10 (2)	0	0	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	A+AVD	11 (2)	7 (1)	4 (<1)	3 (<1)	0	0
	ABVD	3 (1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Cholestasis and jaundice of hepatic origin (SMQ)	A+AVD	2 (<1)	1 (<1)	0	0	0	0
	ABVD	1 (<1)	1 (<1)	0	0	0	0
Hepatitis, non-infectious (SMQ)	A+AVD	1 (<1)	1 (<1)	1 (<1)	0	0	0
	ABVD	0	0	0	0	0	0

Source: 0114\mpi\0068\ICR_BIO\dev\adhoc\programs\tables\ADT97.3.1.63-hep.sas, run date 15 May 2018: 08:49.
(a) Hepatoxicity includes: Cholestasis and jaundice of hepatic origin (SMQ) Broad; Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) Broad; Hepatitis, non-infectious (SMQ) Broad and Liver related investigations, signs and symptoms(SMQ) Broad.
MedDRA dictionary Version 19.0 was applied.

Thrombocytopenia and Anaemia

Table 50 ECHELON-1: Treatment-Emergent Thrombocytopenia and Anaemia Events (Safety Population)

		All	Drug Related	≥Grade 3	Serious Adverse Event	Rslt. in Study Drug Disc.	Fatal
Subjects with at Least One Treatment-Emergent Thrombocytopenia[a]	A+AVD	30 (5)	28 (4)	12 (2)	1 (<1)	0	0
	ABVD	15 (2)	13 (2)	6 (<1)	1 (<1)	0	0
Subjects with at Least One Treatment-Emergent Anemia[b]	A+AVD	146 (22)	112 (17)	54 (8)	7 (1)	1 (<1)	0
	ABVD	73 (11)	53 (8)	26 (4)	3 (<1)	0	0

Hyperglycaemia

Table 51 ECHELON-1: Treatment-Emergent Hyperglycaemia Events (Safety Population)

		All	Drug Related	≥Grade 3	Serious Adverse Event	Rslt. in Study Drug Disc.	Fatal
Subjects with at Least One Treatment-Emergent Hyperglycemia	A+AVD	198 (30)	116 (18)	31 (5)	14 (2)	1 (<1)	0
	ABVD	89 (14)	34 (5)	11 (2)	4 (<1)	0	0

Source: 0114\mpi\0068\ICR_BIO\dev\adhoc\programs\tables\ADT97.3.1.66-hyperglc.sas, run date 15 May 2018: 08:48.
MedDRA dictionary Version 19.0 was applied.

Second Malignancies

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.

Infections

Table 52 ECHELON-1: Treatment-Emergent Infection Events (Safety Population)

		All	Drug Related	≥Grade 3	Serious Adverse Event	Rslt. in Study Drug Disc.	Fatal
Subjects with at Least One Treatment-Emergent Infection	A+AVD	361 (55)	186 (28)	116 (18)	98 (15)	11 (2)	2 (<1)
	ABVD	331 (50)	158 (24)	66 (10)	59 (9)	8 (1)	4 (<1)

Source: 0114\mpi\0068\ICR_BIO\dev\adhoc\programs\tables\ADT97.3.1.67-infec.sas, run date 14 May 2018: 15:04.
MedDRA dictionary Version 19.0 was applied.

Subgroup analyses

Table 53 ECHELON-1: Overview of Safety (Safety Population With Stage III HL)

	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 54 ECHELON-1: Overview of Safety (Safety Population With Stage IV HL)

	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.

Table 55 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 HL)

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 56 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 HL)

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

On-Study Deaths

The incidences and causes of on-study deaths observed among patients receiving A+AVD or ABVD was comparable across the Safety Population, the subset of Safety Population patients with Stage III HL, the subset of Safety Population patients with no sites of extranodal HL, and the subset of Safety Population patients with Stage IV HL (data not shown)).

Serious Adverse Events

Table 57 ECHELON-1: Treatment-Emergent SAEs Reported for at Least 5 Patients in Either Treatment Arm by PT (Safety Population With Stage III HL)

Preferred Term	A+AVD N=236 n (%)	ABVD N=244 n (%)
Patients with at least 1 Serious Treatment-Emergent Adverse Event	113 (48)	63 (26)
Febrile neutropenia	43 (18)	14 (6)
Pyrexia	17 (7)	7 (3)
Pulmonary embolism	8 (3)	6 (2)
Sepsis	8 (3)	2 (<1)
Abdominal pain	7 (3)	1 (<1)
Pneumonia	7 (3)	4 (2)
Vomiting	5 (2)	0
Pneumonitis	1 (<1)	5 (2)

Source: 0114\mpi\0068\ICR_BIO\dev\primary\programs\tables\ADt15.3.1.22C-tesaept_stagiii.sas, run time 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.
Preferred Term sorted by descending frequency of A+AVD arm

Table 58 ECHELON-1: Treatment-Emergent SAEs Reported for at Least 5 Patients in Either Treatment Arm by PT (Safety Population With Stage IV HL)

Preferred Term	A+AVD N=424 n (%)	ABVD N=413 n (%)
Patients with at least 1 treatment-emergent SAE	170 (40)	114 (28)
Febrile neutropenia	71 (17)	29 (7)
Pyrexia	26 (6)	21 (5)
Neutropenia	15 (4)	2 (<1)
Pneumonia	11 (3)	11 (3)
Constipation	9 (2)	5 (1)
Diarrhoea	9 (2)	1 (<1)
Abdominal pain	7 (2)	3 (<1)
Dehydration	7 (2)	1 (<1)
Neutropenic sepsis	6 (1)	1 (<1)
Sepsis	6 (1)	2 (<1)
Vomiting	6 (1)	3 (<1)
Anemia	5 (1)	2 (<1)
Device-related infection	5 (1)	1 (<1)
Pneumonitis	1 (<1)	7 (2)

Source: m2.7.4 – ECHELON-1, Table 4.g.
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.
Preferred Term sorted by descending frequency of A+AVD arm

Laboratory findings

Serum Chemistry

Post-baseline shifts in serum chemistry values from CTC Grade 0 to Grade 3 reported for the A+AVD patients included gamma glutamyl transferase (GGT) and phosphate (3% of patients each), potassium and glucose (2% each), sodium and ALT (1% each), and AST, alkaline phosphatase, and magnesium (<1% each). Post-baseline shifts from Grade 0 to Grade 4 serum sodium, GGT, potassium, and glucose were reported for <1% of the A+AVD patients each.

Post-baseline shifts from CTC Grade 0 to Grade 3 reported for ABVD patients included sodium (2% of patients), GGT, potassium, phosphate, and glucose (1% each), and ALT, AST, bilirubin, and magnesium (<1% each). Post-baseline shifts from Grade 0 to Grade 4 reported for ABVD patients included serum potassium (1% of patients), and GGT, glucose, sodium, and creatinine (<1% each).

Haematology

A post-baseline shift from Grade 0 to Grade 3 or higher neutrophil count was reported for 332 A+AVD patients (53%), which included a post-baseline shift to Grade 3 neutrophil count for 134 A+AVD patients (21%) and to Grade 4 neutrophil count for 198 A+AVD patients (31%). A post-baseline shift from Grade 1 to Grade 3 or higher was reported for 4 patients (80%), which included a post-baseline shift to Grade 3 for 1 A+AVD patient and a post-baseline shift to Grade 4 neutrophil count for 3 A+AVD patients. A post-baseline shift from Grade 0 to Grade 3 or higher neutrophil count was reported for 357 ABVD patients (56%), which included a shift to Grade 3 neutrophil count for 184 patients (29%) and to Grade 4 neutrophil count for 173 patients (27%). A post-baseline shift from Grade 1 to Grade 4 neutrophil count was reported for 1 ABVD patient.

A post-baseline shift from Grade 0 to Grade 3 or higher leukocyte count was reported for 178 A+AVD patients (29%), which included a shift to Grade 3 leukocyte count for 152 patients (25%) and to Grade 4 leukocyte count for 26 patients (4%). A shift from Grade 1 to Grade 3 or higher was reported for 3 A+AVD patients (30%). A post-baseline shift from Grade 0 to Grade 3 or higher leukocyte count was reported for 198 ABVD patients (31%), which included a shift to Grade 3 leukocyte count for 177 patients (28%) and to Grade 4 leukocyte count for 21 patients (3%). A shift from Grade 1 to Grade 3 or higher leukocyte count was reported for 6 ABVD patients (86%).

A post-baseline shift from Grade 0 to Grade 3 Hgb concentration was reported for 4 patients (2%) and from Grade 1 to Grade 3 for 12 patients (4%) in the A+AVD treatment arm, and a post-baseline shift in Hgb concentration from Grade 0 to Grade 3 Hgb was reported for 2 patients (<1%) and from Grade 1 to Grade 3 for 9 patients (3%) in the ABVD treatment arm.

A post-baseline shift in platelet count from Grade 0 to Grade 4 and Grade 1 to Grade 3 was reported for 1 A+AVD patient each (<1%), and a post-baseline shift from Grade 0 to Grade 3 was reported for 1 ABVD patient (<1%).

Infusion-Related Reactions (IRR)

At least 1 IRR was reported for 57 A+AVD patients (9%) and 100 ABVD patients (15%), and at least 1 Grade 3 IRR for 3 A+AVD patients (<1%) and 7 ABVD patients (1%). No Grade 4 IRR was reported for either treatment arm. An IRR was reported as an SAE for 2 A+AVD patients and 6 ABVD patients (<1% each) (Table 6.a). Anaphylactic reaction was not reported for any patient in ether treatment arm.

An IRR resulted in at least 1 dose modification for 13 A+AVD patients (2%) and 35 ABVD patients (5%). Dose interruption, the most frequently reported modification for both treatment arms, was reported for 11 A+AVD patients (2%) and 27 ABVD patients (4%). An IRR resulted in premature study

drug discontinuation for 1 patient only in the ABVD treatment arm. The most frequently reported IRR PTs of any grade for the A+AVD patients were nausea, (2% of patients); and vomiting and IRR (1% each). The most frequently reported IRR PTs of any grade for ABVD patients were nausea, vomiting, and pyrexia (3% each); and chills, IRR and infusion site pain (2% each). At least 1 Grade 3 IRR was reported for 3 patients (<1%) in the A+AVD treatment arm 7 patients (1%) in the ABVD treatment arm. Grade 3 IRR was reported for 2 A+AVD patients, and Grade 3 chills, pyrexia, and drug hypersensitivity for 1 A+AVD patient each. Grade 3 pyrexia was reported for 4 ABVD patients, and Grade 3 nausea, vomiting, ADR, and chills for 1 ABVD patient each. No Grade 4 IRRs and no anaphylaxis was reported in the study. An IRR was reported as an SAE for 2 patients in the A+AVD treatment arm and 6 patients (<1% each) in the ABVD treatment arm. IRRs reported as SAEs for the A+AVD patients were Grade 3 drug hypersensitivity (dacarbazine) and IRR (1 patient each). IRRs reported as SAEs for ABVD patients were Grade 3 nausea, vomiting, and ADR (bleomycin); Grade 2 IRR, drug hypersensitivity (dacarbazine), pyrexia, chills, and sinus tachycardia; and Grade 1 increased body temperature (1 patient each).

Immunogenicity

The presence of anti-therapeutic antibodies (ATAs) to brentuximab vedotin was determined for patients in the A+AVD treatment arm and patients with a baseline and at least 1 post-baseline assessment for ATA were categorized as either ATA negative, transiently positive, or persistently positive. Patients who were confirmed to be ATA positive post baseline were also tested for the presence of neutralizing anti-therapeutic antibodies (nATA).

A total of 632 patients of the 662 patients in the A+AVD treatment arm had a baseline and at least 1 post-baseline assessment for ATA (Safety population - Immunogenicity-evaluable patients).

- At baseline, 568 A+AVD patients (90%) were ATA negative and 64 patients (10%) were confirmed to be ATA positive. A total of 523 A+AVD patients (83%) who had a baseline and at least 1 post-baseline assessment were ATA negative, and 109 A+AVD patients (17%) were confirmed to be ATA positive at 1 or more post-baseline assessments.

- Four A+AVD patients (4%) were persistently ATA positive, including 2 patients who were ATA negative at baseline, and 2 patients who were ATA positive at the baseline. A total of 105 A+AVD patients (96%) were transiently ATA positive, including 77 patients (73%) who were ATA negative at baseline and confirmed to be ATA positive after administration of brentuximab vedotin and 28 patients (27%) were confirmed to be ATA positive at baseline and post-baseline assessments.

An ATA titer was reported for 108 of the 109 A+AVD patients who were ATA positive at any post-baseline assessment. Titer status was missing or unknown for 1 patient (1%). A high titer was defined as maximum titer of >25 among all confirmed positive post-baseline assessments and a low titer was defined as a maximum titer of ≤25 among all confirmed positive post-baseline assessments. Among the 108 A+AVD patients for whom titer was measured, a high titer was reported for 2 A+AVD patients (2%) and a low titer for 106 A+AVD patients (97%).

Among the A+AVD patients, at least 1 IRR was reported for 42 ATA-negative patients (8%), and for 13 transiently ATA-positive patients (12%); 10 of the 13 patients were ATA negative at baseline and 3 patients were confirmed ATA positive at baseline No IRRs were reported for the 4 A+AVD patients (<1%) who were persistently ATA positive. An IRR was reported at Cycle 1 for 4 A+AVD patients (6%) who were ATA positive and 28 A+AVD patients (5%) who were ATA negative at baseline.

Safety in special populations

Age

Neutropenia

Advanced age was identified as a risk factor for febrile neutropenia in patients with advanced cHL who received A+AVD or ABVD. Higher incidence of febrile neutropenia was reported across treatment arms for older patients. Febrile neutropenia was reported for 97 A+AVD patients (17%) in the subset aged <60 years compared with 31 A+AVD patients (37%) in the subset aged ≥60 years, and for 35 ABVD patients (6%) in the subset aged <60 years compared with 17 ABVD patients (17%) in the subset aged ≥60 years. Within the age groups 60 years to <70 years and 70 years to <80 years, the incidence of febrile neutropenia was 33% and 44% for the A+AVD patients and 9% and 26%, respectively for ABVD patients. Febrile neutropenia was not reported for the 1 A+AVD patient ≥80 years and was reported for all 3 ABVD patients (100%) ≥80 years.

An assessment was undertaken of the impact of G-CSF primary prophylaxis on safety outcomes for older patients. Ten of the 83 A+AVD patients (12%) and 9 of 43 ABVD patients (21%) who received G-CSF primary prophylaxis in the study were aged 60 years or older. Although a small number of patients aged 60 years or older received G-CSF primary prophylaxis, a trend of improved safety outcomes was noted across treatment arms for these patients compared with those in the same age group who received no G-CSF primary prophylaxis.

Pulmonary related toxicity

Advanced age was identified as a risk factor for pulmonary-related toxicity in patients who received ABVD. The results of an analysis of the incidence of pulmonary-related toxicity for the 2 treatment arms categorized by age showed a higher incidence of ILD (SMQ) events for ABVD patients older than 65 years. No correlation was noted between age and the frequency of ILD events for the A+AVD patients.

At least 1 ILD (SMQ) event of any grade was reported for 12 patients (2%) in the A+AVD treatment arm. This included at least 1 ILD event of any grade for 9 A+AVD patients (2%) in the age range <45 years, 2 A+AVD patients (1%) in the age range of 45 years to 65 years, and 1 A+AVD patient (2%) older than 65 years. Lung infiltration was the only ILD event reported for the subset of the 53 A+AVD patients older than 65 years.

At least 1 ILD (SMQ) event of any grade was reported for 44 patients (7%) in the ABVD treatment arm. This included at least 1 ILD event of any grade for 18 ABVD patients (4%) in the age range <45 years, 14 ABVD patients (7%) in the age range of 45 years to 65 years, and 12 ABVD patients (23%) older than 65 years. Among the 53 ABVD patients older than 65 years, at least 1 ILD event was reported for 12 patients (23%), including at least 1 Grade 3 or higher ILD event for 6 patients (11%), and a Grade 5 (fatal) ILD event for 1 patient (2%). The most commonly reported ILD events of any grade for ABVD patients older than 65 years were pulmonary toxicity, reported for 6 patients (11%), pneumonitis, reported for 3 patients (6%), and pulmonary fibrosis, reported for 2 patients (4%). An ILD event was reported as an SAE for 3 ABVD patients (6%) older than 65 years.

Safety in the Elderly Subset with Stage IV HL

The Safety population used for these analyses included patients who received at least 1 dose of study drug; Safety population patients were analysed according to their actual treatment received.

Table 59 ECHELON-1: Overall Summary of Treatment-Emergent Adverse Events (Safety Population with Stage IV HL Aged ≥60 Years

	A+AVD N=51 n (%)	ABVD N=64 n (%)
Any adverse event	51 (100)	63 (98)
Drug-related adverse event	51 (100)	59 (92)
Grade 3 or higher adverse event	46 (90)	54 (84)
Drug-related Grade 3 or higher adverse event	45 (88)	47 (73)
Serious adverse event	31 (61)	30 (47)
Drug-related serious adverse event	29 (57)	22 (34)
Adverse events resulting in study drug or dose discontinuation	10 (20)	18 (28)
Adverse event resulting in dose modification	37 (73)	43 (67)
Dose held	2 (4)	2 (3)
Dose interrupted	1 (2)	7 (11)
Dose reduced	18 (35)	13 (20)
Dose delayed	29 (57)	38 (59)
On-study deaths	2 (4)	3 (5)
Deaths due to drug-related adverse events	2 (4)	2 (3)

Source: 0114\mpi\0068\ICR_BIO\dev\primary\programs\tables\ADT15.3.1.1M-teae_agegrp_stagiv.sas, run date 11 June 2018: 12:41.
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.
A patient counts once for each type of event.
Drug or Dose discontinued permanently indicates at least one individual drug within frontline therapy is discontinued.
On-study deaths are defined as deaths that occur within 30 days of the last dose of frontline therapy. Those which occur after this date are considered as deaths occurring during the follow-up period.
MedDRA dictionary Version 19.0 was applied.
Dose modification includes dose held, dose interrupted, dose reduced and dose delayed.

Table 60 ECHELON-1: Summary of Treatment-Emergent Grade 3 and 4 Neutropenia (Safety Population - Subjects With Stage IV HL: Elderly Age group ≥60 Years)

	A+AVD (N=51) n (%)	ABVD (N=64) n (%)
Treatment-Emergent	41 (80)	44 (69)
Grade 3	12 (24)	9 (14)
Grade 4	27 (53)	30 (47)
Drug-Related	41 (80)	40 (63)
Grade 3	13 (25)	7 (11)
Grade 4	26 (51)	28 (44)
Serious Adverse Events	2 (4)	1 (2)
Grade 3	1 (2)	0
Grade 4	1 (2)	1 (2)

Source: 0114\mpi\0068\ICR_BIO\dev\primary\programs\tables\ADt15.3.1.53F-neutgr34_agegrp_stagiv.sas, run date 09 June 2018: 09:50.
Preferred term of Neutropenia and Neutrophil Count Decreased are counted as Neutropenia.
A patient counts once for the highest CTCAE grade.

Hepatic and renal impairment

Patients with hepatic or severe renal impairment were excluded from enrolment in the ECHELON-1.

Table 61 ECHELON-1: Overview of patients with ≥1 Treatment-Emergent Adverse Event by renal function status (safety population)

Renal Function	Tx Rec'd N	All TEAEs	Drug Related TEAEs	≥ Grade 3	SAE	Resulted in Drug Discontinuation
Normal						
	A+AVD 569	560 (98)	549 (96)	468 (82)	234 (41)	68 (12)
	ABVD 558	547 (98)	524 (94)	354 (63)	133 (24)	78 (14)
Mild impairment	A+AVD 76	76 (100)	75 (99)	67 (88)	42 (55)	18 (24)
	ABVD 77	75 (97)	69 (90)	59 (77)	34 (44)	20 (26)
Moderate impairment	A+AVD 9	9 (100)	9 (100)	9 (100)	4 (44)	1 (11)
	ABVD 18	18 (100)	18 (100)	16 (89)	9 (50)	6 (33)

Paediatric patients

No data is available in children and adolescents younger than 18 years.

Pregnancy

A total of 40 pregnancies (3%) were reported for patients and an additional 38 pregnancies (3%) for the partners of study patients. A total of 24 pregnancies (4%) were reported for the A+AVD treatment arm, and 16 pregnancies (2%) for the ABVD treatment arm. A total of 11 live births (46%) were reported for the A+AVD patients and 4 live births (25%) were reported for ABVD patients.

Pregnancy was also reported for 18 partners of the A+AVD patients and 20 partners (3% each) of ABVD patients. A total of 8 live births (44%) were reported for the partners of the A+AVD patients, and 9 live births (45%) were reported for the partners of ABVD patients. No stillbirths were reported for either treatment arm.

Post marketing experience

No data from post marketing experience in the proposed new indication were submitted.

2.5.1. Discussion on clinical safety

Safety results are presented as of 20 April 2017 cut-off for data analysis. The Safety population consisted of 662 patients in the A+AVD treatment arm and 659 patients in the ABVD treatment arm. The safety cohort is sufficient for assessment of the safety profile in combination with AVD.

Both A+AVD and ABVD were administered IV on Days 1 and 15 of each 28-day cycle. Patients in both treatment arms could receive up to 6 cycles of study treatment. A median of 6 cycles (range 1 to 6 cycles) was reported for both treatment arms, administered over a similar m

edian duration of approximately 24 weeks (range 2.0 to 48.9 weeks). Approximately 95% of patients in both treatment arms completed the protocol-defined study treatment, e.g. the relative dose intensity, duration of treatment, and number of maximum completed cycles of individual regimen components was similar between treatment arms.

The studied population consisted of a fit first line HL population with advanced disease (36% stadium III and 64% stadium IV). The initial time since diagnosis was <1 month in both arms, median age was 35 years (A+AVD) vs 37 years (ABVD) 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%). The majority of patients had no bone marrow involvement (76%), and no B symptoms (75%) and 33% no extra-nodal sites involved. The baseline disease characteristics were well balanced between treatment arms.

In the ECHELON-1 trial almost all patients experienced 1 TEAE of any grade in both treatment arms (99% A+AVD vs 98% ABVD). At least 1 grade 3 or higher TEAE was reported for 83% in A+AVD and 66% in the ABVD arm and at least 1 drug-related SAE for 240 A+AVD patient (36%) and for 125 ABVD patients (19%). The higher toxicity of the A+AVD regimen is also reflected in the medical resource utilization, which was slightly higher in the A+AVD arm (36% vs. 28% in the ABVD arm). 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 AE profile resulted in the use of an anti-emetic as concomitant medication in approximately 75% of the cases in both arms.

As of the 20 April 2017 cut-off for data analysis, a total of 67 deaths were reported in the study. This included 9 on-study deaths for the A+AVD treatment arm, 8 of which were considered treatment-related, and 13 on-study deaths for the ABVD treatment arm, 7 of which were considered treatment-related. On-study deaths for the majority of the A+AVD patients were reported during Cycle 1 and were related to neutropenia, febrile neutropenia and its associated complications, including infections, sepsis and septic shock, none of these patients had received G-CSF prophylaxis. The majority of on-study deaths for ABVD patients were reported during Cycle 5 or Cycle 6, and were related to pulmonary toxicity, which is a known risk factor of bleomycine.

An AE resulting in a dose modification was more often reported for A+AVD then ABVD (64% vs 44%). Dose delay was the most frequently reported dose modification for patients across treatment arms. An AE resulted in premature study drug discontinuation for 88 A+AVD patients (13%) and 105 ABVD patients (16%). Neuropathy-related and toxicity and febrile neutropenia accounted for the majority of premature study drug discontinuations reported for A+AVD patients, whereas pulmonary-related toxicity accounted for the majority of discontinuations for ABVD patients.

Adverse events of clinical interest

The results of the special adverse events of interest (febrile neutropenia and infection, PN, and pulmonary-related toxicity, hepatotoxicity, thrombocytopenia, anaemia, hyperglycaemia, infections and secondary malignancies) showed for all AESIs a higher rate in A+AVD arm versus the ABVD arm, both overall as well as drug-related. For secondary primary malignancies (SPM), to date the rate of SPM is low and similar across arms (1.5% A+AVD and 2% ABVD) although the follow up time is too short to draw definitive conclusions. Data from the 10 year extension of the ECHELON-1 study will be needed to assess the rate of SPM (see RMP). Treatment-emergent neutropenia (PTs of neutropenia and decreased neutrophil count) of any grade was often reported in both arms (69% A+AVD and 55% ABVD). In the A+AVD arm neutropenia was more frequently reported as grade 4 and the highest incidence of febrile neutropenia was reported during Cycle 1 for both treatment arms. Upper respiratory tract infection (URTI) was the most frequently reported infection-related PT within 7 days of Grade 3/4 neutropenia or febrile neutropenia across treatment arms, but there was no remarkable difference between the treatments. After approximately 70% of enrollment was completed study physicians were sent a letter recommending primary prophylaxis with G-CSF in accordance with the international guidelines for neutropenia management. When comparing the safety profile of patients with and without G-CSF for both treatment arms a decrease of adverse events is observed. G-CSF primary prophylaxis was defined as G-CSF given by Day 5 of study treatment. By this definition, 83 A+AVD patients and 43 ABVD patients received G-CSF primary prophylaxis.

Introducing G-CSF prophylaxis resulted in fewer dose reductions and dose delays as shown by comparing G-CSF (n= 83) and no G-CSF prophylaxis (n= 579) for patients in the A+AVD arm, even though with prophylaxis 35% of the patients still required a dose delay, 20% a dose reduction and 10% discontinued permanently with brentuximab vedotin. As expected, G-CSF prophylaxis declined the incidence of neutropenia (69% risk reduction in treatment-emergent neutropenia) and associated complications of febrile neutropenia and infection, but a higher frequency of bone pain (a known side effect of G-CSF) was reported (see SmPC section 4.2 and 4.4).

Prophylactic treatment of G-CSF was observed to lead to improved tolerability of treatment regimen which might lead to less dose reductions and subsequently to higher exposure to the treatment regimen. As more patients in the A+AVD arm received G-CSF prophylaxis it could be assumed that efficacy results for these might thus be hampered due to the addition of G-CSF and the small number of events in the prophylaxis arm (11 patients with A+AVD and 14 ABVD). G-CSF prophylaxis seemed to have an impact on efficacy outcomes - although not statistically significant. G-CSF prophylaxis is recommended for all patients (see SmPC section 4.4). In ECHELON-1, pulmonary-related toxicity, including more severe and fatal events, was reported for a higher proportion of ABVD patients than A+AVD patients. Advanced age was identified as a potential risk factor for pulmonary-related toxicity for patients treated with ABVD. The most frequently reported TEAEs that resulted in premature study drug discontinuation for ABVD patients were dyspnoea (4% of patients); pulmonary toxicity, cough, and decreased carbon monoxide diffusing capacity (2% each); and pneumonitis (1%). The death of 7 ABVD patients was considered to be treatment-related according to the investigator assessment, and the majority of these deaths was associated with pulmonary-related toxicity. A higher frequency of ILD (SMQ) events was reported for the ABVD treatment and ILD events were associated with severe clinical outcomes including on-study death and premature study drug discontinuation. Altogether these findings confirm the already known toxicity profile of the ABVD treatment.

PN was a clinically important side effect for patients in both treatment arms and was reported for a higher proportion of the A+AVD patients; PN (SMQ) event of any grade was reported for 67% A+AVD patients and 43% ABVD patients. Most PN (SMQ) events were either Grade 1 or Grade 2. At least 1 Grade 3 PN event was reported for 10% of the A+AVD patients and for 2% of the ABVD patients. Grade 4 polyneuropathy was the only Grade 4 PN event reported in the study and was reported for 1 A+AVD patient.

Peripheral sensory neuropathy accounted for the highest proportion of PN (SMQ) events across treatment arms. At least 1 dose reduction for PN was reported for 138 A+AVD patients (31%) and 32 ABVD patients (11%). PN resulted in premature study drug discontinuation for 44 A+AVD patients and 11 ABVD patients. Resolution or improvement was reported for 51% patients A+AVD and 61% ABVD patients at EOT and for 67% A+AVD patients and 75% ABVD patients at the time of the last follow-up assessment.

The incidence of PN in ECHELON-1 was similar to the monotherapy trials AETHERA and ALCANZA (each 67%). For patients in ECHELON-1 the median onset of PN was earlier (8 weeks vs. 12-14 weeks in monotherapy). The median time to resolution or improvement in the A+AVD arm was shorter (14.5 weeks vs 16-23 weeks) compared to monotherapy. However, a higher number of patients had ongoing Grade 2 and 3 events at last follow-up compared to monotherapy with brentuximab vedotin. Resolution or improvement of PN was reported for 335 A+AVD patients (76%) with a median follow-up duration of 133 weeks (approximately 31 months. Comparing these data with the studies SG035-0003, SG035-0004, AETHERA [SGN35-005], and ALCANZA [C25001]) 82-85% had resolution or improvement of their peripheral neuropathy symptoms at the time of last evaluation with the median follow up time ranging from 48.9 to 98 weeks. Dose, schedule and concomitant use of vinblastine could potentially be factors contributing to the somewhat lower incidence and shorter time to onset. Guidance is provided in the SmPC with respect to dosing recommendations in case of PN (see SmPC section 4.2).

This incidence of ATA was similar to that observed in the Pivotal Phase 2 Population as well as that observed in the ALCANZA study. Overall, in the A+AVD treatment arm, there was no association between ATA or nATA status and response. Infusion related reactions (IRRs) occur in patients 9% of the patients treated with A+AVD, which is lower than the previous study in HL (AETHERA study (15%). Currently premedication is only administered in patients with prior infusion-related reactions. IRRs that resulted in a dose modification were reported for a higher proportion in the ABVD treatment arm (5% versus 2%). For patients in the A+AVD treatment arm no correlation was identified between the patient's ATA or nATA status and the incidence of IRRs. The included safety information in the SmPC section 4.4 is considered sufficient.

Fewer on-study deaths occurred among patients age >60 years on the A+AVD arm versus the ABVD arm. In both treatment arms, a higher percentage of patients age 60 years or older had dose modifications, including dose delays, dose reductions, and dose discontinuations. The overall incidence of TEAEs in patients age 60 years or older was generally similar across treatment arms. The incidence of febrile neutropenia was higher among patients age >60 years versus patients < 60 years in both treatment arms. G-CSF prophylaxis reduced the incidence of febrile neutropenia in patients aged ≥60 years in both treatment arms. A comparison of effect size for patients aged <60 and ≥60 years is however not possible due to the small number of patients.

The incidence of ILDs was higher in the subgroup of patients aged >65 years in the ABVD arm (N=1 vs N=12).

The Applicant performed subgroup analysis for Stage IV and extranodal sites>1 analysis. A+AVD treatment shows a distinct safety profile than ABVD. The type of AEs, SAEs, TEAEs was comparable across the Safety Population and do not differ with the presence of extranodal disease or disease staging (III/IV). No new risks were identified in these subgroups. Patients with stage III disease have more drug discontinuations compared to stage IV and the ITT population (mainly neuropathy and neutropenia as reason- 19% A+AVD stage III versus 10% A+AVD stage IV patients with both stage III and IV 16% for ABVD). There were more SAEs in stage III group compared to stage IV (48% vs 40%) and compared to stage IV fewer neutropenia ≥Grade 3 AEs, drug-related neutropenias overall and Grade 3 were observed. Grade 4 was comparable between the subgroups. No apparent difference is

noted for treatment emergent febrile neutropenia. More subjects with stage III disease had resolution of peripheral neuropathy and fewer ongoing events compared to stage IV. Altogether it appears as though the stage III patients experienced slightly more toxicity then stage IV patients.

For ABVD patients management of pulmonary toxicity by bleomycine can in part be managed by the introduction of a PET guided approach for discontinuation of bleomycine after a negative PET after 2 cycles (Johnson et al, 2016) reducing its toxicity without affecting PFS. This approach was not incorporated in the design of the ECHELON-1 study which is unfortunate but due to the timing of the guidelines and start of the ECHELON-1 study understood. However, the toxicity of the ABVD treatment in the trial with respect to pulmonary toxicity might be overestimated compared to current clinical practice.

The incidence in TEAE in stage IV elderly patients was similar in A+AVD versus ABVD. Elderly patients require more dose modifications, however this also holds true for the ABVD arm. Elderly patients have an increased risk for febrile neutropenia with the A+AVD treatment. Only a small proportion of patients >60 years had received prophylaxis in the pivotal trial.

All relevant safety information has been included in the updated SmPC (see sections 4.4 and 4.8).

2.5.2. Conclusions on clinical safety

Overall, no new safety concerns have been identified with A+AVD treatment.

The CHMP considers the following measures necessary to address issues related to safety:

- Submission of regular updates/ final report from the 10-year extension of the ECHELON-1 trial.

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

The MAH submitted an updated RMP version 15, in response to comments made in the previous round of assessment. The PRAC considered that the risk management plan version 15 is acceptable.

No changes were made to the list of safety concerns, pharmacovigilance plan or risk minimisations measures as a result of the new indication.

The CHMP endorsed the Risk Management Plan version 15 with the following content:

Safety concerns

Important identified risks	Peripheral neuropathy (sensory and motor) Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia) Infections (including bacteraemia, sepsis, septic shock and opportunistic infections)

	Infusion-related reactions Hyperglycaemia Anti-drug antibodies
Important potential risks	Severe hepatotoxicity Pulmonary toxicity Thymus depletion (paediatric)
Missing information	Long term safety

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
C25006: Ph 4, open-label, single-arm study of brentuximab vedotin in patients with r/r sALCL (SOB 010) Status: Ongoing	Single-agent efficacy (ORR, duration of tumor control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT; OS), safety and tolerability, PK, immunogenicity	Anti-drug antibodies	Primary CSR	Q1 2021
MA25101 (PASS): Observational cohort study of the safety of brentuximab vedotin in the treatment of r/r CD30+ HL and r/r sALCL (SOB 008 & SOB 009) Ongoing	Safety; identification of potential risk factors for peripheral neuropathy	Peripheral neuropathy (sensory & motor); Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia and anaemia); Infections (including bacteremia, sepsis, septic shock, and opportunistic infections); IRRs; hyperglycemia; Severe hepatotoxicity, Pulmonary toxicity (devoid of concomitant bleomycin); longer-term safety	Interim CSR Second Interim analysis Final CSR	Apr 2016 (completed) Within the annual renewal 2017 (completed) Dec 2020
Category 3 - Required additional pharmacovigilance activities				
SGN35-014: Randomized,	Multi-agent efficacy (PFS, OS, CR); safety	Peripheral neuropathy (sensory	CSR (primary endpoint):	Sep 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in frontline treatment of patients with CD30 positive mature T cell lymphomas (MTCLs) (MEA 015) Ongoing		& motor); IRRs; ADAs		
C25002: Ph 1/2 PIP study of brentuximab vedotin in pediatric patients with r/r sALCL or HL Ongoing	Safety; PK; pediatric maximum tolerated dose (MTD) and/or RP2D o Immunogenicity, antitumor activity	Safety in pediatrics; thymus depletion (pediatric); ADAs	CSR (primary analysis) CSR addendum (LTFU): Study Initiation Date (FPFV): Date of Completion (LPLV):	Dec 2016 (fulfilled) Aug 2017 Initiation after Positive benefit-risk in adults Oct 2017 (Completion date deferred)
C25004: An Open-Label Study of Brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients with Advanced Stage Newly Diagnosed Hodgkin Lymphoma [PIP Study 3] Planned	Safety; determination of MTD or highest HPD in combination Evaluation of PK, immunogenicity, activity of combination therapy, and mobilization of peripheral blood stem cells for ASCT	Safety in pediatrics; thymus depletion (pediatric)	LPO	On/before Dec 2020

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Peripheral Neuropathy (Sensory and Motor)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC sections 4.2 and 4.4 where there are recommendations regarding monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, burning sensation, neuropathic pain or weakness) and the possibility of	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** SGN35-014 and MA25101

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	delaying or reducing the dose in patients who experience new or worsening neuropathy. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None	
Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Sections 4.2 and 4.4 where there are recommendations for patients to have a full blood count prior to administration of each dose of brentuximab vedotin and for close monitoring of patients who develop neutropenia. If patients develop febrile neutropenia, they should be managed according to best medical practice. Dose delays should be considered in patients who develop neutropenia and growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia in monotherapy with brentuximab vedotin. In combination therapy for the frontline treatment of HL, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MA25101
Infections (including bacteraemia, sepsis, septic shock and opportunistic infections)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation for patients to be carefully monitored during treatment for the emergence of possible serious infections and opportunistic infections. Package Leaflet section 2 and section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MA25101

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status **Additional risk minimisation measures:** None	
Infusion-Related Reactions (IRRs)	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where there is information about the possibility of patients developing immediate and delayed infusion-related reactions (IRRs) including anaphylactic reactions and a recommendation that administration of brentuximab vedotin should either be interrupted or immediately and permanently discontinued and appropriate medical therapy administered, if an IRR or anaphylactic reaction occurs. The SmPC also recommend restarting the infusion at a slower rate after symptom resolution and pre-medicating patients who have experienced a prior IRR with pre-medications such as paracetamol, an antihistamine, and a corticosteroid. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** SGN35-014, C25002 and MA25101
Hyperglycaemia	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that any patient who experiences hyperglycemia should have their serum glucose closely monitored and antidiabetic treatment should be administered as appropriate. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MA25101
Anti-drug Antibodies (ADAs)	**Routine risk minimisation measures**: SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.4, where there is a statement that a higher incidence of infusion related reactions (IRRs) has been observed in patients with persistently positive Anti-Drug Antibodies (ADAs) relative to patients with transiently positive ADA and never positive ADA. It is recommended that the infusion should be interrupted if patients develop IRRs. Legal status **Additional risk minimisation measures:** None	None **Additional pharmacovigilance activities:** MA25101
Severe hepatotoxicity	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that patients receiving Brentuximab vedotin therapy should have a liver function test before initiating treatment and routinely monitored during treatment with brentuximab vedotin. Patients who experience hepatotoxicity may require a dose delay, change in dose, or discontinuation of brentuximab vedotin. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MA25101

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Pulmonary toxicity	**Routine risk minimisation measures:** SmPC Section 4.8 SmPC Sections 4.3 and 4.4 prohibits the combined use of brentuximab vedotin and bleomycin as it causes pulmonary toxicity. The SmPC also contain a recommendation that if new or worsening pulmonary symptoms are observed, a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Brentuximab vedotin therapy should be stopped during evaluation and until symptomatic improvement. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MA25101
Thymus Depletion (Paediatric)	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 5.3 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** C25002 and C25004
Long term safety	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 5.1 Legal status **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MA25101

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the PI is brought in line with the latest QRD template version 10 and editorial changes were made throughout the PI which were reviewed and accepted by the CHMP.

2.7.1. User consultation

The MAH provided justification for not performing a full user consultation with target patient groups on the package leaflet. The changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).

3.1.2. Available therapies and unmet medical need

In patients who present with advanced disease, 30-40% 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 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) versus that obtained with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) as frontline treatment for adult patients with CD30+ stadium III/IV HL. Primary endpoint was mPFS. A subgroup analysis was performed for patients with Stage IV HL and no or 1 or more sites of extranodal HL.

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 by disease stage showed that patients with stage IV disease may experience more benefit of A+AVD. A+AVD patients with Stage III HL or no sites of extranodal HL seemed to have smaller efficacy effects relative to ABVD than seen in the ITT and in stage IV patients. Of the ITT population, 846 patients (63%) had Stage IV disease. There were no relevant differences in the patient and disease characteristics at baseline between the two arms.

The key secondary endpoint OS showed no evidence of a survival advantage or disadvantage for A+AVD compared to ABVD in the ITT (stratified HR 0.728, 95% CI, 0.448; 1.184, p=0.199) at the interim analysis. For stage IV patients an advantage of A+AVD over ABVD was observed (HR= 0.51 (95% CI [0.27, 0.97], p-value=0.037).

Other secondary efficacy endpoints including CR rate and ORR at the end of randomization regimen, CR rate at the end of first-line therapy, and the rate of PET negativity at the end of Cycle 2, duration of response (DOR), duration of complete remission (DOCR), disease-free survival (DFS) and event-free survival (EFS), all had a trend in favour of A + AVD in both the ITT and Stage IV population.

Elderly patients with stage IV HL have a trend towards a slightly favourable mPFS treated with A+AVD versus ABVD mPFS per IRF: HR age ≥60 = 0.804 (95% CI: 0.42 to 1.53), p = 0.506 and HR for age ≥65 = 0.777 (95% CI: 0.36 to 1.67), p = 0.515).

3.3. Uncertainties and limitations about favourable effects

Median mPFS and OS were not yet reached in either treatment arm. Update of mPFS results will not be provided, which limits the precision of the mPFS data for the subgroups due to the current high censoring rates and low event rates. OS data are very immature (Stage III 14 events (6%) A+AVD, 12 events (5%) ABVD; Stage IV; A+AVD 14, ABVD 26 events). Final analysis of OS data will be performed after 112 deaths have occurred.

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 amendment of the ECHELON-1 study to include an extension of 10 year will be able to provide some data on next line treatment although a thorough assessment of the efficacy of retreatment will likely not be feasible.

3.4. Unfavourable effects

No new safety signals have been observed with the A+AVD or the ABVD treatment. The type of AEs, SAEs, TEAEs was for the most part comparable across the Safety Population and subgroups of extranodal disease or disease staging (III/IV). No new risks were identified in these subgroups.

Patients with stage III disease have more drug discontinuations compared to stage IV and the ITT population (mainly neuropathy and neutropenia as reason). Also there were more SAEs in stage III group compared to stage IV (48% vs 40%). It appears as though the stage III patients experience slightly more toxicity then stage IV patients.

Premature study drug discontinuation occurred for 88 patients (13%) in the A+AVD treatment arm and 105 patients (16%) in the ABVD treatment arm. Neuropathy related and febrile neutropenia accounted for the majority of the study drug discontinuations in the A+AVD treatment arm, whereas pulmonary toxicity accounted for the majority of study drug discontinuations in the ABVD treatment arm. AE resulting in a dose modification was more often reported for A+AVD then ABVD (64% vs 44%), also mostly related to neutropenia and neuropathy events.

On study deaths were reported for 9 patients in the A+AVD arm (8 treatment related) and 13 in the ABVD arm (7 related). On-study deaths for the majority of the A+AVD patients were reported during

Cycle 1 and were related to neutropenia and its associated complications. The majority of on-study deaths for ABVD patients were reported during Cycle 5 or Cycle 6, and were related to pulmonary toxicity.

Peripheral neuropathy events of any grade were reported for 67% of the A+AVD and 43% of the ABVD treated patients. Most PN events were either grade 1 or 2. Peripheral sensory neuropathy accounted for the highest proportion of PN (SMQ) events reported. Peripheral neuropathy was manageable with dose reduction of brentuximab and resolved or improved over time. Thus, the risks are known and manageable by recommendations in the SmPC and risk minimisation activities in the RMP.

At least 1 Interstitial lung disease (SMQ) event (any grade) was reported for 12 patients (2%) in the A+AVD and 44 patients (7%) in the ABVD treatment arm. At least 1 Grade 3 or higher ILD event was reported for <1% vs.3%, respectively, and a SAE in <1% vs. 3%, including 3 ABVD patients with a Grade 5 (fatal) ILD event. The most frequently reported ILD (SMQ) events of any grade for ABVD patients were pneumonitis pulmonary toxicity and interstitial lung disease.

Infusion related reactions (IRRs) occurred in 9% of the patients treated with A+AVD and 15% of the ABVD patients.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety follow up is limited. The extension study of the ECHELON-1 trial will provide additional results to further characterise the safety profile of Adcetris in combination with doxorubicin, vinblastine and dacarbazine (AVD) in this setting.

The rate of secondary primary malignancies (SPM) was low and similar across arms (1.5% A+AVD and 2% ABVD) although the follow up time was too short to draw definitive conclusions. Data from the 10 year extension of the ECHELON-1 study will be needed to assess the rate of SPM.

3.6. Effects Table

Table 63. Effects Table for ADCETRIS indicated for previously untreated adult patients with CD30+ Stage IV Hodgkin lymphoma (HL) in combination with AVD

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	ITT: Probability at 2 years	82.1 (78.8 – 85.0) % ITT: HR 0.77 (95% CI 0.6-0.98, p=0.035) Stage IV: HR 0.71 (95% 0.53-.96, p=0. 0.023	77.2 (73.7 – 80.4) %	Active-controlled study (ITT: n = 1334). High censoring rates in the pre-specified subgroup analysis of stage IV (79%). No robust data in elderly	C25003

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	therapy for HL after completion of frontline therapy)					
CR	Complete remission	Rate at the end of randomised treatment	73%	70%		
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)			
OS	Time from randomization to date of death.	ITT: Probability of survival at 2 years	96.6% ITT: HR 0.728 (95% CI 0.448, 1.184, p=0.199) Stage IV: HR 0.507 (95%CI 0.265, 0.971)	94.2%	Interim analysis, very small number of events per treatment arm (ITT: n= 28 A+AVD, n= 39 ABVD) and in pre-specified subgroup analysis of stage IV (n= 14 A+AVD, n= 26 ABVD)	
Unfavourable Effects						
At least 1 TEAE grade 3 or higher	Incidence as percentage of patients from the safety population	%	83 *reported for ≥10% neutropenia, febrile neutropenia, and decreased neutrophil count*	66 *reported for ≥ 10% neutropenia and decreased neutrophil count*	The incidence in the stage IV patients was comparable (83% A+AVD and 67% ABVD	
Drug related SAE	Incidence as percentage of patients from the safety population	%	36	19	The incidence in the stage IV patients was comparable (33% A+AVD and 20% ABVD)	
ILD event	Treatment-emergent interstitial lung disease (ILD based on MedDRA SMQ)	Patients	12 (2%)	44 (7%)		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
AE resulting in dose modification	Incidence as percentage of patients from the safety population	%	64 *The most commonly reported TEAEs; neutropenia, febrile neutropenia, peripheral sensory neuropathy and PN, and pyrexia.*	44 *The most commonly reported TEAEs; neutropenia and febrile neutropenia*	A dose delay was the most frequently reported dose modification for both treatment arms.	
AE resulting in premature study drug discontinuation	Incidence as percentage of patients from the safety population	%	13 *PN and febrile neutropenia accounted for the majority*	16 *pulmonary toxicity accounted for the majority*		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Brentuximab vedotin +AVD treatment resulted in a statistically significant improvement in IRF-based mPFS compared to ABVD treatment in the ITT, which was consistent across several sensitivity analyses.

The MAH requests a subgroup indication limited to stage IV HL patients. The subgroup analyses show that patients with stage IV disease (HR mPFS: 0.711 (95% CI 0.529, 0.956) or 1 or more extranodal sites (mPFS HR 0.699 (95% CI 0.518, 0.943) seem to experience more benefit of A+AVD when compared with the ITT population (HR=0.770 [95% CI 0.603, 0.983]; p=0.035). A+AVD patients with Stage III HL (HR=0.922, [95% CI 0.599-1.419]) or no sites of extranodal HL (HR=1.042, [95% CI 0.670- 1.619]) had apparently poorer efficacy outcomes when compared with the ITT population and the stage IV patients. For stage IV patients an OS advantage of A+AVD over ABVD was observed (HR= 0.51 (95% CI [0.27, 0.97], p-value=0.037), which provides only some support for the mPFS data as this was based on a very limited number of patients. The secondary endpoint response rate results were similar for both treatment arms irrespective of stage III or IV.

The safety profile of the A+AVD treatment is distinct from ABVD. Frequencies of several known ADRs, as well as of treatment discontinuation due to AEs, dose delays and dose reductions appeared higher than that of ABVD treatment. 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. These could be partially managed with dose modifications and G-CSF prophylaxis and

were in line with what is known for brentuximab vedotin as monotherapy and for the backbone chemotherapy.

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). It is noted that stage III patients have more drug discontinuations compared to stage IV and the ITT population (mainly neuropathy and neutropenia as reason), more SAEs in stage III group compared to stage IV (48% vs 40%).

Stage IV elderly patients have a slightly favourable mPFS point estimate treated with A+AVD versus ABVD was observed, though the low number of events introduce considerable uncertainty regarding the true effect of the treatment. With respect to safety, the incidence in TEAE in stage IV elderly patients was similar in A+AVD versus ABVD. In general, A+AVD toxicity is severe and elderly patients require more dose modifications, however this also holds true for the ABVD arm. Elderly patients have an increased risk for febrile neutropenia with the A+AVD treatment. In the elderly patients there was a limited use of G-CSF prophylaxis (12% A+AVD 9% ABVD patients). In general the ECHELON-1 study consisted of fit HL patients (ECOG score 0 or 1). Ultimately treatment of elderly stage IV HL patients will depend on performance scores, risk factors and comorbidities and might be aimed at avoiding bleomycin toxicity. As such another treatment option besides ABVD is considered as benefit also for elderly stage IV patients. (see SmPC).

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, subsequent therapy and OS. Response data on retreatment and salvage therapy will be collected, as well as additional data with respect to next line treatment, such as the reason for the next therapy and the time period during which symptoms leading to next therapy have existed (e.g., in case there was delay of therapy for any reason).

3.7.2. Balance of benefits and risks

The final indication is restricted in stage IV HL patients supported with data from the ECHELON-1 study. In the context of an overall positive study with inconsistent results among key subgroups, the trend for positive mPFS results with some support from OS data for the stage IV patients (with or without extranodal disease) and the similar safety profile of the A+AVD regimen vs ABVD treatment for stage IV patients, render the benefit/risk of A+AVD in this patient subgroup positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit-risk of Adcetris in previously untreated adult patients with CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) s 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, IIIA and IIIB

Extension of the existing Hodgkin lymphoma (HL) indication to include the frontline treatment of adult patients with CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine (AVD), based on data from ECHELON-1 (C25003), a phase 3 multi-centre, randomised, open-label study comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin, doxorubicin, vinblastine and dacarbazine versus the mPFS obtained with doxorubicin, bleomycin, vinblastine and dacarbazine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10. The MAH also submitted an updated RMP version 15, implementing Revision 2 of the EU-RMP template.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being

received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of the existing Hodgkin lymphoma (HL) indication to include the frontline treatment of adult patients with CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine (AVD), based on data from ECHELON-1 (C25003), a phase 3 multi-centre, randomised, open-label study comparing the modified progression-free survival (mPFS) obtained with brentuximab vedotin, doxorubicin, vinblastine and dacarbazine versus the mPFS obtained with doxorubicin, bleomycin, vinblastine and dacarbazine. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10. The MAH also submitted an updated RMP version 15, implementing Revision 2 of the EU-RMP template.

Summary

Please refer to the Scientific Discussion – Adcetris II-55.