23 April 2026
EMADOC-1700519818-3037106
Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMA/VR/0000304938

Note

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

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Table of contents

List of abbreviations

AE	Adverse event
ASCT	autologous stem cell transplant
AVD	doxorubicin, vinblastine and dacarbazine
BICR	Blinded independent central review
BV	brentuximab vedotin
cHL	classical Hodgkin lymphoma
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CMR	Complete metabolic response
CNS	Central Nervous System
CR	Complete remission
CSR	Clinical Study Report
DBL	Database Lock
DMC	Data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EOT	End of treatment
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GM	Geometric mean
HIV+	Human immunodeficiency virus positive
HL	Hodgkin Lymphoma
HR	Hazard Ratio
IA	Interim Analysis
IF	Information Fraction
INV	Investigator
IPS	International Prognostic Score
ITT	Intent to treat
KM	Kaplan Meier
mcg	Microgram

NALT	New anti-lymphoma treatment
N-AVD	Nivolumab in combination with doxorubicin, vinblastine and dacarbazine
NCI	National Cancer Institute
NOS	Not otherwise specified
OPEN	Oncology Patient Enrolment Network
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed death-ligand-1
PD-L2	Programmed death-ligand-2
PET-RT	Positron emission tomography radiation therapy
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
Q2W	Every two weeks
R/R	Relapsed/Refractory
RT	Radiotherapy
SAP	Statistical Analysis Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SubQ	Subcutaneous
SWOG	Southwest Oncology Group

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 12 October 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include OPDIVO for the treatment of adults and adolescents 12 years of age and older with previously untreated Stage III or IV classical Hodgkin Lymphoma (cHL), based on results from the pivotal study CA2098UT (SWOG 1826), a Phase 3, randomized, open-label study of nivolumab (Opdivo) + AVD (N-AVD) versus brentuximab vedotin (Adcetris) + AVD (Bv-AVD) in patients (age ≥12 years) with newly diagnosed, advanced stage cHL. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 51.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0138/2024 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0138/2024 was completed.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	13 October 2025
Start of procedure:	1 November 2025
CHMP Rapporteur Assessment Report	19 December 2025
PRAC Rapporteur Assessment Report	6 January 2026
PRAC members comments	8 January 2026
PRAC Outcome	15 January 2026
CHMP members comments	19 January 2026
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 January 2026
Request for supplementary information (RSI)	29 January 2026
CHMP Rapporteur Assessment Report	24 March 2026
PRAC Rapporteur Assessment Report	27 March 2026
PRAC members comments	31 March 2026
Updated PRAC Rapporteur Assessment Report	1 April 2026
PRAC Outcome	10 April 2026
CHMP members comments	12 April 2026
Updated CHMP Rapporteur Assessment Report	16 April 2026
Opinion	23 April 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The World Health Organization's classification of lymphomas distinguishes two major subtypes of Hodgkin Lymphoma (HL), namely, "classical HL" and "nodular lymphocyte predominant HL" (Falini et al, 2023). Classical HL (cHL) is characterized pathologically by the presence of monoclonal lymphoid cells that may be either mononuclear (Hodgkin cells) or multinucleate (Reed-Sternberg cells) (HRS).

Claimed therapeutic indication

OPDIVO in combination with doxorubicin, vinblastine and dacarbazine (AVD) is indicated for adults and adolescents 12 years of age and older with previously untreated Stage III or IV cHL.

Epidemiology

According to GLOBOCAN, in the EU in 2022, there were an estimated 1,381 and 10,973 newly diagnosed cases of HL among individuals age 0 to 19 years and 20 to 85+ years, respectively. The age standardized incidence rates were 1.4 and 3.2 per 100,000, respectively. The highest incidences of HL in the EU are in France, Italy and Spain (https://gco.iarc.fr/today/).

Biologic features

The malignant Hodgkin and Reed Sternberg (HRS) cells are typically surrounded by a heterogeneous infiltrate of reactive T- and B-lymphocytes, eosinophils, macrophages, fibroblasts, and variable amounts of collagen deposition (sclerosis). Research has demonstrated that chromosome 9p24.1/CD274 (PD-L1) PDCD1LG2 (PD-L2) genetic alterations increase the PD-1 ligands expression and are described as a defining feature of cHL. The 9p24 amplicon also contains JAK2 and copy number-dependent JAK2-signal transducers and activators of transcription which can further increase PD1 ligand expression.

Clinical presentation, diagnosis and stage/prognosis

HL is a lymphoid neoplasm which typically affects young adults and presents with painless lymphadenopathy with or without splenomegaly, fever, drenching night sweats, weight loss, and pruritus.

Management

Early line treatment approaches both in the EU and US for children and adults with cHL typically involve combination chemotherapy, with or without radiotherapy (RT), and may include strategies to tailor subsequent therapies based on response (NCCN guideline Pediatric Hodgkin Lymphoma, NCCN guideline Hodgkin Lymphoma, ESMO Guideline 2025, Daw et al 2020). Differences in treatment between adult and paediatric protocols are largely related to age-specific concerns regarding late effects of alkylating agents (infertility, second malignancy), anthracycline (cardiac toxicity), and RT (bone and soft tissue growth, second malignancy, cardiopulmonary sequalae), with an evolution toward treatment protocols limiting the cumulative doses of the above chemotherapies and limiting radiation doses to 15 to 25 Gy of involved lymph node regions only (ESMO Guideline).

Patients with Stage I-II disease are considered to have "early stage" HL and are generally treated with short courses (2-4 cycles) of combination chemotherapy followed by involved field RT for some which affords a cure rate of 90-95%. Patients with Stages III-IV disease are considered to have advanced stage HL. The ESMO guideline recommends that patients ≤60 years should be treated with two cycles of brentuximab vedotin—etoposide—cyclophosphamide—doxorubicin—dacarbazine— dexamethasone (BrECADD), followed by interim PET (iPET). If the iPET is negative (DS 1-3), two additional cycles of BrECADD should be given and if the iPET is positive (DS 4-5), patients should receive four additional cycles of BrECADD. Six cycles of nivolumab (Nivo)-AVD represents an alternative treatment option for patients ≤60 years and is considered the favoured option for patients 60-80 years, although this option is currently not EMA or FDA approved. If Nivo-AVD is unavailable and BrECADD is unsuitable, brentuximab vedotin (BV)-AVD represents a third treatment option. If BV and PD-1 inhibitors are not available, standard treatment options are ABVD or escalated BEACOPDac (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Prednisolone, Dacarbazine) (ESMO Guideline).

For paediatric patients > 12 years the US guideline (NCCN 2025) recommends N-AVD as preferred treatment option with BV-AVE-PC (brentuximab vedotin, with doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide), OEPA (vincristine, etoposide, prednisone, doxorubicin), AEPA (brentuximab vedotin, etoposide, prednisone, doxorubicin) as other recommended options. In certain circumstances (e.g. patient unable to receive checkpoint inhibitors) BV-AVD could be used.

Brentuximab-containing regimens demonstrated improved outcomes (BV-AVD vs ABVD in adult Stage III-IV cHL patients and BV-AVE-PC (brentuximab vedotin, with doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide) vs ABVE-PC in paediatric advanced stage (AS) cHL patients), and these BV-containing regimens became the standard of care for newly diagnosed AS cHL. However, ~20-25% of patients relapse after upfront BV-containing treatments. BV-AVD is also associated with higher rates of neutropenia, sepsis, and peripheral neuropathy compared to ABVD in adult cHL patients, therefore an unmet medical need remains from both an efficacy and safety perspective in the treatment of AS cHL. Additionally, RT use is associated with an increased risk of secondary malignancies, especially breast cancer, and cardiovascular events, therefore avoidance of RT in first-line treatment is vital (Connors et al. 2018, Straus et al. 2021, Ansell at al., 2022). The ongoing EuroNet-PHL-C2 study investigates the option of a risk stratified (defining chemotherapy) and response adapted (defining radiotherapy) in children and adolescents to tailor the amount of treatment to the individual patient and decrease long term complications (NCT02684708).

2.1.2. About the product

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death 1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T cell activity that has been shown to be involved in the control of T cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Nivolumab is approved worldwide for the treatment of multiple tumour types, as monotherapy or in combination with ipilimumab and other medicinal products. Among the currently approved indications, OPDIVO as monotherapy is indicated for the treatment of adult patients with R/R cHL after ASCT and treatment with brentuximab vedotin (Bv) or in combination with Bv for the treatment of children 5 years of age and older, adolescents and adults up to 30 years of age with relapsed or refractory cHL after one prior line of therapy.

2.1.3. The development programme

The primary evidence of efficacy and safety information for the proposed application is provided from the pivotal study CA2098UT, which is a multicentre, randomised, open-label Phase 3 clinical trial for participants with newly diagnosed Stage III-IV cHL.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

BMS-936558 (nivolumab) is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, BMS-936558 is exempt from Environmental Risk Assessment studies in line with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00 Rev. 1- Corr.). BMS-936558 and the product excipients do not pose a significant risk to the environment.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data has been submitted for this new indication. This is agreed, as the new indication is still within the scope of ICH S9 (advanced cancer).

Nivolumab is a protein which degrades naturally in the environment and is unlikely to pose a risk to the environment therefore the absence of ERA studies is justified.

2.2.3. Conclusion on the non-clinical aspects

There are no objections from a non-clinical point of view in this application for a new indication for Opdivo.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

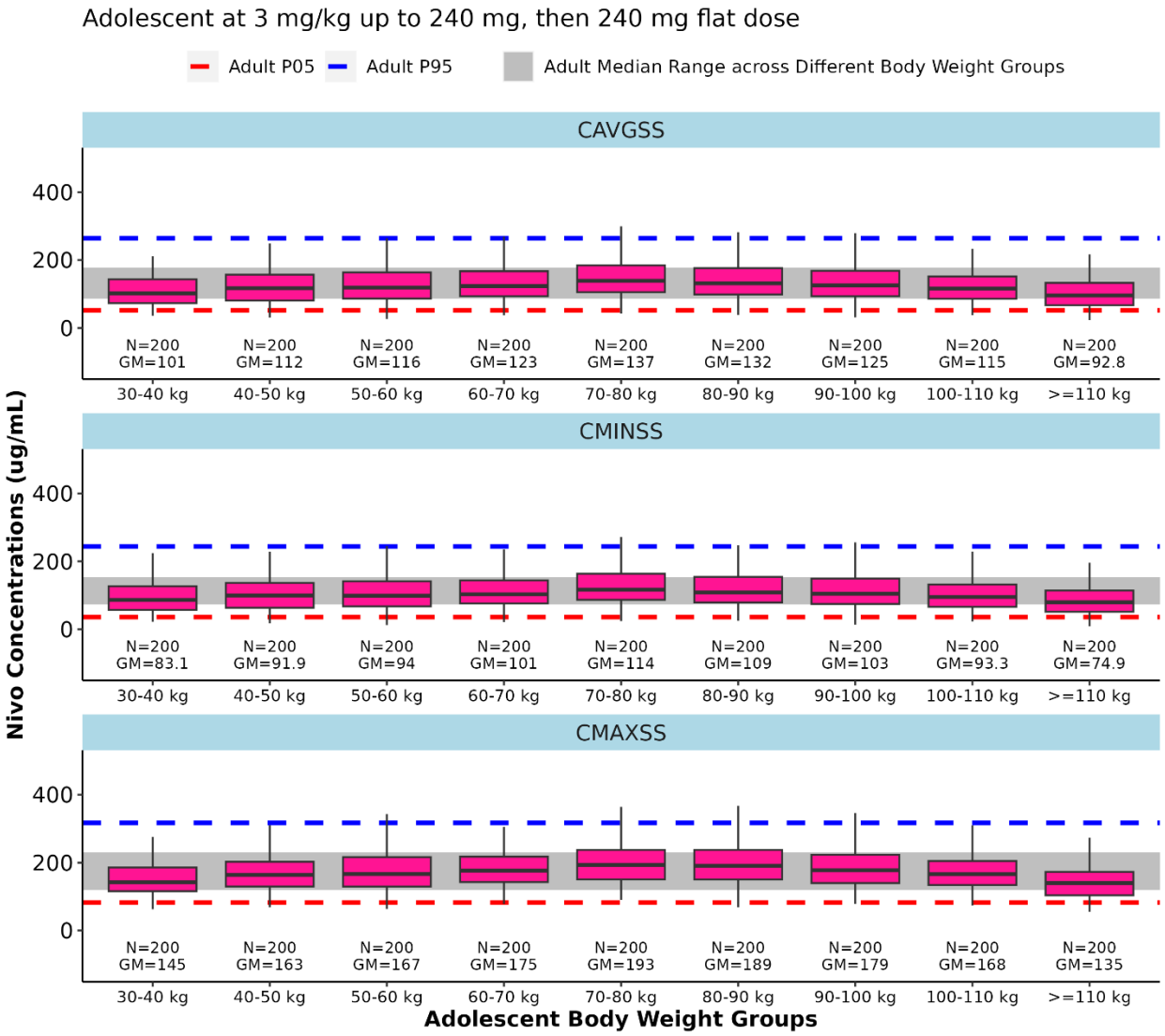
Study	Design/ Primary Objective and Secondary Objectives	No. Randomised/Treated/Eligible Subjects	Population	Regimen and Dose	Study Status
Pivotal Phase 3 Study Supporting Efficacy and Safety					
CA2098UT	Multicentre, randomised, open-label, Phase 3 study of N-AVD vs BV-AVD **Primary objective**: To compare PFS (per INV) in Arm 1 (N-AVD) vs Arm 2 (BV-AVD) **Secondary efficacy objectives**: To compare OS, EFS, CMR rate (by the end of treatment) in Arm 1 (N-AVD) vs Arm 2 (BV-AVD) To compare physician-reported treatment-related AE rates in Arm 1 (N-AVD) vs Arm 2 (BV-AVD) To compare safety and tolerability in Arm 1 (N-AVD) vs Arm 2 (BV-AVD) To compare patient-reported symptoms using selected PRO-CTCAE items in Arm 1 (N-AVD) vs Arm 2 (BV-AVD)	**Arm 1 (N-AVD):** 496/490/470 **Arm 2 (BV-AVD):** 498/490/470	Subjects (age ≥12 years) with newly diagnosed, previously untreated Stage III/IV cHL.	Study treatment was administered on days 1 and 15 of each cycle of 28 days for 6 cycles. **Arm 1 (N-AVD):** **Nivolumab:** 240 mg IV Q2W in subjects ≥18 years. 3 mg/kg (up to 240 mg max) IV Q2W in subjects aged 12 – 17 **Doxorubicin:** 25 mg/m^2 IV **Vinblastine:** 6 mg/m^2 IV **Dacarbazine:** 375 mg/m^2 IV **Arm 2 (BV-AVD):** **BV:** 1.2 mg/kg (max dose 120 mg) IV Q2W Regimen for doxorubicin, vinblastine, and dacarbazine same as in Arm 1. G-CSF (Pegfilgrastim: Adults or paediatric patients ≥ 45 kg: 6 mg paediatric patients < 45 kg: 0.1 g/kg or dose per institutional standards OR Filgrastim: 5mcg/kg per day) was required for patients receiving BV-AVD.	Ongoing. Data cutoff for PFS 51% IF: 15-Dec-2022; DBL: 21-May-2025 minimum follow-up 2.4 months, for efficacy analysis. Longer follow-up data cutoff for PFS 71% IF: 24-Mar-2024; DBL: 21-May-2025, minimum follow-up 17.6 months, for efficacy, safety and other analyses. Limited number of outputs were generated based on an additional data cutoff for PFS 75% IF: 15-Apr-2025; DBL: 05-Aug-2025, minimum follow-up 30.4 months

2.3.2. Pharmacokinetics

PK and immunogenicity data were not collected in the pivotal CA2098UT study. In study CA2098UT, 24.1% of subjects were adolescents (≥12 and <18 years of age). Adults were dosed 240 mg Q2W and adolescents <80kg were dosed 3 mg/kg Q2W and adolescents ≥ 80kg were dosed 240 mg Q2W.

A previously conducted popPK analysis in paediatric and adult subjects with advanced melanoma, other advanced solid tumours, haematological malignancies, and CNS tumours was used for this purpose. This model has been described in detail in procedure EMEA/H/C/003985/II/0125/G supporting the dosing regimen for treatment of adolescents with melanoma. This popPK model included nivolumab PK data from 274 subjects with HL including 46 paediatric subjects. Results showed that adolescent exposures for nivolumab at steady state are comparable to adult exposures. Simulations for the dosing regimen applied in study CA2098UT are shown in **Figure 1**.

Figure 1. Predicted nivolumab exposures for adolescents with Hodgkin Lymphoma at 3 mg/kg up to 240 mg Q2W nivolumab monotherapy



A modelling and simulation-based approach was also used to determine if a flat dosing regimen could be recommended for adolescents (from 12 to < 18 years of age) with cHL weighing ≥ 50 kg rather than implementing a weight cut-off of ≥ 80 kg as was evaluated in CA2098UT.

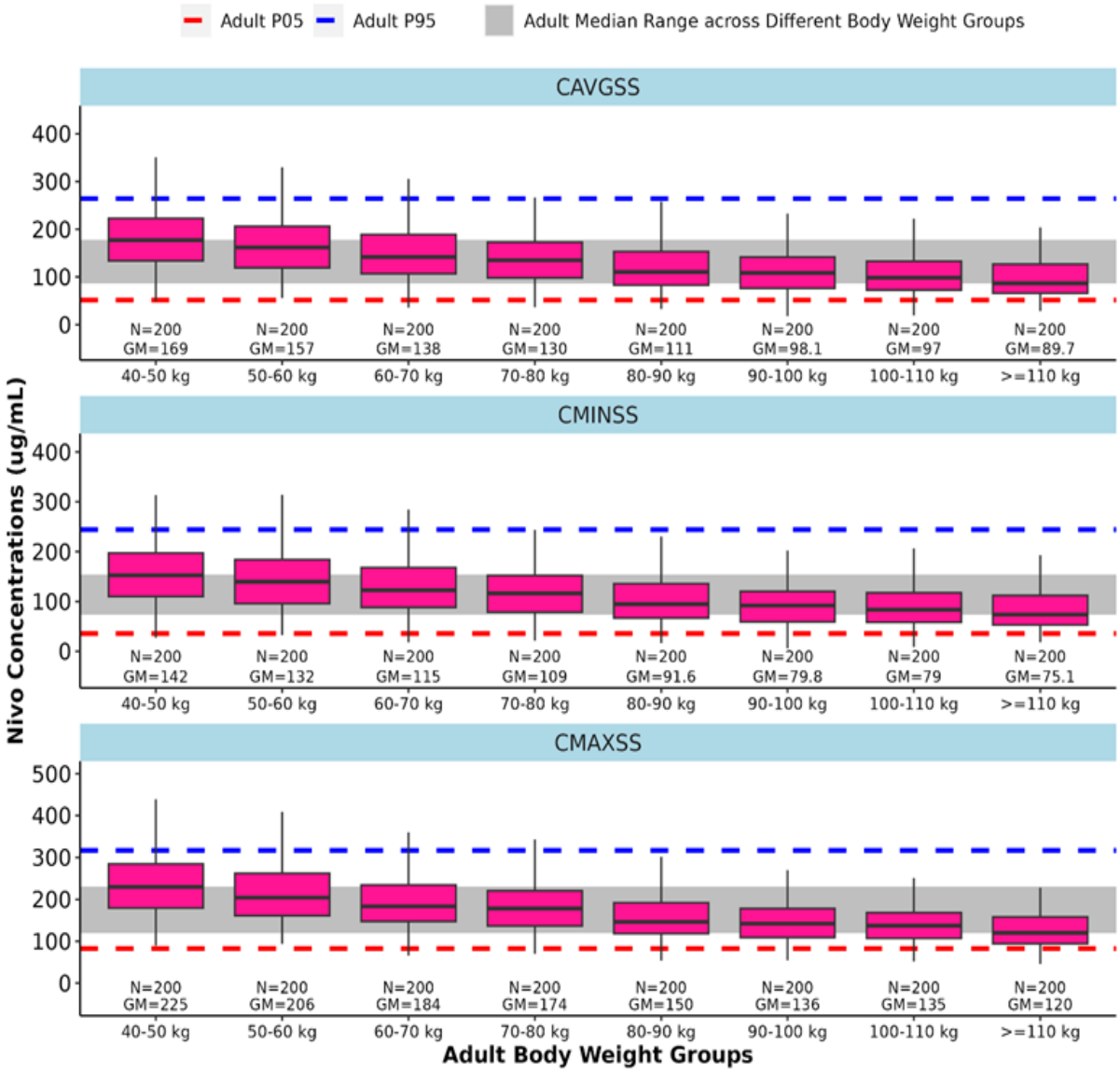
Stochastic simulations were performed using an adolescent population created by random sampling from the NHANES database (2017-2018). The adolescent population included 800 subjects of ages ≥ 12 to < 18 years with body weight, lean body mass (estimated based on height, weight, sex and age), sex, and race information. To ensure sufficient subjects were included in each body weight category (e.g., 30-40 kg), 800 subjects were sampled from the database. Due to the age dependency of baseline eGFR values, the median baseline eGFR of adolescent subjects included in the popPK analysis was used in the simulation.

Another population of adult HL subjects (N = 250) was created by random sampling from the included adult HL subjects. Due to the small number of subjects in certain weight groups (e.g., N = 18 at adult subjects 40-50 kg), all the stochastic simulations were performed 100 times, and the repeated simulations were treated as independent subjects. Two hundred subjects were randomly selected for

each body weight group of adolescents or adults, and then the nivolumab exposures were summarised using plots and tables.

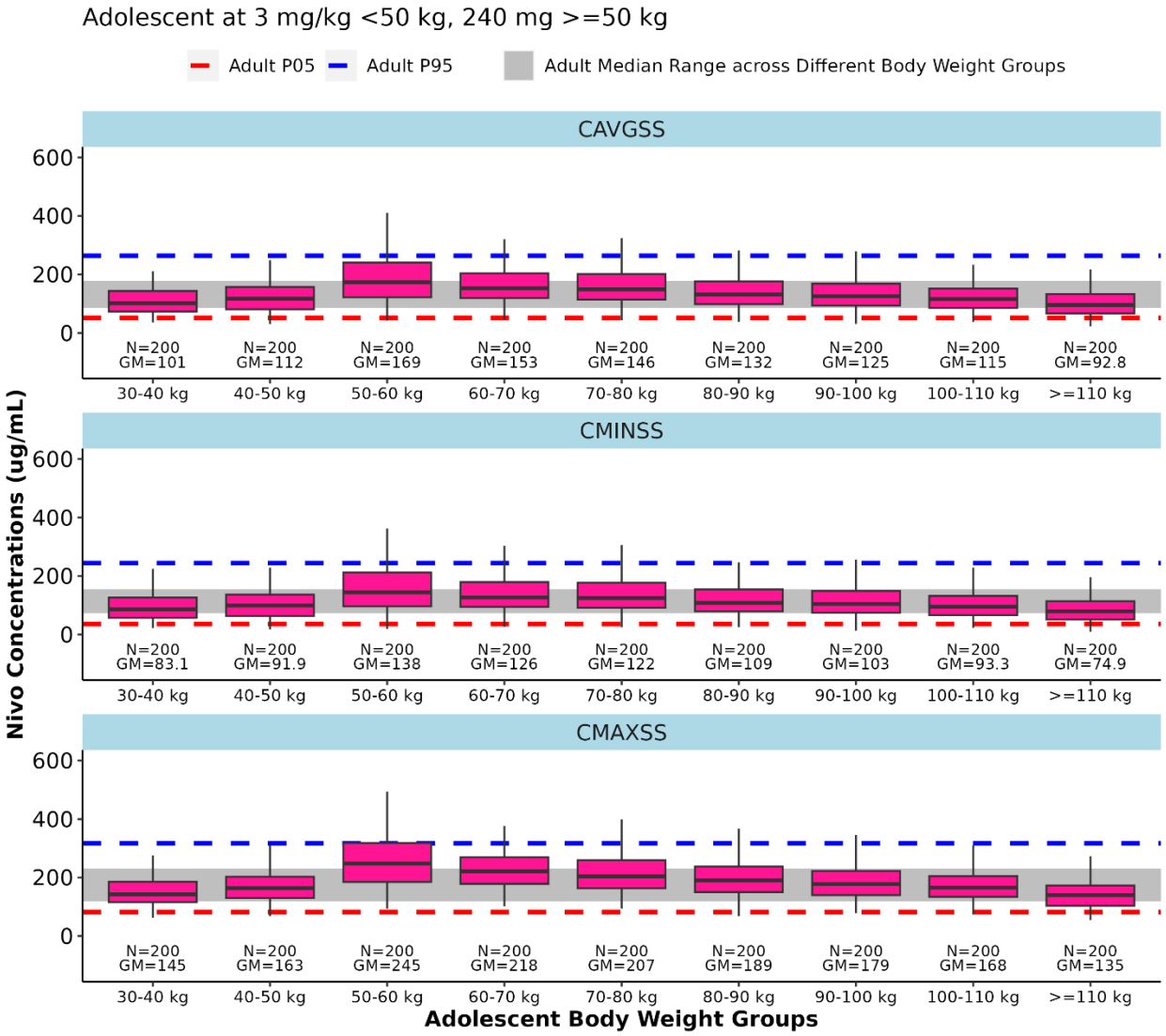
Simulations were performed to predict nivolumab PK in adolescent patients with HL. Steady-state exposures were simulated from the 20th dose of the nivolumab 240 mg IV Q2W regimen, representing exposures at ~1 year following the start of treatment. The simulated exposures by body weight groups for adults with HL following nivolumab 240 mg IV Q2W are presented in Figure 2. The simulated adult exposures were used to define the overall 5th and 95th percentiles of adult exposures (shown as dashed lines), as well as the range of median exposures across body weight groups (shown as a grey shaded area).

Figure 2. Simulated nivolumab exposures for adult Hodgkin lymphoma subjects at 240 mg IV Q2W monotherapy



The simulated exposures by body weight categories (10 kg increments) for adolescents with HL following 240 mg IV Q2W (≥ 50 kg) or 3 mg/kg IV Q2W (< 50 kg) are presented in Figure 3.

Figure 3. Simulated nivolumab exposures for adolescents with Hodgkin lymphoma at 3 mg/kg (< 50 kg) or 240 mg (≥50 kg) IV Q2W monotherapy



Nivolumab exposure measure summaries for adolescents treated with the recommended dosing regimens, and the exposure measures in adult HL patients treated with nivolumab 240 mg IV Q2W are shown in Table 1.

Table 1. Simulated nivolumab exposures for adolescents with HL at doses of 3 mg/kg < 50 kg, 240 mg ≥ 50 kg IV Q2W and adult HL subjects at 240 mg IV Q2W

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range (% Difference)	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
Cavgss	30-40	200	101(42.7)	NA	NA	NA	89.7-169
	40-50	200	112 (43.9)	Yes	200	169 (41.9)	
	50-60	200	169 (45.2)	Yes	200	157 (43.8)	
	60-70	200	153 (41.8)	Yes	200	138 (43)	
	70-80	200	146 (42.1)	Yes	200	130 (43.9)	
	80-90	200	132 (39.8)	Yes	200	111 (45.6)	

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range (% Difference)	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
	90-100	200	125 (41.2)	Yes	200	98.1 (43.7)	
	100-110	200	115 (45.1)	Yes	200	97 (43.9)	
	≥ 110	200	92.8 (45.9)	Yes	200	89.7 (39.7)	
Cminss	30-40	200	83.1 (49.5)	NA	NA	NA	75.1-142
	40-50	200	91.9 (51)	Yes	200	142 (48)	
	50-60	200	138 (52.3)	Yes	200	132 (49.6)	
	60-70	200	126 (48.5)	Yes	200	115 (49.2)	
	70-80	200	122 (48.4)	Yes	200	109 (50.1)	
	80-90	200	109 (46)	Yes	200	91.6 (52.3)	
	90-100	200	103(47.7)	Yes	200	79.8 (50.5)	
	100-110	200	93.3(52.6)	Yes	200	79 (51.5)	
	≥ 110	200	74.9(53.3)	NO (-0.266%)	200	75.1 (45.9)	
Cmaxss	30-40	200	145 (33.7)	NA	NA	NA	120-225
	40-50	200	163 (34.2)	Yes	200	225 (34.2)	
	50-60	200	245 (35)	NO (8.89%)	200	206 (37)	
	60-70	200	218 (32.2)	Yes	200	184 (35)	
	70-80	200	207 (33.4)	Yes	200	174 (36.1)	
	80-90	200	189 (31.7)	Yes	200	150 (36.7)	
	90-100	200	179 (31.8)	Yes	200	136 (34.9)	
	100-110	200	168 (35.3)	Yes	200	135 (33.8)	
	≥ 110	200	135 (35.4)	Yes	200	120 (31.6)	

[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

2.3.3. Discussion on clinical pharmacology

PK and immunogenicity data were not collected for nivolumab and AVD in the pivotal CA2098UT study. This is considered acceptable because pharmacokinetics and immunogenicity of nivolumab are well known. Pharmacokinetics of nivolumab in adolescents and adults with HL have been evaluated previously by popPK analysis (procedure EMEA/H/C/003985/II/0125/G).

In study CA2098UT, a substantial part i.e. 24.1% of the included population were adolescents (≥12 and <18 years of age). Adults were dosed with nivolumab 240 mg Q2W and adolescents <80kg were dosed 3 mg/kg Q2W and adolescents ≥ 80kg were dosed 240 mg Q2W. No differences in efficacy and safety were apparent between adolescents and adults with cHL in study CA2098UT. In that respect the dosing as conducted in study CA2098UT is considered an acceptable dosing regimen for adults and adolescents.

The MAH proposed in this application a dosing regimen for adolescents using a different body-weight cut-off in adolescents of 50 kg, compared to the 80 kg cut-off used in study CA2098UT, based on model-based simulation analyses. The same popPK model was used previously to support the dosing of

treatment of adolescents with melanoma and included nivolumab PK data from 274 subjects with HL including 46 paediatric subjects.

The proposed dosing of 3 mg/kg Q2W up to 50 kg and 240 mg Q2W at ≥50 kg was selected because a flat dose may simplify prescribing and administration of the medicinal product for healthcare providers. With the proposed dosing adolescents weighing 50-80 kg would receive the flat 240 mg dose. Since most of the adolescents will weigh > 50 kg, this would result in a flat dose for most patients.

Further, the proposed dosing with a weight cut-off of 50 kg aligns with the dosing of nivolumab monotherapy or in combination with ipilimumab for treatment of adolescents with melanoma. However, the proposed dosing does not align with the recommended dosing in paediatric and adult patients for treatment of relapsed or refractory cHL in combination with brentuximab vedotin, where no weight cut-off values is included and a 3 mg/kg dosing is recommended. All in all, there is currently no consistency in nivolumab dosing for adolescents and it is agreed with the applicant that a certain consistency should be aimed for.

No PK data for nivolumab + AVD were included in the popPK model and for this model, it was assumed that AVD comedication has no effect on the pharmacokinetics of nivolumab. This assumption is considered reasonable since nivolumab is a monoclonal antibody and not likely subject to interactions.

The model-based simulation analyses showed that nivolumab exposures in adolescents are more closely matched to median adult nivolumab exposures with a weight cut-off value of 80 kg as applied in study CA2098UT than the proposed weight cut-off of 50 kg. The CHMP agreed that the proposed dosing with a cut-off at 50 kg would result in acceptable nivolumab exposures in adolescents considering the flat exposure-response relationships for efficacy and safety. However, as currently there is no consistency for dosing of nivolumab in paediatric population, the CHMP proposed to maintain the posology for adolescents as was conducted in study CA2098UT and this was accepted by the MAH.

The CHMP recommended that the MAH should explore harmonising the dosing of paediatric patients for the various indications in a future regulatory procedure.

2.3.4. Conclusions on clinical pharmacology

As no differences in efficacy and safety were noted between adolescent and adults with cHL in study CA2098UT, the dosing as conducted in study CA2098UT is considered an acceptable dosing regimen for adults and adolescents with cHL. Further support for this is provided by modelling and simulation analyses showing that the median and distribution of the PK in adolescents and adults is comparable with the applied dosing regimens in study CA2098UT.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were submitted.

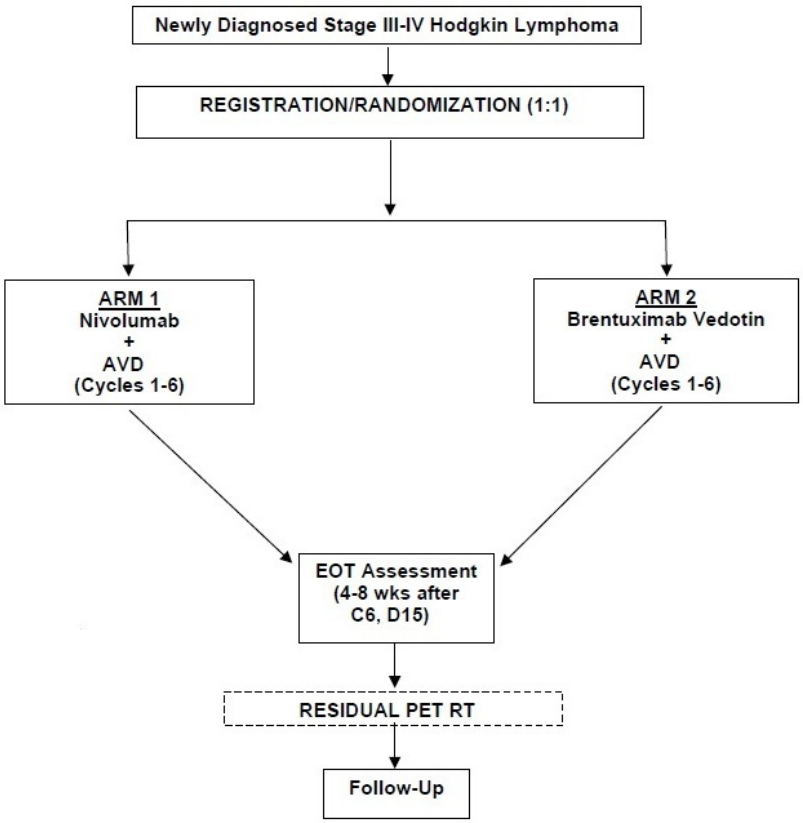
2.4.2. Main study

Study CA2098UT: A phase 3, randomised study of nivolumab (Opdivo) plus AVD or brentuximab vedotin (Adcetris) plus AVD in patients (age ≥12 years) with newly diagnosed, previously advanced stage classical Hodgkin lymphoma.

This study is sponsored by the National Cancer Institute (NCI) and executed by the SWOG Cancer Research Network (hereafter referred to as SWOG) for the National Clinical Trials Network (NCTN).

The study design is depicted in Figure 4.

Figure 4. Study Design Schema for Study CA2098UT



Methods

Study participants

Eligibility criteria

- Disease Related Criteria:
    - All patients must have histologically confirmed newly diagnosed, previously untreated Stage III or IV classical Hodgkin lymphoma (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or not otherwise specified (NOS)). Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible.

- Patients must have bidimensional measurable disease (at least one lesion with longest diameter ≥ 1.5 cm) documented on the Lymphoma Baseline Tumor Assessment Form in Rave.
- Patients must have a whole body or limited whole body PET-CT scan performed within 42 days prior to registration.

- Age criteria: Patients must be ≥12 years of age.
- Subjects did not receive any prior chemotherapy, radiation, or antibody-based treatment for cHL. Steroid pre-treatment was permitted. Subjects did not have prior solid organ transplant, prior allogeneic stem cell transplantation, and did not receive a live vaccine within 30 days prior to planned Day 1 of protocol therapy (e.g. measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid).
- Clinical/Laboratory Criteria:
  - Patients must have a performance status corresponding to Zubrod scores of 0, 1 or 2. Use Lansky for patients ≤17 years of age.
  - Renal function:
    - **Adults (age 18 or older):** Creatinine clearance ≥ 30 mL/min.
    - **Paediatric patients (age 12-17):** Measured or calculated creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m2, or Serum creatinine ≤ 1.5x institutional upper limit of normal (IULN), or a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
< 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
16 -17 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR *(96)* utilizing child length and stature data published by the CDC.
*calculated based on institutional standard

  - Patients must have adequate hepatic function, evidenced by the following*: Total bilirubin ≤2 x IULN, and AST and ALT ≤ 3x IULN * unless due to Gilbert's disease, lymphomatous involvement of liver or vanishing bile duct syndrome
  - Patients must have adequate cardiac function defined as follows: Patients must have an echocardiogram (ECHO), MUGA, or functional cardiac imaging scan with a left ventricular ejection (LVEF) ≥50% or a shortening fraction of ≥27%.
  - Patients with known human immunodeficiency virus (HIV) infection must be receiving anti-retroviral therapy and have an undetectable or unquantifiable viral load at their most recent viral load test within 6 months prior to registration.
  - Patients must not have known active Hepatitis B (HBV) or Hepatitis C Virus (HCV) at date of registration. Patients with previously treated HBV or HCV that have an undetectable viral load within 6 months prior to registration and no residual hepatic impairment are eligible.
  - Patients must not have any known central nervous system lymphoma.

- Patients must not have a history of or active interstitial pneumonitis or interstitial lung disease.
- Patients must not have had a diagnosis of inherited or acquired immunodeficiency.
- Patients must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to registration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Steroid use for the control of Hodgkin lymphoma symptoms is allowable, but must be discontinued prior to Cycle1, Day1.
- Patients with peripheral neuropathy must have < Grade 2 at date of registration.
- Patients must not have active autoimmune disease that has required systemic treatment in past 2 years.
- Females of childbearing potential must not be pregnant or nursing, and have a negative pregnancy test within 28 days prior to registration.

Treatments

The planned treatment duration in Study CA2098UT was 6 cycles of 28 days each, with study treatment administered on Days 1 and 15 of each cycle. The selection and timing of the dosing for Arm 1 and Arm 2 are presented below.

Table 2. Treatment Regimen in Arm 1 (N-AVD) of Study CA2098UT

Drug Product	Subjects	Dose	Route	Day	Schedule
Doxorubicin	All subjects	25 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Vinblastine	All subjects	6 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Dacarbazine	All subjects	375 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Nivolumab	Age 18 or older	240 mg	IV	Days 1 and 15	Every cycle x 6 cycles
Nivolumab	Age 12-17	3 mg/kg (up to 240 mg max)	IV	Days 1 and 15	Every cycle x 6 cycles

Table 3. Treatment Regimen in Arm 2 (BV-AVD) of Study CA2098UT

Drug Product	Dose	Route	Day	Schedule
Doxorubicin	25 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Vinblastine	6 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Dacarbazine	375 mg/m^2	IV	Days 1 and 15	Every cycle x 6 cycles
Brentuximab vedotin	1.2 mg/kg (max dose 120 mg)	IV	Days 1 and 15	Every cycle x 6 cycles

Drug Product	Dose	Route	Day	Schedule
G-CSF Pegfilgrastim OR Filgrastim	**Pegfilgrastim:** Adults or paediatric subjects ≥ 45 kg: 6 mg Paediatric subjects < 45 kg: 0.1 mg/kg or dose per institutional standards OR **Filgrastim:** 5mcg/kg per day	**Pegfilgrastim:** SubQ OR **Filgrastim:** SubQ or IV For subjects aged 12-17: SubQ is preferred.	**Pegfilgrastim:** All subjects: **D2 & D16.** On-body injector kit is allowable. OR **Filgrastim** All subjects: for 5 days (eg, Days 6 - 10, Days 21-25) but could be adjusted if more or less was needed, was required to be no less than 2 days between study treatment days, or in accordance with institutional procedure.	Every cycle x 6 cycles

The use of G-CSF was required for subjects in the BV-AVD arm as a prophylactic premedication as detailed in the Adcetris label and optional for subjects in the N-AVD arm. 481 (98.2%) subjects in the BV-AVD arm and 279 (56.9%) subjects in the N-AVD arm received G-CSF.

Dose escalation or reduction of nivolumab was not permitted. A higher proportion of subjects had dose reductions of doxorubicin, vinblastine and dacarbazine in the BV-AVD arm (4.9%, 10.8% and 4.1%, respectively) than in the N-AVD arm (2.2%, 3.9% and 3.5%, respectively).

The indication for radiotherapy (RT) will be based on the end-of-treatment imaging evaluation performed upon completion of 6 cycles of systemic therapy (4-8 weeks after the last dose of study drug). In general terms, RT will be delivered when patients have 1-2 sites initially involved with HL that achieve only a partial response and have a Deauville score of 4 or 5.

Objectives

Primary objective: To compare Progression free survival (PFS) per investigator (INV) in Arm 1 (N-AVD) vs Arm 2 (BV-AVD).

Secondary objectives:

a) To compare overall survival (OS) in patients randomised to N-AVD versus BV-AVD.

b) To compare event-free survival (EFS) in patients randomised to N-AVD versus BV-AVD.

c) To compare the metabolic complete response (CR) rate at the end of treatment in patients randomised to N-AVD versus BV-AVD.

d) To compare the physician-reported treatment-related adverse event rates between arms stratified by age groups.

e) To compare patient-reported symptoms using selected PRO-CTCAE items between arms stratified by age groups.

f) To compare the safety and tolerability of N-AVD versus that of BV-AVD.

Outcomes/endpoints

The primary endpoint was PFS per INV. There were 3 definitions for PFS:

- Primary definition (Protocol definition): time from date of randomisation to date of first observation per INV assessment of progressive disease according to the 2014 Lugano classification, or death due to any cause, whichever occurred first. Subjects without a PFS event at the time of analysis were censored at the last known alive date. This definition did not censor on subsequent anti-cancer therapy nor missing two or more consecutive scheduled assessments.
- Secondary definition: Similar to the primary definition, however, this definition censored for subsequent anti-cancer therapy. This is a sensitivity analysis.
- Alternative definition: Similar to the secondary definition, however, this definition was also censored for missing two or more consecutive scheduled assessments. This is a sensitivity analysis

PET-CT response assessment

Primary response assessment by PET-CT must occur 4-8 weeks after Cycle 6, Day 15 or at time of end-of-treatment in event that protocol treatment is discontinued early (for any reason), whichever occurs first.

Although it has been a standard of care to perform interim PET-CT scans (e.g. after Cycle 2), in patients with HL undergoing initial treatment, CA2098UTprotocol treatment is NOT intended to be PET response-adapted therapy. For this reason, interim PET-CT scans are not required per protocol unless the investigator declared (at the time of patient registration) intent-to-treat with radiation therapy according to protocol guidelines.

BICR-assessed PFS analysis:

- A sensitivity analysis was performed on PFS events assessed by IRC and will follow the same methodology as PFS per INV.

The secondary endpoint OS is defined from date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

The secondary endpoint EFS (per INV) is defined from date of registration to date of first occurrence of EFS event. Patients last known to be alive and without EFS event are censored at date of last contact.

EFS events are defined as:

- Disease progression/relapse.
- Administration of non-protocol specified systemic anti-lymphoma therapy (i.e. salvage therapy) at any time after initiation of protocol therapy.

    o Administration of non-protocol specified systemic anti-lymphoma therapy for residual or relapsed Hodgkin lymphoma (whether or not confirmed by biopsy) in the absence of formal progression of disease according to the Lugano classification

- Administration of any non-protocol specified radiation therapy at any time after initiation of protocol therapy:

    o Administration of radiation therapy in a patient who was not declared eligible for radiation therapy at registration

    o Administration of radiation in a patient who was declared eligible for radiation therapy but does not meet protocol-specified criteria for use of radiation.

There were two definitions for EFS:

- Primary: from date of randomisation to date of first occurrence of any event of disease progression/relapse per investigator assessment, administration of non-protocol specified systemic anti-lymphoma therapy, administration of non-protocol specified RT therapy, or
- Alternative: similar to the primary definition, however, this definition censored for subsequent anti-cancer therapy or missing two or more consecutive scheduled assessments.

The secondary endpoint CMR per INV is defined as the number of participants who achieve CMR by the end of treatment divided by the total number of subjects randomised to each arm using 2014 Lugano classification.

Sample size

Based on previous data, the 2-year PFS for BV-AVD arm (Arm 2) was estimated to be approximately 84%. Prior PFS data in patients with advanced stage Hodgkin lymphoma indicates that a proportion of patients may be long-term non-progressing patients. An exponential cure rate model is assumed for both arms with 70% long term non-progressing patients on the BV-AVD arm (Arm 2) and 74% on the N-AVD arm (Arm 1). In addition, among the fraction of patients with risk of disease progression, a hazard ratio of 1.67 is assumed between the arms.

The PFS model is as follows: PFS at year t is equal to $0.70+0.30\times\exp(-0.38t)$ for the BV-AVD arm (Arm 2), and $0.74+ 0.26\times\exp(-0.38t/1.67)$ for the N-AVD arm (Arm 1).

The power calculations are based on log-rank testing of simulated data sets from the survival cure models described above. At the end of the study, this corresponds to an average hazard ratio (based on 10,000 simulated hazard ratios from the Cox model) of 1.58.

940 eligible patients are expected to be accrued over 4 years with a total of 987 patients assuming an expected ineligible rate of 5% (6% of enrolled patients were deemed ineligible based on central pathology review of SWOG study S0816). The analysis is event-based and planned to occur after achieving 179 events across arms, which will be reached after approximately 2 additional years of follow-up from the last randomised patients. The power to detect a change in PFS corresponding to a 2-year PFS in the BV-AVD arm (Arm 2) of 84% versus 86% in the N-AVD arm (Arm 1). The power calculations assume uniform patient entry and a one-sided stratified log-rank test at 2.5% significance level.

The following justifications of sample size relate to secondary endpoints.

- Based on previous data, the estimated 2-year OS in the BV-AVD arm (Arm 2) was 96%. Assuming that OS in the N-AVD arm (Arm 1) will follow an exponential distribution, with 4 years of accrual, 2 additional years of follow-up and a total of 61 deaths by end of study, a stratified log-rank test at a two-sided α-level of 0.05 will have 90% power to detect a hazard

ratio of 2.8 (corresponding to an improvement in the 2-year OS from 96% in the BV-AVD arm [Arm 2] to 98.5% in the N-AVD arm [Arm 1]).

- Based on an estimated 2-year modified EFS of 82% in the BV-AVD arm (Arm 2), and an average hazard ratio 1.54 at least 195 events could be anticipated under the alternative hypothesis. With 940 eligible patients, the log of hazard ratio can be estimated to within ± 0.28 (95% confidence).

Randomisation

Patients were randomised to either Arm 1 (N-AVD) or Arm 2 (BV-AVD) in a 1:1 ratio. Randomisation into treatment arms was stratified by:

- Age (years): 12-17 vs 18-60 vs > 60.
- IPS: 0-3 vs 4-7.
- Pre-specified plan to use Residual PET Radiation Therapy (Residual PET-RT): yes vs no.

Blinding (masking)

This is an open-label study. However, blinded independent central review (BICR) by Imaging and Radiation Oncology Core (IROC) of the primary endpoint (PFS) and any review of aggregate study data by SWOG and the MAH study team were performed in a blinded manner before any treatment unblinding.

Statistical methods

In the original protocol and kept throughout the trial, efficacy interim analyses (IA) were prespecified for PFS at 50% (IA2) and 75% (IA3) of the planned 179 PFS events. IA1 was for futility only; the other IAs could also suggest to stop the trial for futility. For efficacy interim analyses a modified Haybittle rule was used (0.005 for IA2 and IA3, 0.021 for the final analysis at 100% of 179 PFS events).

Time to event endpoints (PFS, OS, EFS) were compared via stratified log-rank test on randomised population. The hazard ratio between treatment arms and its corresponding two-sided (100(1-[2*α])% CI) was estimated using a stratified Cox proportional hazards model, with treatment as a factor and age, international prognostic score and pre-specified plan to use residual PET-RT as stratification factors. Kaplan-Meier methods were used to estimate and display the survival function for each treatment group. Two-sided 95% CI for median PFS were derived from the KM estimate and corresponding CIs were derived based on Greenwood's formula for variance derivation and the log-log transformation applied on the survival function.

CMR was compared between arms (nominal p-value) and difference between arms was estimated with the stratified Cochran-Mantel-Haenszel test adjusted for the stratification factors. CMR rate will be reported based on the randomised population. Patients with missing CMR assessment by end of treatment will be treated as non-responders. All CMR assessments after study treatment discontinuation will be included in the analysis.

Results

Participant flow

Overall, 994 subjects were enrolled and randomised (496 to the N-AVD arm and 498 to the BV-AVD arm) at 256 sites in 2 countries. Of the 994 randomised subjects, 980 subjects were treated (490 in the N-AVD arm and 490 in the BV-AVD arm, the subject disposition is presented per 51% IF (IA2) and 71% IF (Table 4; Table 5).

Table 4. Subject Disposition in Study CA2098UT (15-Dec-2022 Data Cutoff)

Status (%)	N-AVD N = 490	BV-AVD N = 490
ONGOING TREATMENT	60 (12.2)	55 (11.2)
COMPLETED TREATMENT	398 (81.2)	382 (78.0)
DISCONTINUED TREATMENT	32 (6.5)	53 (10.8)
REASON FOR DISCONTINUATION OF TREATMENT		
ADVERSE EVENT	19 (3.9)	14 (2.9)
PATIENT WITHDRAWAL	6 (1.2)	13 (2.7)
DISEASE PROGRESSION	0	8 (1.6)
DEATH	2 (0.4)	6 (1.2)
OTHER	5 (1.0)	12 (2.4)
ONGOING STUDY	480 (98.0)	466 (95.1)
DISCONTINUED STUDY	10 (2.0)	24 (4.9)
REASON FOR DISCONTINUATION OF STUDY		
PATIENT LOST TO FOLLOW-UP	3 (0.6)	1 (0.2)
PATIENT REFUSED FOLLOW-UP	3 (0.6)	10 (2.0)
DEATH	3 (0.6)	11 (2.2)
OTHER	1 (0.2)	2 (0.4)

Table 5. Subject Disposition in Study CA2098UT (24-Mar-2024 Data Cutoff)

Status (%)	N-AVD N = 490	BV-AVD N = 490
ONGOING TREATMENT	0	0
COMPLETED TREATMENT	455 (92.9)	435 (88.8)
DISCONTINUED TREATMENT	35 (7.1)	55 (11.2)
REASON FOR DISCONTINUATION OF TREATMENT		
ADVERSE EVENT	19 (3.9)	15 (3.1)
PATIENT WITHDRAWAL	9 (1.8)	14 (2.9)
DISEASE PROGRESSION	0	8 (1.6)
DEATH	2 (0.4)	6 (1.2)
OTHER	5 (1.0)	12 (2.4)
ONGOING STUDY	467 (95.3)	456 (93.1)
DISCONTINUED STUDY	23 (4.7)	34 (6.9)
REASON FOR DISCONTINUATION OF STUDY		
PATIENT LOST TO FOLLOW-UP	4 (0.8)	1 (0.2)
PATIENT REFUSED FOLLOW-UP	7 (1.4)	15 (3.1)
DEATH	7 (1.4)	14 (2.9)

Status (%)	N-AVD N = 490	BV-AVD N = 490
OTHER	5 (1.0)	4 (0.8)

Recruitment

Study start date: 29 August 2019 (First patient Randomised Date).

Data cut-off date for final report: 24-May-2024.

Conduct of the study

The original protocol for this study was dated 08-May-2019. As of the 24-Mar-2024 data cutoff date, there were a total of 6 global revisions (Table 6).

Table 6. Summary of Key Changes to Protocol of study CA2098UT

Document (Amendment)/Date	Summary of Key Changes
Original Protocol dated 08-May-2019	N/A
Protocol Amendment 01 dated 27-Jan-2021	Amendment clarified questions pertaining to eligibility, treatment, institutional standards for dose rounding, dose modifications, definition of PFS used in analysis and scheduled protocol assessments. In addition, it incorporated guidance for conduct during the COVID-19 pandemic, and incorporated CCTG participation
Protocol Amendment 02 dated 11-Mar-2021	Revised Comprehensive Adverse Events and Potential Risks list (CAEPR, Version 2.4, December 2, 2020) for nivolumab has been inserted in the protocol, and the associated risk information in the informed consent documents has been revised.
Protocol Amendment 03 dated 07-Apr-2021	Amended to include additional signature lines on the Consent Addendum.
Protocol Amendment 04 dated 05-Oct-2022	Revised to include a new translational medicine study on banked Circulating Tumour DNA specimen. An appendix section was added to include the Circulating Tumour DNA (ctDNA) Translational Medicine component.
Protocol Amendment 05 dated 07-Aug-2023	Revised Comprehensive Adverse Events and Potential Risks list (CAEPR, Version 2.5, June 10, 2023) for nivolumab has been inserted in the protocol, and the associated risk information in the informed consent documents has been revised.
Protocol Amendment 06 dated 02-Sep-2023	Allow for the submission of two additional, previously collected, scans based on protocol defined specifications. Additionally, eligibility criteria for inclusion in primary and secondary analyses based on the completion of PRO instruments have been clarified.

SWOG identified and informed BMS of 13 treatment-related major protocol deviations which have occurred in Study CA2098UT. BMS has classified these deviations as important protocol deviations (IPDs). IPDs are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being (Table 7).

Table 7. Summary of important Protocol Deviations in study CA2098UT - All Randomised Subjects

Category	N-AVD N = 496	BV-AVD N = 498	Total N = 994
Subjects with at Least 1 Important Deviation	**5 (1.0)**	**8 (1.6)**	**13 (1.3)**
Discontinuation	4 (0.8)	6 (1.2)	10 (1.0)
Inclusion/Exclusion Criteria	1 (0.2)	2 (0.4)	3 (0.3)

Note: Other non-important protocol deviations are held at study sites per SWOG SOP.

Changes to planned analysis

Table 8. Changes of key methodological and statistical aspects in study CA2098UT

	Original protocol (8 May 2019) (unchanged into last protocol version 6, 2 September 2023)	**SAP v1 (BMS) (18 November 2022) i.e. clarification of own analyses.**	**FDA requests and FDA requested analyses 27 May 2021 (provided as additional analysis in SAP v1).**	**Other/later unplanned changes**
PFS censoring rules	Censoring: 1) Patients last known to be alive and without report of progression are censored at date of last contact. ("primary definition" in CSR)	Censoring for: 1) incomplete or no baseline assessment and no death in the study => baseline censoring 2) no evaluable assessments on study and no death=> baseline censoring 3) no disease progression and no death => date of last contact (elaboration of "primary definition")	Censoring as for BMS and for: 4) unplanned anti-cancer therapy (including consolidative RT*) prior to death or documented progression* => last adequate assessment before or on start. ("secondary definition" in amendment 6) 5) two or more missed assessments => last adequate assessment before. ("alternative definition" in CSR)	CSR (dated 29-SEPT-2025) Alternative definition PFS analysis not performed (as not in line with primary estimand PFS) "Secondary definition of PFS" added: like the 'primary definition' but with censoring of anti-cancer therapy.

PFS additional analyses	1) PFS sensitivity analysis with PFS censored/not-censored at start non-protocol therapy ("secondary definition" in CSR: censoring for subsequent anti-cancer therapy)	As protocol and: 2) restricted mean survival time if serious time by treatment interaction in Cox regression 3) multivariate stratified Cox regression adjusted for sex, race, stage at diagnosis, disease symptoms, ECOG 4) interaction test in stratified Cox model for the factors as used for adjusted Cox regression and additionally age, international prognostic score, prespecified use of residual PET radiotherapy	5) re-randomisation p-value 6) PFS assessed by IRC on a random sample of 50%; concordance rate and cross-tabulation of PFS by IRC and inv.; If disconcordance < 25% then PFS per inv. as primary analysis, otherwise additional patients should be analysed by IRC	
PFS by IRC		Independent central review of PFS and any review of aggregate study data by SWOG and BMS team. Sample of 50% from the randomised patients initially proposed by BMS	Minimal FDA requirement: audit of random sample with PFS per IRC to assess concordance between PFS per inv. and PFS per IRC	FDA requirement per 17-MAY-2024: IRC review of all all images of all patients (both at 15-Dec-2022 and 24-Mar-2024 data cutoffs)

EFS events	a) disease progression/relapse b) death c) non-protocol specified systemic therapy or radiation after initiation of protocol therapy. * systemic anti-lymphoma therapy for residual or relapsed Hodgkin lymphoma (whether or not confirmed by biopsy) in the absence of formal Lugano progression of disease * radiation therapy in a patient who was not declared eligible for radiation therapy at registration * radiation therapy in a patient who was declared eligible for radiation therapy but does not meet protocol-specified criteria for use of radiation ("primary definition" in CSR)		Alternative definition required by FDA: events are: a) disease progression/relapse per investigator b) death c) an efficacy reason by inv, other than disease progression/relapse that leads to start any non-protocol new anti-lymphoma treatment (for instance imaging, physical finding or test suggestive of residual disease). Event date is the date of the finding, not the NALT date	CSR (dated 29-SEPT-2025) similar to the primary definition in CSR but as extra events: c) (see FDA) d) biopsy-proven residual disease ("Alternative definition" in CSR)
EFS censoring	Censoring: Patients last known to be alive and without EFS event are censored at date of last contact.	Censoring for: 1) incomplete or no baseline assessment and no death in the study => baseline censoring 2) no evaluable assessments on study and no death=> baseline censoring 3) no disease progression/relapse, anti-lymphoma therapy, non-protocol specified RT, and no death => date of last contact ("primary definition" in CSR)	Censoring as BMS 1), 2) but: 3) => 3)': no EFS events and not missing more than 1 planned assessments. 4) missing more than 1 planned assessments	Censoring 1), 2), 3) and 4) ("Alternative definition" in CSR)
CMR		Stratified CMH-test and difference estimate; If CMR missing at end of treatment: non-response	Missing two or more consecutive scheduled assessments: non-responder	

Primary	Randomised eligible (to verify for histologic diagnosis by retrospective central pathology review)	All randomised (to keep covariate balance)	All randomised and Sensitivity analysis on the randomised eligible patients	
Multiple testing	No multiple testing strategy across primary and (some of) the secondary outcomes prespecified	OS hierarchically tested once after PFS ()	Missing information on whether and which secondary endpoints are formally tested should be provided	
Group seq. l testing	Only critical p-values prespecified for superiority testing PFS. IA 1 (25% of 179 PFS events): N/A IA 2 (50% of 179): 0.005 IA 3 (75% of 179): 0.005 FA (100% of 179): 0.021	Critical values clarified as from modified Haybittle group sequental testing	Missing information which group-sequential test is used should be provided	CSR (dated 29-SEPT-2025): follow-up analysis at 71% (24-MAR-2024) instead of 75% of 179 events, because event rate slowed down; waiting for 75% (7 more events) would take 1 year longer; plus 15 months follow-up available.
	Dynamic balancing randomisation scheme		Re-randomisation p-values requested for stratified tests (PFS, EFS, CMR, OS)	
	Cure model: 0.70+0.30*exp(-0.38t) BV-AVD 0.74+ .26*exp (-.38t/1.67) N-AVD used for sample size		In analysis: use mixture cure model to estimate: * cure rate/fraction * HR in uncured patients	Only performed on 15-APR-2025 due to need of sufficient follow-up for estimating cure rates
Estimand			Implementation of FDA Estimands	

Primary analysis is based on a preplanned IA2 of the primary endpoint of PFS for N-AVD vs BV-AVD in subjects with cHL. The pre-specified IA2 PFS analysis was at 51% information fraction (IF) (instead of 50% IF per protocol) as it was based on the same data cutoff date used by SWOG for their 50% IF PFS original analysis, the slight difference is due to the slightly different populations and additional data cleaning after the SWOG/DMC analysis.

Additional data are also presented with a longer-FU analysis using the 24-Mar-2024 clinical data cutoff corresponding to a minimum follow-up of 17.6 months and a median follow-up of 29.0 months (median of the time from randomisation to last known alive date) at 71% IF.

For a more comprehensive assessment of long-term benefit, even if descriptive, the MAH also included additional 75% PFS IF data from a later data cutoff with a minimum follow up of 30.4 months (cutoff: 15-Apr-2025; DBL: 05-Aug-2025).

Baseline data

Overall, 994 subjects were enrolled and randomised at 256 sites in 2 countries. Baseline characteristics are summarised in Table **9**-Table **11**.

Table 9. Demographic Characteristics Summary in study CA2098UT - All Randomised Subjects

	N-AVD N = 496	BV-AVD N = 498	Total N = 994
AGE (YEARS)			
N	496	498	994
MEAN	31.9	31.6	31.8
MEDIAN	27.0	26.0	27.0
MIN, MAX	12, 83	12, 81	12, 83
Q1, Q3	18.0, 43.0	18.0, 42.0	18.0, 42.0
SD	17.20	16.92	17.05
AGE CATEGORIZATION (%)			
>= 12 AND < 18	120 (24.2)	120 (24.1)	240 (24.1)
>= 18 AND <= 60	326 (65.7)	329 (66.1)	655 (65.9)
> 60	50 (10.1)	49 (9.8)	99 (10.0)
AGE CATEGORIZATION (%)			
< 65	465 (93.8)	469 (94.2)	934 (94.0)
>= 65	31 (6.3)	29 (5.8)	60 (6.0)
SEX (%)			
MALE	276 (55.6)	280 (56.2)	556 (55.9)
FEMALE	220 (44.4)	218 (43.8)	438 (44.1)
RACE (%)			
AMERICAN INDIAN OR ALASKA NATIVE	3 (0.6)	1 (0.2)	4 (0.4)
ASIAN	12 (2.4)	18 (3.6)	30 (3.0)
BLACK OR AFRICAN AMERICAN	59 (11.9)	60 (12.0)	119 (12.0)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.2)	1 (0.2)	2 (0.2)
WHITE	379 (76.4)	369 (74.1)	748 (75.3)
UNKNOWN	40 (8.1)	42 (8.4)	82 (8.2)
OTHER	2 (0.4)	7 (1.4)	9 (0.9)
ETHNICITY (%)			
HISPANIC OR LATINO	68 (13.7)	59 (11.8)	127 (12.8)
NOT HISPANIC OR LATINO	401 (80.8)	413 (82.9)	814 (81.9)
UNKNOWN	27 (5.4)	26 (5.2)	53 (5.3)
REGION (%)			
US	480 (96.8)	484 (97.2)	964 (97.0)
CANADA	16 (3.2)	14 (2.8)	30 (3.0)

Table 10. Baseline Disease Characteristics Summary in study CA2098UT - All Randomised Subjects

	N-AVD N = 496	BV-AVD N 498	Total N = 994
IPS			
0 - 3	338 (68.1)	338 (67.9)	676 (68.0)
4 - 7	158 (31.9)	160 (32.1)	318 (32.0)
PLANNED USE OF RESIDUAL PET-RT			
YES	291 (58.7)	292 (58.6)	583 (58.7)
NO	205 (41.3)	206 (41.4)	411 (41.3)

	N-AVD N = 496	BV-AVD N 498	Total N = 994
BULKY DISEASE			
YES	157 (31.7)	132 (26.5)	289 (29.1)
NO	339 (68.3)	366 (73.5)	705 (70.9)
BASELINE WEIGHT (KG)			
N	495	498	993
MEAN	77.83	77.90	77.87
MEDIAN	74.70	73.35	74.10
MIN, MAX	27.4, 177.8	24.8, 223.8	24.8, 223.8
Q1, Q3	60.50, 92.10	61.10, 89.60	60.90, 90.90
SD	23.654	24.343	23.990
BASELINE HEIGHT (CM)			
N	494	496	990
MEAN	170.87	171.65	171.26
MEDIAN	171.00	172.45	172.00
MIN, MAX	141.0, 198.1	133.0, 200.1	133.0, 200.1
Q1, Q3	163.00, 179.00	165.00, 178.70	163.50, 178.80
SD	10.705	10.115	10.416
BASELINE BMI (KG/M^2)			
N	494	496	990
MEAN	26.44	26.26	26.35
MEDIAN	25.14	24.82	24.99
MIN, MAX	13.2, 60.1	14.0, 75.0	13.2, 75.0
Q1, Q3	21.25, 30.37	21.22, 29.26	21.22, 29.92
SD	7.061	7.408	7.234
SYMPTOMS			
FEVER, WEIGHT LOSS, AND/OR NIGHT SWEATS	292 (58.9)	283 (56.8)	575 (57.8)
NO SYMPTOMS	204 (41.1)	215 (43.2)	419 (42.2)
TIME FROM INITIAL DISEASE DIAGNOSIS TO RANDOMISATION (YEARS)			
N	495	498	993
MEAN	0.07	0.07	0.07
MEDIAN	0.05	0.05	0.05
MIN, MAX	0.0, 1.2	0.0, 6.3	0.0, 6.3
Q1, Q3	0.03, 0.08	0.02, 0.08	0.03, 0.08
SD	0.108	0.286	0.216
STAGE OF DISEASE AT DIAGNOSIS			

	N-AVD N = 496	BV-AVD N 498	Total N = 994
STAGE III	188 (37.9)	171 (34.3)	359 (36.1)
STAGE IV	306 (61.7)	325 (65.3)	631 (63.5)
NOT REPORTED	2 (0.4)	2 (0.4)	4 (0.4)
HIV+			
YES	11 (2.2)	6 (1.2)	17 (1.7)
NO	485 (97.8)	492 (98.8)	977 (98.3)
PERFORMANCE STATUS (ECOG)			
0	274 (55.2)	287 (57.6)	561 (56.4)
1	192 (38.7)	189 (38.0)	381 (38.3)
2	30 (6.0)	22 (4.4)	52 (5.2)

Table 11. Summary of the Study Population by Age Category- All Randomised Subjects (Study CA2098UT)

	N-AVD N = 496	BV-AVD N = 498	Total N = 994
AGE CATEGORISATION (%)			
>=12 and < 18	120 (24.2)	120 (24.1)	240 (24.1)
>=18 and <=60	326 (65.7)	329 (66.1)	655 (65.9)
>60 and <=75	44 (8.9)	44 (8.8)	88 (8.9)
>75 and <=80	4 (0.8)	4 (0.8)	8 (0.8)
>80	2 (0.4)	1 (0.2)	3 (0.3)
>=12 and < 18	120 (24.2)	120 (24.1)	240 (24.1)
>=18 and <=60	326 (65.7)	329 (66.1)	655 (65.9)
>60 and <=75	44 (8.9)	44 (8.8)	88 (8.9)
>75	6 (1.2)	5 (1.0)	11 (1.1)

Numbers analysed

Table 12. Analysis Populations for Study CA2098UT

Population	N-AVD (Arm 1)	BV-AVD (Arm 2)	Total
Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number.	--	--	994
Randomised subjects (for Efficacy Analysis): All subjects who were randomised in the Oncology Patient Enrollment Network. Subjects were analysed according to the randomised treatment assignment ITT.	496	498	994

Population	N-AVD (Arm 1)	BV-AVD (Arm 2)	Total
Randomised Eligible subjects (for Sensitivity Analysis): All randomised subjects, eligible based on inclusion and exclusion criteria .	486	483	969
Treated subjects (for Safety Analysis): All randomised subjects who received at least one dose of study treatment.	490	490	980
All PRO-CTCAE Evaluable subjects: All subjects in the treated population with a valid PRO-CTCAE assessment at baseline and at least one valid post-baseline assessment.	456	442	898

Outcomes and estimation

The median duration of therapy was similar in the 2 treatment arms based on both 15-Dec-2022 data cutoff and 24-Mar-2024 data cutoff and most subjects received study drug for > 5 months (median 5.55 in both arms).

As of the 24-Mar-2024 cutoff, the median time to treatment discontinuation was 5.09 months in the N-AVD arm and 5.13 months in the BV-AVD arm. Most treated subjects in the N-AVD (range: 68.4% - 74.7%) and BV-AVD (range: 47.1% - 63.9%) arms received their study medication without any dose modification. The most common reason for dose modification was adverse event.

Table 13. PFS - All Randomised Subjects study CA2098UT (DCO 15-Dec-2022 and 24-Mar-2024)

	N-AVD N = 496	BV-AVD N = 498	N-AVD N = 496	BV-AVD N = 498
	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff	
Primary Endpoint				
PFS per Investigator, primary definition				
# Events/# Subjects, n/N (%)	28/496 (5.6)	62/498 (12.4)	43/496 (8.7)	83/498 (16.7)
Median PFS (95% CI), mo.[a]	N.A.	N.A.	N.A.	N.A.
HR[b] - Superiority Analysis	0.42		0.46	
(99% CI)	(0.24, 0.77)		N.A.	
(95% CI)	(0.27, 0.67)		(0.32, 0.67)	
P-value[c]	< 0.0001		N.A.	
Re-randomisation p-value[d]	< 0.0001		N.A.	
PFS rates* (95% CI), %[a]				
6 months	N.A.	N.A.	99.0 (97.6, 99.6)	96.3 (94.1, 97.6)
12 months	N.A.	N.A.	95.9 (93.7, 97.3)	85.4 (81.9, 88.3)
18 months	N.A.	N.A.	94.2 (91.7, 95.9)	83.9 (80.3, 86.9)

[a] Based on Kaplan-Meier estimates

[b] HR in N-AVD/BV-AVD

Figure 5. Kaplan-Meier Plot of Progression-free Survival per Investigator (Based on 15-Dec-2022 data cutoff), Primary Definition - All Randomised Subjects in Study CA2098UT

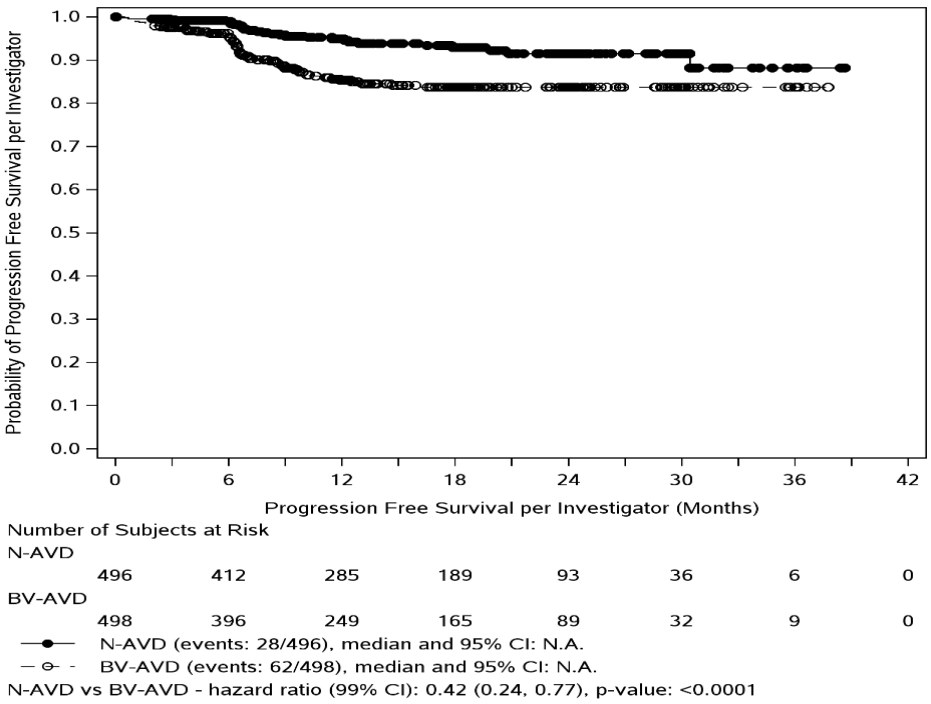


Table 14. PFS - All Randomised Subjects, study CA2098UT (DCO 15-Apr-2025)

	N-AVD N = 496	BV-AVD N = 498
Primary Endpoint		
PFS per Investigator, primary definition		
Events, n (%)	48/496 (9.7)	87/498 (17.5)
Median PFS (95% CI), mo.	N.A.	N.A.
HR (95% CI)[b]	0.49 (0.34, 0.70)	
PFS rates (95% CI), %[a]		
6 months	99.0 (97.6, 99.6)	96.3 (94.1, 97.6)
12 months	95.9 (93.7, 97.3)	85.4 (81.9, 88.3)
18 months	94.2 (91.8, 96.0)	83.9 (80.3, 86.9)
24 months	93.0 (90.3, 94.9)	83.5 (79.8, 86.5)
30 months	91.9 (89.1, 94.0)	83.0 (79.4, 86.1)

[a] Based on Kaplan-Meier estimates
[b] HR in N-AVD/BV-AVD

Figure 6. Kaplan-Meier Plot of Progression-free Survival per Investigator (Based on 15-Apr-2025 data cutoff), Primary Definition - All Randomised Subjects in Study CA2098UT

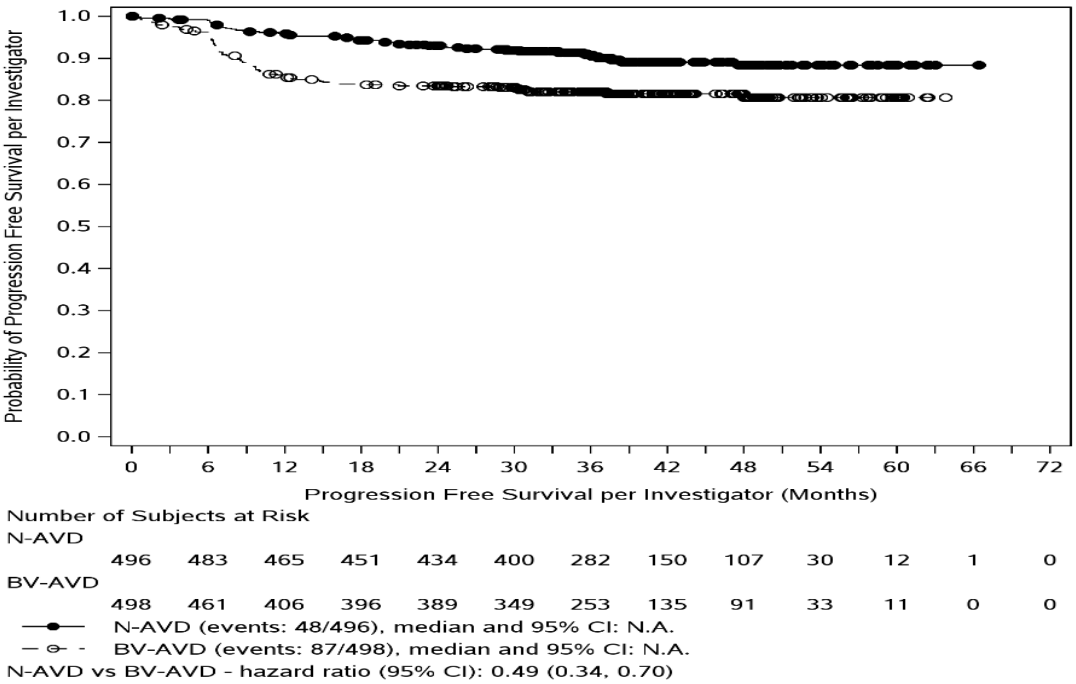


Table 15. Reason for Censoring, Progression-free Survival per Investigator (15-Apr-2025 data cutoff), Primary Definition - All Randomised Subjects Study CA2098UT

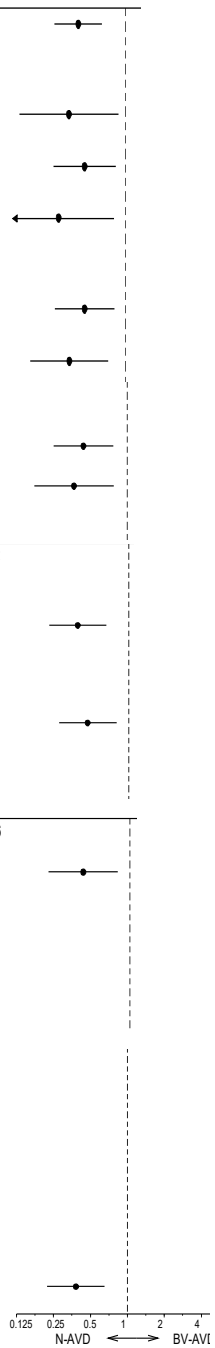
	N-AVD N = 496	BV-AVD N = 498
NUMBER OF EVENTS (%)	48 (9.7)	87 (17.5)
TYPE OF EVENTS (%)		
PROGRESSION (1)	40 (8.1)	72 (14.5)
DEATH	8 (1.6)	15 (3.0)
NUMBER OF SUBJECTS CENSORED (%)	448 (90.3)	411 (82.5)
CENSORED ON DATE OF RANDOMISATION	5 (1.0)	16 (3.2)
INCOMPLETE OR NO BASELINE TUMOR ASSESSMENT AND NO DEATH	1 (0.2)	3 (0.6)
NEVER TREATED	1 (0.2)	2 (0.4)
OTHER	0	1 (0.2)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH	4 (0.8)	13 (2.6)
NEVER TREATED	3 (0.6)	6 (1.2)
OTHER	1 (0.2)	7 (1.4)
CENSORED ON DATE OF LAST ADEQUATE ASSESSMENT ON-STUDY	443 (89.3)	395 (79.3)
STILL ON-TREATMENT	0	0
ON RESIDUAL PET RADIATION THERAPY	0	0
IN FOLLOW-UP	412 (83.1)	373 (74.9)
OFF STUDY	31 (6.3)	22 (4.4)
LOST TO FOLLOW-UP	10 (2.0)	5 (1.0)
PATIENT REFUSED FOLLOW-UP	15 (3.0)	13 (2.6)
OTHER	6 (1.2)	4 (0.8)

Subgroup analyses:

Based on 15-Dec-2022 data cutoff, the PFS advantage observed in subjects who received N-AVD compared to BV-AVD was consistent across all pre-specified subgroups with sufficient number of subjects (Figure 7). The advantage was sustained at 24-Mar-2024 and 15-Apr-2025 data cutoff (data not shown).

Figure 7. Forest Plot of Treatment Effect on Progression-free Survival per Investigator (Based on 15-Dec-2022 data cutoff) in Pre-Defined Subsets, Primary Definition - All Randomised Subjects in Study CA2098UT

		Nivolumab + AVD			Brentuximab Vedotin + AVD			Stratified	
	N	N of Events (N of Subjects)	mPFS (95% CI)	12-month PFS (95% CI)	N of Events (N of Subjects)	mPFS (95% CI)	12-month PFS (95% CI)	Hazard Ratio (95% CI) N-AVD vs. BV-AVD	Interaction p-value
Overall	994	28 (496)	N.A.	N.A.	64 (498)	N.A.	N.A.	0.41 (0.26, 0.64)	
Age Categorization									0.8484
>= 12 and < 18	240	6 (120)	N.A.	N.A.	17 (120)	N.A.	N.A.	0.35 (0.14, 0.88)	
>= 18 and <= 60	655	17 (326)	N.A.	N.A.	34 (329)	N.A.	N.A.	0.46 (0.26, 0.83)	
> 60	99	5 (50)	30.46 (30.46, N.A.)	N.A.	13 (49)	N.A. (9.49, N.A.)	N.A.	0.28 (0.10, 0.80)	
IPS									0.5409
0 - 3	676	18 (338)	N.A.	N.A.	38 (338)	N.A.	N.A.	0.46 (0.26, 0.81)	
4 - 7	318	10 (158)	N.A.	N.A.	26 (160)	N.A.	N.A.	0.35 (0.17. 0.72)	
Sex									0.7151
Male	556	18 (276)	N.A.	N.A.	40 (280)	N.A.	N.A.	0.44 (0.25, 0.77)	
Female	438	10 (220)	N.A.	N.A.	24 (218)	N.A.	N.A.	0.37 (0.18, 0.78)	
Stage Of Disease At Diagnosis									0.6062
Stage III	359	9 (188)	N.A.	N.A.	16 (171)	N.A.	N.A.	N.A.	
Stage IV	631	19 (306)	N.A.	N.A.	48 (325)	N.A.	N.A.	0.39 (0.23, 0.66)	
Not Reported	4	0 (2)	N.A.	N.A.	0 (2)	N.A.	N.A.	N.A.	
Symptoms									0.4421
Fever, Weight Loss, and/or Night Sweats	575	20 (292)	N.A.	N.A.	40 (283)	N.A.	N.A.	0.46 (0.27, 0.80)	
No Symptoms	419	8 (204)	N.A.	N.A.	24 (215)	N.A.	N.A.	N.A.	
Performance Status (ECOG)									0.2906
0	561	13 (274)	N.A.	N.A.	32 (287)	N.A.	N.A.	0.42 (0.22, 0.80)	
1	381	8 (192)	N.A.	N.A.	27 (189)	N.A.	N.A.	N.A.	
2	52	7 (30)	N.A.	N.A.	5 (22)	N.A.	N.A.	N.A.	
Race									0.4937
American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander	36	1 (16)	N.A.	N.A.	1 (20)	N.A.	N.A.	N.A.	
Black or African American	119	3 (59)	N.A.	N.A.	10 (60)	N.A.	N.A.	N.A.	
White	748	19 (379)	N.A.	N.A.	47 (369)	N.A.	N.A.	0.38 (0.22, 0.65)	
Other	91	5 (42)	N.A.	N.A.	6 (49)	N.A.	N.A.	N.A.	



HR and median estimate are not computed for subset categories with less than 10 events (with the exception of age categorization IPS, and PET-RT) per treatment group. Hazard ratio with 95% CIs at each level of the subgroups are estimated by stratified Cox proportional hazards model with randomisation stratification factors as stratification factors (excluding the subgroup variable), treatment and subgroup levels as fixed factors and an interaction term between treatment and the corresponding subgroup variable.

Sensitivity analysis

Progression-free Survival per Investigator, Secondary Definition

In all randomised subjects, treatment with N-AVD resulted in improved PFS compared to BV-AVD in advanced stage cHL at both 15-Dec-2022 data cutoff (HR = 0.41 (95% CI: 0.26, 0.64)) and 24-Mar-2024 data cutoff (HR = 0.42 (95% CI: 0.29, 0.63)) as well as based on 15-Apr-2025 data cutoff (HR = 0.48 (95% CI: 0.33, 0.69)).

Supportive Analysis of Progression-free Survival per BICR

- PFS per BICR according to the primary definition:

N-AVD demonstrated improved BICR-assessed PFS over BV-AVD at both data cutoffs: BICR-assessed PFS: HR = 0.50 (95% CI: 0.33, 0.77) at 15-Dec-2022 data cutoff; HR =0.53 (95% CI: 0.37, 0.75) at 24-Mar-2024 data cutoff.

A high concordance rate between INV-assessed and BICR-assessed PFS was observed at both the 15-Dec-2022 (94.5%) and the 24-Mar-2024 (93.8%) cutoffs. PFS per BICR for DCO 15-Apr-2025 was not reported.

- PFS per BICR according to the secondary definition:

The results for PFS per BICR assessment, secondary definition, for N-AVD vs BV-AVD in all randomised subjects were consistent with the results of PFS per INV at both 15-Dec-2022 data cutoff (HR=0.50; 95% CI: 0.33, 0.77) and 24-Mar-2024 data cutoff (HR=0.53; 95% CI: 0.37, 0.75). PFS per BICR for DCO 15-Apr-2025 was not reported.

Secondary endpoints

Overall Survival

The minimum follow-up for OS at the 15-Dec-2022 data cutoff was 2.4 months. Updated data form 24-Mar-2024 data cutoff and 15-Apr-2025 data cutoff with a minimum follow-up for OS of 17.6 months resp. 30.4 months showed similar results, interpretation is limited based on immature data.

Table 16. Overall Survival - All Randomised Eligible Subjects in Study CA2098UT

	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff		Based on 15-Apr-2025 data cutoff	
	N-AVD N = 486	BV-AVD N = 483	N-AVD N = 486	BV-AVD N = 483	N-AVD N = 486	BV-AVD N = 483
# EVENTS / # SUBJECTS (%)	4(0.8)	12 (2.4)	8 (1.6)	15 (3.0)	9 (1.8)	17 (3.4)
MEDIAN OS (MONTHS) (1) (95% CI)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff		Based on 15-Apr-2025 data cutoff	
	N-AVD N = 486	BV-AVD N = 483	N-AVD N = 486	BV-AVD N = 483	N-AVD N = 486	BV-AVD N = 483
HR (A)	0.32		0.43		0.47	
(95% CI)	(0.10, 1.00)		(0.17, 1.07)		(0.21, 1.07)	

(1) Based on Kaplan-Meier Estimates

(A) Hazard Ratio is N-AVD over BV-AVD from Cox proportional hazard model stratified by age (12-17 vs. 18-60 vs. > 60 years), IPS (0-3 vs. 4-7), and pre-specified plan to use Residual PET Radiation Therapy (yes vs. no) as performed by Oncology Patient Enrolment Network (OPEN).

Event-free survival per Investigator

N-AVD demonstrated improvement in EFS per INV compared with BV-AVD at 15-Dec-2022 data cutoff (HR = 0.55 (95% CI: 0.38, 0.81)), 24-Mar-2024 data cutoff (HR = 0.58 (95% CI: 0.42, 0.80)) and 15-Apr-2025 data cut-off (HR = 0.61 (95% CI: 0.44, 0.83)).

EFS by alternative (secondary) definition was similar as to the primary definition: N-AVD demonstrated improvement in EFS per INV compared with BV-AVD at 15-Dec-2022 data cutoff (HR = 0.56 (95% CI: 0.39, 0.81)), 24-Mar-2024 data cutoff (HR = 0.57 (95% CI: 0.41, 0.79)) and not presented for the 15-Apr-2025 data cut-off (HR = 0.61 (95% CI: 0.44, 0.83)).

2.4.2.1.1. Complete Metabolic Response

Complete metabolic response rate per INV was presented for IA2 (15-Dec-2022) and 24-Mar-2024 (Table 17).

Table 17. Complete Metabolic Response at End of Treatment per Investigator (Based on 15-Dec-2022 data cutoff and 24-Mar-2024 data cutoff) - All Randomised Subjects in Study CA2098UT

	Number of Subjects (%)			
	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff	
	N-AVD N = 496	BV-AVD N = 498	N-AVD N = 496	BV-AVD N = 498
METABOLIC RESPONSE				
COMPLETE METABOLIC RESPONSE (CR)	331 (66.7)	277 (55.6)	392 (79.0)	321 (64.5)
PARTIAL METABOLIC RESPONSE (PR)	39 (7.9)	49 (9.8)	41 (8.3)	56 (11.2)
NO METABOLIC RESPONSE (SD)	4 (0.8)	8 (1.6)	5 (1.0)	9 (1.8)
PROGRESSIVE METABOLIC DISEASE (PD)	11 (2.2)	28 (5.6)	11 (2.2)	31 (6.2)
UNABLE TO ASSESS (UA)	14 (2.8)	24 (4.8)	16 (3.2)	31 (6.2)
NOT REPORTED	97 (19.6)	112 (22.5)	31 (6.3)	50 (10.0)
COMPLETE METABOLIC RESPONSE RATE (1) (95% CI)	331/496 (66.7%) (62.4, 70.9)	277/498 (55.6%) (51.1, 60.0)	392/496 (79.0%) (75.2, 82.5)	321/498 (64.5%) (60.1, 68.7)
DISEASE CONTROL RATE (1) (95% CI)	374/496 (75.4%) (71.4, 79.1)	334/498 (67.1%) (62.7, 71.2)	438/496 (88.3%) (85.1, 91.0)	386/498 (77.5%) (73.6, 81.1)

	Number of Subjects (%)			
	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff	
	N-AVD N = 496	BV-AVD N = 498	N-AVD N = 496	BV-AVD N = 498
DIFFERENCE OF COMPLETE METABOLIC RESPONSE RATES (2, 3) (95% CI)	11.3% (5.4, 17.2)		14.7% (9.2, 20.1)	
MEASUREMENT BASED RESPONSE				
COMPLETE RESPONSE (CR)	15 (3.0)	9 (1.8)	17 (3.4)	9 (1.8)
PARTIAL RESPONSE (PR)	14 (2.8)	3 (0.6)	15 (3.0)	3 (0.6)
NO RESPONSE OR STABLE DISEASE (SD)	0	0	0	0
PROGRESSIVE DISEASE (PD)	0	1 (0.2)	0	2 (0.4)
UNABLE TO ASSESS (UA)	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.4)
NOT REPORTED	466 (94.0)	483 (97.0)	463 (93.3)	482 (96.8)

Denominator is the number of randomised subjects. Patients with missing CMR assessment by EOT will be treated as non-responders.

(1) Confidence interval based on the Clopper and Pearson method.

(2) Strata adjusted difference in rate based on Cochran-Mantel-Haenszel (CMH)

(3) Stratified by age (12-17 vs. 18-60 vs. > 60 years), IPS (0-3 vs. 4-7), and pre-specified plan to use Residual PET Radiation Therapy (yes vs. no) as performed by Oncology Patient Enrolment Network (OPEN).

Exploratory endpoints

PRO-CTCAE

Adults

Completion rates for adult subjects was >90% for baseline and on-treatment questionnaire, however, the follow-up questionnaire completion rates were consistently higher in the N-AVD arm (>70%) during the 9-36 months after randomisation, compared to < 70% in the BV-AVD arm.

In general, the percentages of subjects reporting Level 1 (none) symptoms were higher in the N-AVD arm. The symptoms of peripheral neuropathy (numbness or tingling in hands or feet), aching muscles, and aching joints were more frequently reported in subjects receiving BV-AVD treatment, and were more severe compared to the N-AVD arm.

Adolescents

Completion rates for adolescents was >80% for baseline and on-treatment questionnaire (slightly higher completion rates observed in the N-AVD arm), however, the follow-up questionnaire completion rates were consistently higher in the N-AVD arm (>60%) during the 9-36 months after randomisation, compared to <60% in the BV-AVD arm.

During treatment, many PRO-CTCAE symptoms worsened, with higher frequency and severity generally observed in the BV-AVD arm. After treatment completion, these symptoms gradually returned to baseline levels in both arms, and some continued to improve over time. A few symptoms showed improvement during treatment and after treatment completion for both arms, including shortness of breath, cough, pain, and itchy skin.

Radiotherapy

Per protocol, 58.7% of subjects declared planned use of residual PET-RT based on investigator discretion. Among eligible subjects who declared the intent-to-treat with residual PET-RT, the number who actually received PET-RT following completion of systemic therapy was low in both arms, 3 (1.0%) subjects in each treatment arm at the 15-Dec-2022 data cutoff and 3 (1.0%) subjects in the N-AVD arm and 4 (1.4%) subjects in the BV-AVD arm at the 24-Mar-2024 data cutoff. Reasons for no-intent for post-treatment RT were not collected.

Similarly, the number of subjects who received non-protocol anti-lymphoma RT as part of subsequent therapy was limited in both arms (N=8/496 (1.6%) in N-AVD vs 11/498 (2.2%) in BV-AVD).

Ancillary analyses

Not applicable.

Summary of main study

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

Table 1. Summary of Efficacy for trial CA2098UT

Title: A phase 3, randomised study of nivolumab (Opdivo) plus AVD or brentuximab vedotin (Adcetris) plus AVD in patients (age ≥12 years) with newly diagnosed advanced stage classical Hodgkin lymphoma.			
Study identifier	CA2098UT (SWOG 1826)		
Design	Multicentre, randomised, open-label phase 3 clinical trial for participants with newly diagnosed, previously untreated advanced stage (III-IV) cHL. Once enrolled, patients were randomised to either Arm 1 (N-AVD) or Arm 2 (BV-AVD) in a 1:1 ratio		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		13.3 months (51%IF, IA2) not applicable 10 years after randomisation
Hypothesis	Superiority		
Treatments groups	N-AVD		N-AVD 6x28 day cycles, 496 randomised
	BV-AVD		BV-AVD 6x28 day cycles, 498 randomised
Endpoints and definitions	Primary endpoint	PFS	time from date of randomisation to date of first observation per investigator assessment of progressive disease according to the 2014 Lugano classification, or death due to any cause, whichever occurs first

	Secondary endpoint	OS	time from date of randomisation to date of death due to any cause. OS was censored on the last date a subject was known to be alive	
	Secondary endpoint	EFS	date of randomisation to date of first occurrence of any event of disease progression/relapse per investigator assessment, administration of non-protocol specified systemic anti-lymphoma therapy, administration of non-protocol specified RT therapy, or death due to any cause.	
	Secondary endpoint	CMR	the number of participants who achieve Complete Metabolic Response by the end of treatment divided by the total number of participants randomised to each arm	
Database lock	15-Dec-2022 (IA2)			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group		N-AVD	BV-AVD
	Number of subjects		496	498
	PFS per inv./subjects (%)		28/496 (5.6%)	62/498 (12.4%)
	OS events/subjects (%)		4/496 (0.8%)	12/498 (2.4%)
	EFS per inv./number of subjects (%)		43/496 (8.7%)	73/498 (14.7%)
	CMR/number of subjects (%)		331/496 (66.7%)	277/498 (55.6%)
	95% CI		62.4, 70.9	51.1, 60.0
Effect estimate per comparison	Primary endpoint - PFS per inv		Comparison groups	N-AVD vs BV-AVD
			HR	0.42

		95%CI	0.27, 0.67
		P-value	p<0.0001
	Secondary endpoint - OS	Comparison groups	N-AVD vs BV-AVD
		HR	0.32
		95%CI	0.10, 1.00
		P-value	n.s.
	Secondary endpoint - EFS per inv.	Comparison groups	N-AVD vs BV-AVD
		HR	0.55
		95%CI	0.38, 0.81
		P-value	n.a.
Notes	Updated data was presented for PFS, OS and EFS with DBL 24-Mar-2024 and 15-Apr-2025		

Clinical studies in special populations

In paediatric patients, the results for PFS per INV, PFS per BICR, EFS per INV, and CMR in paediatric patients were consistent with the results for the overall population at both data cutoffs and were in favour of the N-AVD arm (Table 18). There were no deaths reported in the N-AVD arm, and only 1 death reported in the BV-AVD arm at both data cutoffs.

Table 18. Summary of Efficacy - All Paediatric Randomised Subjects in study CA2098UT

	N-AVD N = 120	**BV-AVD N = 120**	**N-AVD N = 120**	**BV-AVD N = 120**
	Based on 15-Dec-2022 data cutoff		**Based on 24-Mar-2024 data cutoff**	
PFS per Investigator, primary definition				
# Events/# Subjects, n/N (%)	6/120 (5.0)	17/120 (14.2)	8/120 (6.7)	22/120 (18.3)
Median PFS (95% CI), mo.[a]	N.A.	N.A.	N.A.	N.A.
HR[b]	0.34		0.34	
(95% CI)	(0.14, 0.87)		(0.15, 0.77)	
PFS rates (95% CI), %[a,c]				
6 months			99.2 (94.2,99.9)	98.3 (93.5, 99.6)
12 months			95.8 (90.2, 98.2)	84.0 (76.0, 89.5)

	N-AVD N = 120	BV-AVD N = 120	N-AVD N = 120	BV-AVD N = 120
	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff	
18 months			95.8 (90.2, 98.2)	83.1 (75.0, 88.7)
24 months			N.A.	N.A.
PFS per BICR, primary definition				
# Events/ # Subjects, n/N (%)	4/120 (3.3)	14/120 (11.7)	7/120 (5.8)	19/120 (15.8)
Median PFS (95% CI), mo.[a]	N.A.	N.A.	N.A.	N.A.
HR[b]	0.27		0.35	
(95% CI)	(0.09, 0.82)		(0.15, 0.83)	
PFS rates (95% CI), %[a,c]				
6 months			99.2 (94.1,99.9)	98.3 (93.3,99.6)
12 months			97.5 (92.3,99.2)	86.2 (78.4,91.3)
18 months			97.5 (92.3, 99.2)	85.3 (77.4,90.6)
24 months			N.A.	N.A.
OS				
# Events/# Subjects, n/N (%)	0/120	1/120 (0.8)	0/120	1/120 (0.8)
Median OS (95% CI), mo.[a]	N.A.	N.A.	N.A.	N.A.
HR[b]	0.00		0.00	
(95% CI)	(0.00, N.A.)		(0.00, N.A.)	
EFS per Investigator, primary definition				
# Events/# Subjects, n/N (%)	10/120 (8.3)	19/120 (15.8)	14/120 (11.7)	24/120 (20.0)
Median EFS (95% CI), mo.[a]	N.A.	N.A.	N.A.	N.A.
HR[b]	0.53		0.57	
(95% CI)	(0.24, 1.13)		(0.30, 1.11)	
EFS rates (95% CI), %[a,c]				
6 months			95.8 (90.2,98.2)	97.5 (92.5,99.2)
12 months			91.6 (85.0,95.4)	82.3 (74.1,88.1)
18 months			91.6 (85.0, 95.4)	81.4 (73.2,87.3)
24 months			N.A.	N.A.
CMR at End of Treatment per Investigator[d]				
Complete metabolic response rate, n (%)	89/120	63/120 (52.5%)	99/120 (82.5%)	73/120 (60.8%)

	N-AVD N = 120	BV-AVD N = 120	N-AVD N = 120	BV-AVD N = 120
	Based on 15-Dec-2022 data cutoff		Based on 24-Mar-2024 data cutoff	
	(74.2%)			
95% CI[e]	(65.4, 81.7)	(43.2, 61.7)	(74.5, 88.8)	(51.5, 69.6)

[a]Based on Kaplan-Meier estimates. [b]HR is N-AVD over BV-AVD from Cox proportional hazard model stratified by IPS (0-3 vs 4-7), and pre-specified plan to use residual PET-RT (yes vs no) as performed by Oncology Patient Enrolment Network (OPEN). [c] N.A: Not Available: Rates are requested up to 18 months. [d]Denominator is the number of randomised subjects. Patients with missing CMR assessment by EOT will be treated as non-responders. [e]CI based on the Clopper and Pearson method. [f]Strata adjusted difference in rate based on Cochran-Mantel-Haenszel (CMH). [g]Stratified by IPS (0-3 vs. 4-7), and pre-specified plan to use Residual PET Radiation Therapy (yes vs. no) as performed by OPEN.

2.4.3. Discussion on clinical efficacy

With the current submitted variation the MAH proposes an extension of the indication to include "OPDIVO in combination with doxorubicin, vinblastine and dacarbazine (AVD) is indicated for adults and adolescents 12 years of age and older with previously untreated Stage III or IV cHL".

Design and conduct of clinical studies

Clinical efficacy in frontline HL patients has been investigated in study CA2098UT, a multicentre, randomised, open-label, Phase 3 clinical study in adults and adolescents (age ≥12 and <18 years) with histologically confirmed, newly diagnosed, previously untreated advanced stage (III-IV) cHL (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or NOS) comparing PFS obtained with N-AVD (n=496) versus BV-AVD (n=498).

Patients with active autoimmune disease requiring systemic treatment in the past 2 years, patients with > Grade 2 peripheral neuropathy, CNS lymphoma, and patients with active interstitial pneumonitis or interstitial lung disease were excluded from the clinical trial of nivolumab in combination with AVD chemotherapy. In the absence of data, nivolumab in combination with AVD chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

The dose of nivolumab differed for adults and adolescents (12 - <18 yrs). Adults and adolescents (12 years of age and older weighing at least 80 kg) received 240 mg nivolumab Q2W and adolescents (12 years of age and older weighing less than 80 kg) received 3 mg/kg Q2W (refer to pharmacology section for discussion).

The application provides results for the primary endpoint of investigator-assessed PFS at the pre-specified IA2 from pivotal Study CA2098UT (data cutoff 15-Dec-2022). In addition, results with longer follow-up (minimum follow-up of 17.6 months [time from last subject's randomisation to clinical data cutoff date]) based on a data cutoff of 24-Mar-2024 and a 3rd data cut was conducted at the 75% PFS IF based on the 15-Apr-2025 clinical data cutoff with a minimum follow up of 30.4 months.

The only prespecified analyses considered relevant are those laid down in the last document before start of patient enrolment. This is the original protocol from the academic group (SWOG) executing the

trial. Many late changes were made by the MAH (one month before the first efficacy interim analysis, i.e., in the SAP); also some changes seem to arise after results were known (i.e. the CSR). These changes affect PFS censoring rules, EFS event definition and censoring rules, adding independent review, and testing of OS. These changes are partly in response to FDA advice, which was provided when 20 months of the total 37 months recruitment passed, so also late in the trial process. Even though some changes cannot be traced back to the SAP or to FDA requests. These late changes can be considered as supportive analyses only. Importantly, the "primary definition" of the primary endpoint (PFS) in the CSR is that of the original protocol and this definition can therefore be considered prespecified. This analysis is in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). As testing of OS was only added in the SAP, after full recruitment, OS cannot be considered formally tested (which is of no consequence as OS had a p-value > 0.05).

The only scheduled scans for PFS were at pre-registration and end of treatment at 6.5-7.5 months to establish response; all other scans for assessment of progression were only performed if clinical assessment (every three months in the first year) raised suspicion of progression. Given the study was open-label, this can in principle cause differences in timing of scans (e.g. investigators may decide to perform a scan earlier in the control arm). Because cure is expected and actually observed (as seen with the plateaus in the PFS curves), the clinical benefit is clearer in milestones such as at 1 and 2 year follow-up. For these milestones, only events observed at those milestones are relevant and therefore differences in timing of assessment (earlier than those milestones) will not alter the efficacy interpretation, i.e., the difference in plateaus (cure rates) as main measure of clinical benefit. It is also noted that an analysis counting events of unplanned scans only at the next scheduled scans is of limited value as there were only two scheduled scans mentioned.

PFS was defined according to 2 definitions; only the first definition can be considered prespecified; it is also in line with EMA guidance. The secondary definition (censoring for new anti-cancer therapy, prespecified as sensitivity analysis in the academic original protocol) can be considered supportive. EFS (according to the primary definition) is also aligned with the originally planned EFS and supports that the benefit in difference in plateaus is present when new (non-protocol) therapy is considered a failure.

The post-hoc independent review of PFS was ultimately based on all collected scans. As there was little informative censoring (few cases where PFS was determined by investigator but not by independent review), the PFS by IRC is considered interpretable.

Efficacy data and additional analyses

Overall, 994 subjects were enrolled and randomised (496 to the N-AVD arm and 498 to the BV-AVD arm) in 2 countries (Canada and US). The MAH has clarified that available treatment options for treatment-naive, advanced stage cHL in the US and EU at the time of subject enrolment in CA2098UT Study were similar and based on data from the ECHELON-1 study and German Hodgkin Study Group HD studies, no different outcome in the EU subjects to US/Canada subjects is expected.

Baseline demographic and disease characteristics in all randomised subjects were in general balanced between the N-AVD and BV-AVD treatment arms and representative of frontline HL patients. The studied population consists of 24.1% paediatric patients (age 12-<18) and 75.9% adults of which 10.0% > 60 years. A significant part of the studied population presented with characteristics associated with a favourable prognosis, e.g. 68% of subjects had low risk disease (baseline IPS 0-3), 42.2% presented without B symptoms, and 70.9% did not have bulky disease at baseline. In addition,

small imbalances are observed with respect to the baseline disease characteristics such as number of patients with bulky disease (68.3% N-AVD vs 73.5% BV-AVD) and disease stage at diagnosis (stage IV 61.7% N-AVD vs 65.3% BV-AVD). A multivariate interaction and subgroup analysis investigating the PFS for patients with disease with less favourable prognosis (IPI score 4-7, B symptoms, bulky disease and/or age, stage) showed that each less favourable prognostic factor on its own did not effect-modify PFS in this trial. For the combination of both stage IV disease and IPS 4–7 sufficient patients (N=279) were available to show that N-AVD vs BV-AVD was superior.

Based on the 15-Dec-2022 DCO (PFS 51% IF), N-AVD treatment demonstrated a statistically significant improvement of PFS per INV compared to BV-AVD treatment (HR = 0.42 (95% CI: 0.24, 0.77); stratified log-rank test 1-sided p-value < 0.0001). This hazard ratio was maintained at the 24-Mar-2024 DCO (HR = 0.46 (95% CI: 0.32, 0.67) and 15-Apr-2025 DCO (HR = 0.49 (95% CI: 0.34, 0.70)). The last DCO was presented with a median follow up of 36.67 months and a minimum of 30.4 months. The median PFS was not reached in the last DCO, which is understandable given the apparent cure rates above 50%. Possibly informative reasons for censoring (lost to follow-up, patient withdrawal from follow-up, and "other" reasons) were similar between arms.

Subjects received up to 6 cycles of treatment, with a median treatment duration of 5.55 months for both N-AVD and BV-AVD arms. The difference in PFS between the two treatment arms is more pronounced at 12- and 18-months following completion of therapy, which is as expected as relapses in cHL peak early at 12–18 months after treatment initiation. Given the presence of cure (plateaus in the Kaplan-Meier curve), the difference between arms is not well captured by a hazard ratio (proportional hazard assumption was also not supported as also apparent from the time with treatment interaction analysis by the MAH). The difference in plateaus is a better effect measure. Clinical relevance of the observed PFS difference between N-AVD vs BV-AVD are best estimated at the last DCO (15-April-2025) and are 91.9% (95%-CI from 89.1 to 94.0%) vs 83.0% (95%-CI from 79.4 to 86.1%) at 30 months. Thus, a PFS rate of approximately 10% difference in the KM-plateau phase in favor of N-AVD in the frontline treatment of HL can be considered a small but clinically relevant difference.

A high concordance rate between INV-assessed and BICR-assessed PFS was observed at both the 15-Dec-2022 and the 24-Mar-2024 data cutoffs (94.5% and 93.8%, respectively at subject level).

The Forest plot of PFS for predefined subsets was in general consistent in favour of N-AVD. A specified subgroup analysis for elderly (e.g. 61-75 years, > 80 years) was not performed (only >60 years) and is not feasible in light of the limited number of events (at DCO 15-Apr-2025 resp. 10 N-AVD vs 19 BV-AVD).

The 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 ASCT. The secondary endpoint OS was immature at the primary DCO (15-Dec-2022) with numerically fewer OS events observed in the N-AVD arm (4/496 events) vs the BV-AVD arm (12/498 events) (HR 0.32, 95% CI: 0.10, 1.0 OS remained immature also at the last DCO (15-Apr-2025) with 9 (out of 496) events in the N-AVD arm and 17 events (out of 483) in the BV-AVD arm (HR 0.47, 95% CI: 0.21, 1.07). No difference in informative censoring reasons was present in the 15-Apr-2025 cut-off (7.3% vs 7.0%): lost-to-follow up (2.2% vs 1.0), refusal of follow-up (3.6% vs 5.0%), other (1.4% vs 1.0%).

EFS per primary definition demonstrated improvement in EFS per INV of N-AVD compared with BV-AVD at 15-Dec-2022 data cutoff (HR = 0.55 (95% CI: 0.38, 0.81)) with consistent results at later DCO. EFS per secondary definition was similar as the primary definition.

Complete metabolic response rate (CMR) per INV was presented for IA2 (15-Dec-2022) and 24-Mar-2024. No IRC assessment of CMR has been presented. Increased CMR was observed for N-AVD vs BV-

AVD (N-AVD 66.7% vs 55.6% based on the 15-Dec-2022 DCO; 79.0% vs 64.5% based on 24-March-2024 DCO). With DCO 15-DEC-2022 to the DCO 24-MAR-2024 there was a large increase in CMR as by then all subjects had completed treatment.

The number of patients that received PET-RT following completion of systemic therapy was very low in both arms (N=3/291 in N-AVD vs N=4/292 in BV-AVD) but reasons for no-intent for post-treatment RT were not collected and thus information on the patient characteristics used by the investigators to determine the intent for RT cannot be provided. This limits accurate assessment of the value of and necessity for RT in this patient population.

Approval of nivolumab in 1L could results in retreatment with nivolumab in later lines of HL treatment. The CHMP recommended that the MAH obtains additional data on retreatment with nivolumab in patients with HL.

PRO-CTCAE were collected but interpretation is difficult in this open label study, which is also reflected in the higher completion rate for the N-AVD arm compared to BV-AVD arm (for both adults and adolescents). The symptoms of peripheral neuropathy were more frequently reported in subjects receiving BV-AVD treatment and were more severe compared to the N-AVD arm. This is in line with the safety profile of BV-AVD (refer to safety section).

Assessment of paediatric data on clinical efficacy

In paediatric patients, N-AVD treatment improved PFS per INV compared to BV-AVD treatment at both the 15-Dec-2022 data cutoff (PFS 51% IF) (HR = 0.34 (95% CI: 0.14, 0.87) and the 24-Mar-2024 data cutoff (PFS 71% IF) (HR = 0.34 (95% CI: 0.15, 0.77)). The results for PFS per INV, PFS per BICR, EFS per INV, and CMR in paediatric patients were consistent with the results for the overall population at both data cutoffs and were in favour of the N-AVD arm.

2.4.4. Conclusions on the clinical efficacy

The pivotal study CA2098UT has shown superiority of N-AVD versus BV-AVD on PFS supported by secondary endpoint EFS and CMR. The Forest plot of PFS for predefined subsets (including adolescents) was in general consistently in favour of N-AVD. A difference in PFS rate at the plateau of the curve of app. 10% in favor of N-AVD in the frontline treatment of HL can be considered a small but clinically relevant difference.

2.5. Clinical safety

Introduction

Safety data from the pivotal study CA2098UT were submitted.

Data from different data cutoffs were provided:

- Primary analysis with a data cutoff date of 15-Dec-2022 (based on PFS, 51% IF)
- Longer follow-up data with a data cutoff date of 24-Mar-2024 (based on PFS, 71% IF)
- Third additional analysis with a data cutoff date of 15-Apr-2025 (PFS 75% IF)

Data from cutoff date with the longest follow-up (15-Apr-2025) are used in this report when available. SAEs, IMAEs, OESIs and the paediatric subgroup analyses were not updated, therefore the data cutoff of 24-Mar-2024 was used. The used data cutoff is mentioned in the table caption.

Study CA2098UT utilized the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. All AEs were coded using the MedDRA dictionary.

Patient exposure

Overall, 994 subjects were enrolled and randomised (496 to the N-AVD arm and 498 to the BV-AVD arm). In the N-AVD arm 6 patients were not treated due to patient withdrawal (n=2) or other reasons (n=4). In the BV-AVD arm 8 patients were not treated due to patient withdrawal (n=5) and other reasons (n=3). In total 980 subjects were treated (490 in the N-AVD arm and 490 in the BV-AVD arm). Drug exposure was provided for the 24-Mar-2024 data cutoff; all patients completed or discontinued treatment at the 24-Mar-2024 data cutoff. The duration of exposure to study therapy is shown in Table 19.

Table 19. Duration of Study CA2098UT Therapy Summary (24-Mar-2024 data cutoff)- All Treated Subjects.

Duration of therapy (months)	**N-AVD N = 490**	**BV-AVD N = 490**
Nivolumab		
Mean (Min, Max)	5.41(0.3, 7.1)	N.A.
Median	5.55	N.A.
Brentuximab vedotin		
Mean (Min, Max)	N.A.	5.11 (0.4, 7.3)
Median	N.A.	5.55
Doxorubicin		
Mean (Min, Max)	5.47 (0.3, 7.1)	5.37 (0.4, 7.4)
Median	5.55	5.59
Vinblastine		
Mean (Min, Max)	5.47 (0.3, 7.1)	5.33 (0.4, 7.4)
Median	5.55	5.55
Dacarbazine		
Mean (Min, Max)	5.49 (0.3, 7.1)	5.37 (0.4, 7.4)
Median	5.55	5.59

Cumulative Dose and Relative Dose Intensity for nivolumab, brentuximab vedotin and the AVD backbone in the paediatric, adult and overall study populations are summarised in Table 20-Table ***22***.

Table 20. Cumulative Dose and Relative Dose Intensity Summary - Nivolumab - All Treated Subjects Study CA2098UT (24-Mar-2024 data cutoff)

	Paediatric N = 120	**Adults N = 370**	**Overall N = 490**
Nivolumab (N Cycles)			
>=1 Cycle	120 (100.0)	370 (100.0)	490 (100.0)
>=2 Cycles	118 (98.3)	362 (97.8)	480 (98.0)
>=3 Cycles	114 (95.0)	359 (97.0)	473 (96.5)
>=4 Cycles	110 (91.7)	351 (94.9)	461 (94.1)
>=5 Cycles	109 (90.8)	343 (92.7)	452 (92.2)
>=6 Cycles	104 (86.7)	330 (89.2)	434 (88.6)
Mean (SD)	5.6 (1.09)	5.7 (0.95)	5.7 (0.99)
Median (Min – Max)	6.0 (1 - 6)	6.0 (1 - 6)	6.0 (1 - 6)
Cumulative dose (mg)			
Mean (SD)	2048.9 (659.71)	2713.2 (492.62)	
Median (Min – Max)	2058.5 (185 - 2880)	2880.0 (240 - 2928)	
Actual dose intensity (mg/week)			
Mean (SD)	87.95 (21.546)	114.84 (8.933)	108.26 (17.528)
Median (Min – Max)	88.13 (39.5 - 120.7)	118.94 (56.0 - 186.7)	116.32 (39.5 - 186.7)
Relative dose intensity			
>= 110%	2 (1.7)	1 (0.3)	3 (0.6)
90% to < 110%	94 (78.3)	318 (85.9)	412 (84.1)
70% to < 90%	20 (16.7)	48 (13.0)	68 (13.9)
50% to < 70%	2 (1.7)	2 (0.5)	4 (0.8)
< 50%	2 (1.7)	1 (0.3)	3 (0.6)

Table 21. Cumulative Dose and Relative Dose Intensity Summary – Brentuximab vedotin - All Treated Subjects Study CA2098UT (24-Mar-2024 data cutoff)

	Paediatric N = 120	**Adults N = 370**	**Overall N = 490**
Brentuximab vedotin (N Cycles)			
>=1 Cycle	120 (100.0)	370 (100.0)	490 (100.0)
>=2 Cycles	118 (98.3)	351 (94.9)	469 (95.7)
>=3 Cycles	118 (98.3)	335 (90.5)	452 (92.5)
>=4 Cycles	115 (95.8)	310 (83.8)	425 (86.7)
>=5 Cycles	108 (90.0)	278 (75.1)	386 (78.8)
>=6 Cycles	106 (88.3)	237 (64.1)	343 (70.0)
Mean (SD)	5.7 (0.90)	5.1 (1.49)	5.2 (1.39)
Median (Min – Max)	6.0 (1 - 6)	6.0 (1 - 6)	6.0 (1 - 6)
Cumulative dose (mg)			
Mean (SD)	847.0 (241.51)	887.3 (326.87)	
Median (Min – Max)	834.0 (82 – 1440)	912.0 (6 – 1620)	
Actual dose intensity (mg/week)			

Mean (SD)	36.22 (8.518)	42.46 (9.624)	40.93 (9.734)
Median (Min – Max)	35.85 (16.7 – 57.6)	41.45 (0.4 – 70.0)	39.74 (0.4 – 70.0)
Relative dose intensity			
>= 110%	0	2 (0.5)	2 (0.4)
90% to < 110%	106 (88.3)	245 (66.2)	351 (71.6)
70% to < 90%	13 (10.8)	104 (28.1)	117 (23.9)
50% to < 70%	1 (0.8)	16 (4.3)	17 (3.5)
< 50%	0	3 (0.8)	3 (0.6)

Table 22. Cumulative dose and relative dose intensity of AVD-backbone- All Treated Subjects Study CA2098UT (24-Mar-2024 data cutoff)

	N-AVD N = 490	**BV-AVD N = 490**
Doxorubicin		
N Cycles		
>=1 Cycle	490 (100.0)	490 (100.0)
>=2 Cycles	480 (98.0)	474 (96.7)
>=3 Cycles	478 (97.6)	464 (94.7)
>=4 Cycles	456 (93.1)	445 (90.9)
>=5 Cycles	436 (89.0)	422 (86.1)
>=6 Cycles	416 (84.9)	401 (81.8)
Mean (SD)	5.6 (1.02)	5.5 (1.22)
Median (Min – Max)	6 (1 – 6)	6 (1 – 6)
Relative dose intensity		
>= 110%	1 (0.2)	1 (0.2)
90% to < 110%	439 (89.6)	424 (86.5)
70% to < 90%	48 (9.8)	60 (12.1)
50% to < 70%	2 (0.4)	5 (1.0)
< 50%	0	0
Vinblastine		
N Cycles		
>=1 Cycle	490 (100.0)	490 (100.0)
>=2 Cycles	480 (98.0)	474 (96.7)
>=3 Cycles	477 (97.3)	464 (94.7)
>=4 Cycles	456 (93.1)	442 (90.4)
>=5 Cycles	435 (88.8)	418 (85.3)
>=6 Cycles	416 (84.9)	388 (79.2)
Mean (SD)	5.6 (1.03)	5.5 (1.23)
Median (Min – Max)	6 (1 – 6)	6 (1 – 6)
Relative dose intensity		
>= 110%	2 (0.4)	2 (0.4)
90% to < 110%	409 (83.5)	391 (79.8)
70% to < 90%	75 (15.1)	89 (18.2)
50% to < 70%	5 (1.0)	8 (1.6)

< 50%	0	0
Dacarbazine		
N Cycles		
>=1 Cycle	490 (100.0)	490 (100.0)
>=2 Cycles	481 (98.2)	474 (96.7)
>=3 Cycles	479 (97.8)	464 (94.7)
>=4 Cycles	458 (93.5)	445 (90.8)
>=5 Cycles	438 (89.4)	422 (86.1)
>=6 Cycles	417 (85.1)	399 (81.4)
Mean (SD)	5.6 (0.99)	5.5 (1.22)
Median (Min – Max)	6 (1 – 6)	6 (1 – 6)
Relative dose intensity		
>= 110%	1 (0.2)	1 (0.2)
90% to < 110%	437 (89.2)	435 (88.8)
70% to < 90%	50 (10.2)	50 (10.2)
50% to < 70%	2 (0.4)	3 (0.6)
< 50%	0	1 (0.2)

Planned, protocol-specified residual PET-RT was administered in 3 (1.0%) subjects in the N-AVD arm and 4 (1.4%) subjects in the BV-AVD arm at the 24-Mar-2024 data cutoff.

The use of G-CSF was required for subjects in the BV-AVD arm as a prophylactic premedication as detailed in the Adcetris label and optional for subjects in the N-AVD arm. In the N-AVD arm 279/490 (56.9%) of patients received G-CSF, mainly as primary prophylaxis within 72 hours of C1D1 (203/279; 72.8%). G-CSF use was more common in patients ≥65 years (70.0%) compared to patients <18 years (62.5%) and 18-64 years (53.8%). Of the 304 patients with neutropenia, 170 (55.9%) received G-CSF. Of the 186 patients without neutropenia, 109 (58.6%) received G-CSF.

In total 71 (14.5%) subjects in the N-AVD arm and 53 (10.8%) subjects in the BV-AVD arm had concomitant use of systemic corticosteroids.

Dose escalation or reduction of nivolumab was not permitted. Dose reductions and dose delays are described in Table 23 (N-AVD) and Table 24 (BV-AVD).

Table 23. Dose delays and dose reductions N-AVD arm, Study CA2098UT (24-Mar-2024 data cutoff)

N-AVD N=490				
	Nivolumab	**Doxorubicine**	**Vinblastine**	**Dacarbazine**
Dose delays				
Number of cycles with dose delayed per subject (%)				
0	397 (81.0)	393 (80.2)	393 (80.2)	397 (81.0)
1	76 (15.5)	79 (16.1)	78 (15.9)	79 (16.1)
2	12 (2.4)	13 (2.7)	14 (2.9)	13 (2.7)
3	4 (0.8)	4 (0.8)	4 (0.8)	4 (0.8)
≥4	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Reason for dose delay (%)				
AE	68 (58.6)	73 (60.2)	71 (58.2)	73 (60.3)
Patient refusal/noncompliance	14 (12.1)	14 (11.6)	14 (11.6)	14 (11.6)

Scheduling	9 (7.8)	9 (7.4)	9 (7.4)	9 (7.4)
Other	19 (16.4)	19 (15.7)	18 (14.8)	19 (15.7)
Not reported	6 (5.2)	6 (5.0)	10 (8.2)	6 (5.0)
Length of dose delay (%)				
4 – 7 days	67 (57.8)	70 (57.9)	70 (57.4)	70 (57.9)
8 – 14 days	36 (31.0)	36 (29.8)	36 (29.5)	36 (29.8)
15 – 28 days	13 (11.2)	15 (12.4)	16 (13.1)	15 (12.4)
Dose reductions				
Number of cycles with dose reduction per subject (%)				
0	487 (99.4)	479 (97.8)	471 (96.1)	473 (96.5)
1	3 (0.6)	11 (2.2)	17 (3.5)	16 (3.3)
2	0	0	1 (0.2)	0
3	0	0	1 (0.2)	1 (0.2)
≥4	0	0	0	0
Reason for dose reduction (%)				
AE	2 (66.7)	9 (81.8)	20 (90.9	7 (36.8)
Other	1 (33.3)	2 (18.2)	2 (9.1)	12 (63.2)

Table 24. Dose delays and dose reductions BV-AVD arm, Study CA2098UT (24-Mar-2024 data cutoff)

BV-AVD N=490				
	Brentuximab vedotin	**Doxorubicine**	**Vinblastine**	**Dacarbazine**
Dose delays				
Number of cycles with dose delayed per subject (%)				
0	371 (75.7)	360 (73.5)	359 (73.3)	359 (73.3)
1	92 (18.8)	98 (20.0)	100 (20.4)	99 (20.2)
2	20 (4.1)	24 (4.9)	23 (4.7)	24 (4.9)
3	6 (1.2)	7 (1.4)	7 (1.4)	7 (1.4)
≥4	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Reason for dose delay (%)				
AE	74 (47.7)	105 (61.0)	106 (61.6)	110 (63.6)
Patient refusal/noncompliance	15 (9.7)	17 (9.9)	17 (9.9)	17 (9.8)
Scheduling	13 (9.0)	14 (8.1)	14 (8.1)	14 (8.1)
Other	23 (14.8)	26 (15.1)	25 (14.5)	25 (14.5)
Not reported	29 (18.7)	10 (5.8)	10 (5.8)	7 (4.0)
Length of dose delay (%)				
4 – 7 days	90 (58.1)	98 (57.0)	98 (57.0)	99 (57.2)
8 – 14 days	47 (30.3)	52 (30.2)	52 (30.2)	53 (30.6)
15 – 28 days	18 (11.6)	22 (12.8)	22 (12.8)	21 (12.1)
Dose reductions				
Number of cycles with dose reduction per subject (%)				
0	354 (72.2)	466 (95.1)	437 (89.2)	470 (95.9)
1	119 (24.3)	19 (3.9)	44 (9.0)	13 (2.7)
2	11 (2.2)	5 (1.0)	7 (1.4)	7 (1.4)
3	2 (0.4)	0	0	0

≥4	4 (0.8)	0	2 (0.4)	0
Reason for dose reduction (%)				
AE	153 (92.2)	22 (75.9)	53 (77.9)	14 (51.9)
Dosing error	0	1 (3.4)	2 (2.9)	3 (11.1)
Other	13 (7.8)	6 (20.7)	13 (19.1)	10 (37.0)

Adverse events

AEs (all causality) were reported for most subjects in both treatment arms (Table 25).

Table 25. Adverse Events by Worst CTC Grade Reported in ≥ 25% - All Treated Subjects Study CA2098UT (15-Apr-2025 data cutoff)

	N-AVD N = 490			**BV-AVD N = 490**		
System Organ Class (%) Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
Total subjects with an event	479 (97.8)	346 (70.6)	3 (0.6)	482 (98.4)	285 (58.2)	9 (1.8)
Gastrointestinal disorders	437 (89.2)	35 (7.1)	0	448 (91.4)	70 (14.3)	1 (0.2)
Nausea	345 (70.4)	8 (1.6)	0	365 (74.5)	17 (3.5)	0
Constipation	241 (49.2)	1 (0.2)	0	248 (50.6)	9 (1.8)	0
Vomiting	164 (33.5)	10 (2.0)	0	188 (38.4)	14 (2.9)	1 (0.2)
Diarrhoea	135 (27.6)	10 (2.0)	0	176 (35.9)	11 (2.2)	0
Stomatitis	150 (30.6)	10 (2.0)	0	136 (27.8)	13 (2.7)	0
Abdominal pain	107 (21.8)	5 (1.0)	0	181 (36.9)	15 (3.1)	0
Investigations	405 (82.7)	285 (58.2)	0	362 (73.9)	174 (35.5)	0
Neutrophil count decreased	299 (61.0)	251 (51.2)	0	177 (36.1)	136 (27.8)	0
White blood cell count decreased	221 (45.1)	81 (16.5)	0	146 (29.8)	67 (13.7)	0
Transaminases increased	297 (60.6)	43 (8.8)	0	329 (67.1)	52 (10.6)	0
Lymphocyte count decreased	127 (25.9)	39 (8.0)	0	130 (26.5)	46 (9.4)	0
General disorders and administration site conditions	376 (76.7)	18 (3.7)	0	354 (72.2)	21 (4.3)	1 (0.2)
Fatigue	289 (59.0)	5 (1.0)	0	284 (58.0)	12 (2.4)	0
Nervous system disorders	315 (64.3)	18 (3.7)	0	381 (77.8)	61 (12.4)	0
Peripheral sensory neuropathy	201 (41.1)	6 (1.2)	0	321 (65.5)	42 (8.6)	0
Headache	117 (23.9)	5 (1.0)	0	124 (25.3)	6 (1.2)	0
Metabolism and nutrition disorders	303 (61.8)	30 (6.1)	0	326 (66.5)	51 (10.4)	1 (0.2)
Hyperglycaemia	146 (29.8)	4 (0.8)	0	152 (31.0)	10 (2.0)	0
Decreased appetite	80 (16.3)	2 (0.4)	0	126 (25.7)	8 (1.6)	0
Blood and lymphatic system disorders	283 (57.8)	65 (13.3)	0	283 (57.8)	72 (14.7)	0
Anaemia	255 (52.0)	34 (6.9)	0	258 (52.7)	51 (10.4)	0

Skin and subcutaneous tissue disorders	280 (57.1)	5 (1.0)	0	301 (61.4)	2 (0.4)	0
Alopecia	111 (22.7)	0	0	137 (28.0)	0	0
Musculoskeletal and connective tissue disorders	264 (53.9)	10 (2.0)	0	314 (64.1)	27 (5.5)	0
Bone Pain	72 (14.7)	3 (0.6)	0	143 (29.2)	11 (2.2)	0

No individual preferred term within the SOC and AEs within the SOC infections and infestations was observed. The total number of events reported were similar between the two arms (37.3% versus 38.2%) for N-AVD and Bv-AVD respectively.

Musculoskeletal pain a composite term which includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain, arthralgia and jaw pain was observed in 42.7% of patients in the N-AVD arm.

Drug-related adverse events

Drug-related AEs were AEs that were attributed to study drug (nivolumab, BV, doxorubicin, vinblastine, dacarbazine), as recorded on the CRF. Drug-related AEs (on treatment) were reported for most subjects in both treatment arms (Table 26). On-treatment was defined from first dose date to end-of-treatment assessment visit date occurring 4-8 weeks after the last dose of study drug or last dose of Residual PET-RT.

Table 26. Drug-related Adverse Events by Worst CTC Grade Reported in ≥ 5% (or ≥ 2% Grade ≥3) - All Treated Subjects, Study CA2098UT (15-Apr-2025 data cutoff)

	N-AVD N = 490			**BV-AVD N = 490**		
System Organ Class (%) Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
Total subjects with an event	470 (95.9)	304 (62.0)	3* (0.6)	468 (95.5)	249 (50.8)	7* (1.4)
Gastrointestinal disorders	407 (83.1)	31 (6.3)	0	420 (85.7)	60 (12.2)	1 (0.2)
Nausea	323 (65.9)	7 (1.4)	0	341 (69.6)	16 (3.3)	0
Constipation	199 (40.6)	1 (0.2)	0	216 (44.1)	9 (1.8)	0
Vomiting	142 (29.0)	9 (1.8)	0	164 (33.5)	12 (2.4)	1 (0.2)
Stomatitis	111 (22.7)	9 (1.8)	0	101 (20.6)	11 (2.2)	0
Diarrhoea	103 (21.0)	8 (1.6)	0	132 (26.9)	9 (1.8)	0
Abdominal pain	63 (12.9)	3 (0.6)	0	112 (22.9)	12 (2.4)	0
Dyspepsia	36 (7.3)	0	0	21 (4.3)	0	0
Oral pain	32 (6.5)	1 (0.2)	0	24 (4.9)	0	0
Gastroesophageal reflux disease	30 (6.1)	0	0	31 (8.4)	0	0
Dry mouth	20 (4.1)	0	0	32 (6.5)	0	0
Investigations	379 (77.3)	263 (53.7)	0	335 (68.4)	165 (33.7)	0
Neutrophil count decreased	279 (56.9)	237 (48.4)	0	170 (34.7)	132 (26.9)	0
White blood cell count decreased	206 (42.0)	76 (15.5)	0	141 (28.8)	66 (13.5)	0

Alanine aminotransferase increased	167 (34.1)	22 (4.5)	0	214 (43.7)	26 (5.3)	0
Aspartate aminotransferase increased	128 (26.1)	10 (2.0)	0	173 (35.3)	14 (2.9)	0
Lymphocyte count decreased	112 (22.9)	34 (6.9)	0	117 (23.9)	43 (8.8)	0
Blood alkaline phosphatase increased	57 (11.6)	0	0	86 (17.6)	0	0
Platelet count decreased	53 (10.8)	8 (1.6)	0	94 (19.2)	17 (3.5)	0
Blood creatinine increased	28 (5.7)	0	0	13 (2.7)	0	0
Blood thyroid stimulating hormone increased	28 (5.7)	0	0	2 (0.4)	0	0
Weight decreased	26 (5.3)	0	0	74 (15.1)	11 (2.2)	0
Blood lactate dehydrogenase increased	18 (3.7)	0	0	26 (5.3)	0	0
General disorders and administration site conditions	298 (60.8)	14 (2.9)	0	294 (60.0)	13 (2.7)	0
Fatigue	237 (48.4)	5 (1.0)	0	252 (51.4)	10 (2.0)	0
Pyrexia	65 (13.3)	5 (1.0)	0	63 (12.9)	2 (0.4)	0
Pain	44 (9.0)	4 (0.8)	0	33 (6.7)	1 (0.2)	0
Nervous system disorders	255 (52.0)	8 (1.6)	0	352 (71.8)	48 (9.8)	0
Peripheral sensory neuropathy	142 (29.0)	4 (0.8)	0	275 (56.1)	38 (7.8)	0
Headache	74 (15.1)	1 (0.2)	0	78 (15.9)	2 (0.4)	0
Dysgeusia	38 (7.8)	0	0	60 (12.2)	0	0
Dizziness	31 (6.3)	0	0	40 (8.2)	0	0
Peripheral motor neuropathy	20 (4.1)	1 (0.2)	0	36 (7.3)	7 (1.4)	0
Blood and lymphatic system disorders	219 (44.7)	52 (10.6)	0	243 (49.6)	63 (12.9)	0
Anaemia	201 (41.0)	28 (5.7)	0	227 (46.3)	43 (8.8)	0
Febrile neutropenia	28 (5.7)	28 (5.7)	0	33 (6.7)	33 (6.7)	0
Skin and subcutaneous tissue disorders	207 (42.2)	5 (1.0)	0	214 (43.7)	1 (0.2)	0
Alopecia	106 (21.6)	0	0	128 (26.1)	0	0
Rash maculo-papular	55 (11.2)	4 (0.8)	0	61 (12.4)	0	0
Pruritus	48 (9.8)	0	0	26 (5.3)	0	0
Metabolism and nutrition disorders	195 (39.8)	14 (2.9)	0	245 (50.0)	36 (7.3)	1(0.2)
Decreased appetite	62 (12.7)	2 (0.4)	0	111 (22.7)	7 (1.3)	0
Hyperglycaemia	57 (11.6)	2 (0.4)	0	70 (14.3)	3 (0.6)	0
Hypoalbuminaemia	44 (9.0)	2 (0.4)	0	42 (8.6)	2 (0.4)	0
Hypocalcaemia	36 (7.3)	0	0	37 (7.6)	1 (0.2)	0
Hypokalaemia	32 (6.5)	3 (0.6)	0	67 (13.7)	15 (3.1)	0
Hyponatraemia	30 (6.1)	1 (0.2)	0	59 (12.0)	2 (0.4)	0
Dehydration	14 (2.9)	4 (0.8)	0	32 (6.5)	3 (1.8)	1 (0.2)
Musculoskeletal and connective tissue disorders	168 (34.3)	8 (1.6)	0	224 (45.7)	21 (4.3)	0
Arthralgia	65 (13.3)	1 (0.2)	0	61 (12.4)	6 (1.2)	0
Myalgia	56 (11.4)	1 (0.2)	0	62 (12.7)	1 (0.2)	0

Bone pain	42 (8.6)	3 (0.6)	0	102 (20.8)	9 (1.8)	0
Back pain	30 (6.1)	0	0	38 (7.8)	4 (0.8)	0
Pain in extremity	23 (4.7)	1 (0.2)	0	40 (8.2)	3 (0.6)	0
Muscular weakness	22 (4.5)	1 (0.2)	0	32 (6.5)	3 (0.6)	0
Respiratory, thoracic and mediastinal disorders	106 (21.6)	8 (1.6)	0	137 (27.0)	17 (3.5)	1 (0.2)
Dyspnoea	45 (9.2)	4 (0.8)	0	61 (12.4)	5 (1.0)	0
Cough	34 (6.9)	0	0	32 (6.5)	0	0
Oropharyngeal pain	17 (3.5)	1 (0.2)	0	28 (5.7)	0	0
Pneumonitis	9 (1.8)	1 (0.2)	0	16 (3.3)	10 (2.0)	1 (0.2)
Vascular disorders	86 (17.6)	13 (2.7)	0	89 (18.2)	17 (3.5)	0
Hypertension	42 (8.6)	3 (0.6)	0	32 (8.8)	8 (1.6)	0
Infections and infestations	72 (14.7)	19 (3.9)	3 (0.6)	95 (19.4)	29 (5.9)	4 (0.8)
Pneumonia	10 (2.0)	6 (1.2)	0	14 (2.9)	8 (1.6)	0
Sepsis	9 (1.8)	6 (1.2)	3 (0.6)	14 (2.9)	10 (2.0)	4 (0.8)
Psychiatric disorders	65 (13.3)	3 (0.6)	0	85 (17.3)	3 (0.6)	0
Insomnia	31 (6.3)	1 (0.2)	0	54 (11.0)	2 (0.4)	0
Anxiety	20 (4.1)	0	0	30 (6.1)	0	0
Endocrine disorders	52 (10.6)	1 (0.2)	0	3 (0.6)	0	0
Hypothyroidism	37 (7.6)	1 (0.2)	0	3 (0.6)	0	0
Injury, poisoning and procedural complications	45 (9.2)	6 (1.2)	0	33 (6.7)	2 (0.4)	0
Infusion related reaction	36 (7.3)	5 (1.0)	0	10 (2.0)	0	0

*Treatment arm N-AVD - All 3 Grade 5 events were reported as sepsis
** Treatment arm BV-AVD - Grade 5 were 1 each of vomiting/dehydration, pneumonitis, cardiac arrest and 4 sepsis

Serious adverse event/deaths/other significant events

Serious adverse events

SAEs during the on-treatment period are shown in Table 27. Drug-related SAEs are reported in Table 28.

Table 27. Serious Adverse Events Summary by Worst CTC Grade Reported in ≥ 2% of Subjects: All Treated Subjects, Study CA2098UT (24-Mar-2024 data cutoff)

	N-AVD N = 490			**BV-AVD N = 490**		
System Organ Class (%) Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
Total subjects with an event	192 (39.2)	135 (27.6)	3 (0.6)	191 (39.0)	121 (24.7)	9 (1.8)
Infections and infestations	56 (11.4)	41 (8.4)	3 (0.6)	58 (11.8)	33 (6.7)	5 (1.0)
COVID-19	14 (2.9)	11 (2.2)	0	10 (2.0)	5 (1.0)	0
Sepsis	12 (2.4)	9 (1.8)	3 (0.6)	15 (3.1)	10 (2.0)	5 (1.0)
Gastrointestinal disorders	55 (11.2)	21 (4.3)	0	84 (17.1)	41 (8.4)	1 (0.2)
Nausea	28 (5.7)	8 (1.6)	0	40 (8.2)	13 (2.7)	0

Vomiting	20 (4.1)	10 (2.0)	0	28 (5.7)	13 (2.7)	1 (0.2)
Constipation	13 (2.7)	0	0	22 (4.5)	7 (1.4)	0
Stomatitis	11 (2.2)	3 (0.6)	0	10 (2.0)	2 (0.4)	0
Abdominal pain	9 (1.8)	1 (0.2)	0	16 (3.3)	7 (1.4)	0
Diarrhoea	7 (1.4)	4 (0.8)	0	10 (2.0)	3 (0.6)	0
Investigations	51 (10.4)	46 (9.4)	0	27 (5.5)	25 (5.1)	0
Neutrophil count decreased	35 (7.1)	34 (6.9)	0	15 (3.1)	15 (3.1)	0
White blood cell count decreased	11 (2.2)	9 (1.8)	0	3 (0.6)	3 (0.6)	0
General disorders and administration site conditions	44 (9.0)	8 (1.6)	0	42 (8.6)	5 (1.0)	1 (0.2)
Pyrexia	33 (6.7)	3 (0.6)	0	29 (5.9)	3 (0.6)	0
Blood and lymphatic system disorders	34 (6.9)	34 (6.9)	0	33 (6.7)	32 (6.5)	0
Febrile neutropenia	28 (5.7)	28 (5.7)	0	28 (5.7)	28 (5.7)	0
Nervous system disorders	23 (4.7)	10 (2.0)	0	26 (5.3)	10 (2.0)	0
Peripheral sensory neuropathy	6 (1.2)	2 (0.4)	0	16 (3.3)	4 (0.8)	0
Metabolism and nutrition disorders	22 (4.5)	16 (3.3)	0	27 (5.5)	17 (3.5)	1 (0.2)
Dehydration	9 (1.8)	8 (1.6)	0	19 (3.9)	10 (2.0)	1 (0.2)
Vascular disorders	19 (3.9)	15 (3.1)	0	19 (3.9)	13 (2.7)	0
Embolism	12 (2.4)	10 (2.0)	0	7 (1.4)	4 (0.8)	0
Injury, poisoning and procedural complications	16 (3.3)	10 (2.0)	0	5 (1.0)	4 (0.8)	0
Infusion related reaction	10 (2.0)	6 (1.2)	0	1 (0.2)	0	0
Respiratory, thoracic, and mediastinal disorders	16 (3.3)	9 (1.8)	0	35 (7.1)	20 (4.1)	1 (0.2)
Pneumonitis	3 (0.6)	1 (0.2)	0	14 (2.9)	11 (2.2)	1 (0.2)

Table 28. Drug-Related Serious Adverse Events by Worst CTC Grade Reported in ≥ 2% of Subjects: All Treated Subjects, Study CA2098UT (24-Mar-2024 data cutoff)

	N-AVD (N = 490)			**BV-AVD (N = 490)**		
System Organ Class (%) Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
Total subjects with an event	145 (29.6)	97 (19.8)	3 (0.6)	154 (31.4)	95 (19.4)	7 (1.4)
Investigations	50 (10.2)	45 (9.2)	0	25 (5.1)	22 (4.5)	0
Neutrophil count decreased	33 (6.7)	32 (6.5)	0	14 (2.9)	14 (2.9)	0
White blood cell count decreased	10 (2.0)	8 (1.6)	0	3 (0.6)	3 (0.6)	0
Gastrointestinal disorders	47 (9.6)	19 (3.9)	0	71 (14.5)	34 (6.9)	1 (0.2)
Nausea	25 (5.1)	7 (1.4)	0	36 (7.3)	12 (2.4)	0
Vomiting	17 (3.5)	9 (1.8)	0	25 (5.1)	11 (2.2)	1 (0.2)
Constipation	12 (2.4)	0	0	19 (3.9)	7 (1.4)	0
Abdominal pain	5 (1.0)	1 (0.2)	0	10 (2.0)	5 (1.0)	0
Blood and lymphatic system disorders	29 (5.9)	29 (5.9)	0	30 (6.1)	30 (6.1)	0

Febrile neutropenia	24 (4.9)	24 (4.9)	0	27 (5.5)	27 (5.5)	0
General disorders and administration site conditions	28 (5.7)	7 (1.4)	0	29 (5.9)	3 (0.6)	0
Pyrexia	23 (4.7)	3 (0.6)	0	24 (4.9)	2 (0.4)	0
Infections and infestations	17 (3.5)	14 (2.9)	3 (0.6)	33 (6.7)	22 (4.5)	4 (0.8)
Sepsis	8 (1.6)	5 (1.0)	3 (0.6)	12 (2.4)	8 (1.6)	4 (0.8)
Nervous system disorders	16 (3.3)	6 (1.2)	0	23 (4.7)	7 (1.4)	0
Peripheral sensory neuropathy	6 (1.2)	2 (0.4)	0	16 (3.3)	4 (0.8)	0
Metabolism and nutrition disorders	13 (2.7)	7 (1.4)	0	21 (4.3)	13 (2.7)	1 (0.2)
Dehydration	5 (1.0)	4 (0.8)	0	16 (3.3)	9 (1.8)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	9 (1.8)	4 (0.8)	0	23 (4.7)	15 (3.1)	1 (0.2)
Pneumonitis	3 (0.6)	1 (0.2)	0	13 (2.7)	10 (2.0)	1 (0.2)

Deaths

As of the 15-Apr-2025 data cutoff, 17 subjects died in the BV-AVD arm and 8 in the N-AVD arm (Table 29). Infection was the most frequently reported cause of death in both arms. There were 5 infection related deaths in the N-AVD arm and 7 in the BV-AVD arm. Zero patients died with the reported cause of death due to COVID-19.

Table 29. Death Summary - All Treated Subjects, Study CA2098UT (15-Apr-2025 data cutoff). Of note, only the primary reason for death is shown.

	N-AVD N = 490	**BV-AVD N = 490**
Number of subjects who died (based on notice of deaths CRF (%)	**8 (1.6)**	**17 (3.5)**
Primary reason for death (%)		
Tumor (Hodgkin lymphoma)	0	4 (0.8)
New primary	0	0
Infection	5 (1.0)	7 (1.4)
Drug related	0	1 (0.2)
Other	3 (0.6)	3 (0.6)
Unknown	0	2 (0.4)
Not reported	1 (0.2)	0
Number of subjects who died within 30 days of last dose (%)	**2 (0.4)**	**8 (1.6)**
Primary reason for death (%)		
Tumor (Hodgkin lymphoma)	0	1 (0.2)
New primary	0	0
Infection	2 (0.4)	4 (0.8)
Drug related	0	1 (0.2)
Other	0	2 (0.4)
Unknown	0	0
Number of subjects who died within 100 days of last dose (%)	**3 (0.6)**	**10 (2.0)**
Primary reason for death (%)		
Tumor (Hodgkin lymphoma)	0	1 (0.2)
New primary	0	0

Infection	3 (0.6)	6 (1.2)
Drug related	0	1 (0.2)
Other	0	2 (0.4)
Unknown	0	0

Overall, there were 3 (0.6%) drug-related AEs leading to death (all reported as sepsis) in the N-AVD arm and 7 (1.4%) drug-related AEs leading to death (1 each reported as vomiting/dehydration, pneumonitis, cardiac arrest and 4 reported as sepsis) in the BV-AVD arm.

Other significant events

Immune-Mediated Adverse Events (IMAE)

IMAEs were defined as specific events considered as potential immune-mediated events by the investigator that meet the following definition:

- those occurring within on-treatment period
- regardless of causality
- treated with immune modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medications (IMMs). Non-endocrine IMAEs that do not require IMMs according to the adverse event management algorithm are not included in outputs as per standard BMS processes which have been utilized in previously approved Opdivo indications by health authorities)
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

IMAE analyses included events, all causality, reported within 4 to 8 weeks after the last dose of study drug. These analyses include subjects who received immune-modulating medication for treatment of the event, except for endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these analyses include events identified by the investigator as IMAEs with no clear alternate etiology and an immune-mediated component.

Reported IMAEs (any grade, by category) are summarised in Table 30.

Table 30. IMAE Summary - All Treated Subjects, Study CA2098UT (24-Mar-2024 data cutoff).

	N-AVD N = 490		**BV-AVD N = 490**	
	Any grade	Grade 3 - 4	Any grade	Grade 3 - 4
All-causality IMAEs treated with IMM, by category				
Diarrhoea/Colitis	3 (0.6)	2 (0.4)	0	0
Hepatitis	9 (1.8)	6 (1.2)	0	0
Pneumonitis	4 (0.8)	1 (0.2)	5 (1.0)	2 (0.4)
Nephritis/Renal Dysfunction	0	0	0	0

Rash	6 (1.2)	0	4 (0.8)	0
Hypersensitivity/Infusion Reactions	4 (0.8)	3 (0.6)	0	0
All-causality Endocrine IMAEs with or without IMM, by category				
Hypothyroidism/Thyroiditis	19 (3.9)	1 (0.2)	1 (0.2)	0
Hypothyroidism	17 (3.5)	1 (0.2)	1 (0.2)	0
Hyperthyroidism	3 (0.6)	0	0	0
Thyroiditis	2 (0.4)	0	0	0
Diabetes Mellitus	0	0	0	0

IMM immune-modulating medications.

Liver function abnormalities

In patients treated with nivolumab in combination with AVD, the incidence of liver function test abnormalities was 41.2% (202/490). Grade 2, Grade 3, and Grade 4 cases were reported in 6.1% (30/490), 4.7% (23/490), and 0.6% (3/490) of patients, respectively.

Other events of special interest (OESI)

OESIs consisted of a list of preferred terms grouped by specific category (e.g., Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease).

Drug-related OESIs are summarised in Table 31.

Table 31. OESI Summary - All Treated Subjects, Study CA2098UT (24-Mar-2024 data cutoff)

	N-AVD N = 490		**BV-AVD N = 490**	
	Any grade	Grade 3 - 4	Any grade	Grade 3 - 4
All-causality OESIs with or without IMM by category				
Pancreatitis	3 (0.6)	2 (0.4)	2 (0.4)	2 (0.4)
Encephalitis	1 (0.2)	0	0	0
Myositis/Rhabdomyolysis	3 (0.6)	0	0	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	1 (0.2)	1 (0.2)
Uveitis	1 (0.2)	0	0	0
Myocarditis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

Laboratory findings

A baseline laboratory summary for all randomised subjects was provided, however post-baseline laboratory data were only recorded in the source documents but not reported in the eCRFs, and therefore, were not reported in the CSR.

Vital signs and physical examination data were not collected in the study.

Safety in special populations

Paediatric safety results (≥ 12 to < 18 years)

The safety profile of N-AVD in paediatric subjects (≥ 12 to < 18 years) is shown in Table 32. AEs reported which were ≥10% more frequent in the paediatric population were ALT increased (50.8% versus 37.8%), vomiting (50.8% versus 33.5%), AST increased (45.8% versus 30.2%), pyrexia (33.3% versus 13.3%), anxiety (27.5% versus 4.1%) and cough (25.0% versus 6.9%) for the paediatric versus the total population.

Peripheral sensory neuropathy was less frequent in the paediatric population (17.5%) compared to the total population (32.2%)

Table 32. Summary of Safety - All Paediatric Treated Subjects, Study CA2098UT (24-Mar-2024 data cutoff)

	No. of Subjects (%)			
	N-AVD N = 120		**BV-AVD N = 120**	
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade3-4**
All-causality SAEs	54 (45.0)	36 (30.0)	46 (38.3)	27 (22.5)
All-causality AEs (≥25% of Subjects in Any Arm, by PT)	117 (97.5)	82 (68.3)	116 (96.7)	75 (62.5)
Nausea	94 (78.3)	4 (3.3)	95 (79.2)	4 (3.3)
Anaemia	73 (60.8)	11 (9.2)	69 (57.5)	12 (10.0)
Neutrophil Count Decreased	71 (59.2)	55 (45.8)	62 (51.7)	50 (41.7)
ALT Increased	61 (50.8)	10 (8.3)	75 (62.5)	10 (8.3)
Vomiting	61 (50.8)	5 (4.2)	58 (48.3)	6 (5.0)
White Blood Cell Count Increased	59 (49.2)	19 (15.8)	54 (45.0)	26 (21.7)
Fatigue	56 (46.7)	0	65 (54.2)	2 (1.7)
AST Increased	55 (45.8)	3 (2.5)	63 (52.5)	7 (5.8)
Hyperglycaemia	43 (35.8)	1 (0.8)	43 (35.8)	1 (0.8)
Constipation	43 (35.8)	0	44 (36.7)	1 (0.8)
Pyrexia	40 (33.3)	3 (2.5)	36 (30.0)	3 (2.5)
Lymphocyte Count Decreased	40 (33.3)	11 (9.2)	42 (35.0)	15 (12.5)
Anxiety	33 (27.5)	0	24 (20.0)	0
Cough	30 (25.0)	0	22 (18.3)	0

	No. of Subjects (%)			
	N-AVD N = 120		BV-AVD N = 120	
	Adverse Event Grades			
Abdominal Pain	30 (25.0)	1 (0.8)	45 (37.5)	3 (2.5)
Headache	29 (24.2)	1 (0.8)	40 (33.3)	1 (0.8)
Stomatitis	27 (22.5)	4 (3.3)	32 (26.7)	1 (0.8)
Peripheral Sensory Neuropathy	21 (17.5)	1 (0.8)	40 (33.3)	1 (0.8)
Platelet Count Decreased	21 (17.5)	2 (1.7)	40 (33.3)	3 (2.5)
Bone Pain	13 (10.8)	0	40 (33.3)	4 (3.3)
Drug-related AEs (≥25% of Subjects in Any Arm, by PT)	116 (96.7)	75 (62.5)	114 (95.0)	71 (59.2)
Nausea	89 (74.2)	3 (2.5)	91 (75.8)	3 (2.5)
Neutrophil Count Decreased	68 (56.7)	53 (44.2)	62 (51.7)	50 (41.7)
Anaemia	64 (53.3)	9 (7.5)	68 (56.7)	11 (9.2)
ALT Increased	57 (47.5)	9 (7.5)	73 (60.8)	10 (8.3)
Vomiting	56 (46.7)	4 (3.3)	53 (44.2)	6 (5.0)
White Blood Cell Count Decreased	55 (45.8)	18 (15.0)	53 (44.2)	26 (21.7)
AST Increased	49 (40.8)	2 (1.7)	62 (51.7)	7 (5.8)
Fatigue	48 (40.0)	0	58 (48.3)	1 (0.8)
Constipation	36 (30.0)	0	40 (33.3)	1 (0.8)
Lymphocyte Count Decreased	36 (30.0)	11 (9.2)	39 (32.5)	15 (12.5)
Abdominal Pain	21 (17.5)	0	36 (30.0)	2 (1.7)
Peripheral Sensory Neuropathy	21 (17.5)	1 (0.8)	39 (32.5)	1 (0.8)
Headache	19 (15.8)	0	32 (26.7)	0
Platelet Count Decreased	19 (15.8)	2 (1.7)	40 (33.3)	3 (2.5)
Bone Pain	9 (7.5)	0	34 (28.3)	3 (2.5)

Elderly population

The safety of N-AVD was evaluated in 30 elderly patients 65 years and older, including 7 patients aged ≥75 years. Serious AEs were more frequent in the elderly population, mainly caused by a higher incidence of hospitalisation/prolongation and important medical events (Table 33). In 10/30 patients aged 65 years and older, a total of 31 serious medically important events were reported. Adverse events resulting in an important medical events reported in >1 patient were neutrophil count decreased (n=8), white blood cell count decreased (n=2) and hypotension (n=2).

Table 33. Summary of On-treatment Adverse Events by Age Group in the N-AVD arm, Study CA2098UT

MedDRA terms	<18 years N=120	18 – 64 years N=340	64 – 74 years N=23	≥75 years N=7
Total subjects with an event	117 (97.5)	334 (98.2)	22 (95.7)	6 (85.7)
Serious AE – Total	54 (45.0)	119 (35.0)	14 (60.9)	4 (57.1)
Fatal (death)	0	1 (0.3)	2 (8.7)	0
Hospitalization/prolongation	43 (35.8)	79 (23.2)	7 (30.4)	3 (42.9)
Life threatening	2 (1.7)	7 (2.1)	1 (4.3)	0
Disability/incapacity	1 (0.8)	1 (0.3)	0	0
Important medical event	10 (8.3)	33 (9.7)	7 (30.4)	2 (28.6)
Psychiatric disorders	46 (38.3)	127 (37.4)	9 (39.1)	1 (14.3)
Nervous system disorders	66 (55.0)	229 (67.4)	14 (60.9)	6 (85.7)
Accident and injuries	9 (7.5)	23 (6.8)	2 (8.7)	1 (14.3)
Cardiac disorders	21 (17.5)	65 (19.1)	5 (21.7)	1 (14.3)
Vascular disorders	32 (26.7)	116 (34.1)	8 (34.8)	2 (28.6)
Cerebrovascular disorders	1 (0.8)	1 (0.3)	0	0
Infections and infestations	44 (36.7)	129 (37.9)	8 (34.8)	2 (28.6)
Anticholinergic syndrome	51 (42.5)	138 (40.6)	9 (39.1)	4 (57.1)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia fractures	14 (11.7)	56 (16.5)	5 (21.7)	3 (42.9)

In patients aged 18 - 64 the incidence of neutrophil count decreased was 81.2% (grade ≥3 58.9%) in the N-AVD arm and 72.2% (grade ≥3 31.3%) in the BV-AVD arm. The incidence of febrile neutropenia was 5.9% (grade ≥3 5.9%) in the N-AVD arm and 7.0% (grade ≥3 7.0%) in the BV-AVD arm. The incidence of infections and infestations was 37.9% (grade ≥3 9.7%) in the N-AVD arm and 37.4% (grade ≥3 9.6%) in the Bv-AVD arm. In patients aged 65 years and older the incidence of neutrophil count decreased was 73.3% (grade ≥3 63.3%) in the N-AVD arm and 75.0% (grade ≥3 42.9%) in the BV-AVD arm. The incidence of febrile neutropenia was 16.7% (grade ≥3 16.7%) in the N-AVD arm and 17.9% (grade ≥3 17.9%) in the BV-AVD arm. The incidence of infections and infestations was 33.3% (grade ≥3 13.3%) in the N-AVD arm and 50.0% (grade ≥3 25.0%) in the BV-AVD arm.

Among the thirty patients aged ≥ 65 years who received nivolumab in combination with AVD, 70% (21/30) were administered G-CSF compared to 56.1% (258/460) in patients < 65 years. The reported

incidence of neutropenia was numerically lower in patients who received G-CSF (52.4%) compared with those who did not (66.7%).

Discontinuation due to adverse events

The most frequently reported AEs leading to discontinuation were hepatic associated AEs (6/19) in the N-AVD arm and respiratory associated AEs (4/15) in the BV-AVD arm as below:

- N-AVD arm: ALT/AST increased (4), transaminitis/autoimmune hepatitis (1) and liver failure (1)
- BV-AVD arm: pneumonitis (2), pulmonary edema (1) and pleural effusion (1)

2.5.1. Discussion on clinical safety

The safety of nivolumab in combination with AVD (doxorubicin, vinblastine, dacarbazine; N-AVD) was assessed based on data from the pivotal phase 3 open-label randomised trial CA2098UT. In this study 980 subjects aged ≥12 years with newly diagnosed advanced stage classical Hodgkin lymphoma were treated (490 in the N-AVD arm and 490 in the BV-AVD arm). The safety data were presented for the total population, with a subgroup analysis for the paediatric population (≥12 - <18 years).

Data from three different data cutoffs were provided. A complete safety data update was provided for the data cutoff of 24-Mar-2024 with a minimum follow-up of 17.6 months. In addition, the overall AEs, drug-related AEs and deaths were also provided with a data cutoff of 15-Apr-2025 with a minimum follow-up of 30.4 months. SAEs, IMAEs, OESIs and the paediatric subgroup analyses were not updated. This is considered acceptable, as the 24-Mar-2024 data cutoff with a median follow-up of 29 months captures the complete on-treatment period and a sufficient part of the post-treatment period to allow safety assessment. Furthermore, during the post-treatment period, only SAEs and drug-related AEs with CTC grade ≥3 were collected.

The majority of patients (88.6%) received the intended 6 cycles of nivolumab and this percentage was similar in paediatrics and adults. AVD dose reductions were more common in the BV-AVD arm compared to the N-AVD arm. Especially vinblastine dose reductions were more frequent in the BV-AVD arm (10.8%) compared to the N-AVD arm (3.9%) and were mainly caused by neurological adverse events and gastrointestinal adverse events. Both neurotoxicity and gastrointestinal events are known ADRs of both vinblastine and brentuximab vedotin, and the overlap in toxicity profile could explain the higher incidence of vinblastine dose reduction in the BV-AVD arm compared to the N-AVD arm.

Per protocol, all patients in the BV-AVD arm received prophylactic G-CSF. In the N-AVD arm G-CSF use was common (56.9%) as 51.2% of patients had a grade ≥3 AE of neutrophil count decreased. A warning for neutropenia and a recommendation to consider G-CSF use is included in the SmPC section 4.4. The number of discontinuations due to adverse events was low (3.9%) and were mainly due to hepatic associated AEs.

Adverse events

Almost all patients in both arms experienced AEs. The most common AEs in the N-AVD arm were nausea (70.4%), neutrophil count decreased (61.0%), fatigue (59.0%) and anaemia (52.0%).

Neutrophil count decreased (61.0% versus 36.1%) and white blood cell count decreased (44.9% versus 29.8%) were higher in the N-AVD arm while peripheral sensory neuropathy (32.2% versus 58.4%), ALT increased (37.8% versus 48.4%), abdominal pain (19.6% versus 34.1%) and bone pain (14.7% versus 29.2%) were higher in the BV-AVD arm. Peripheral neuropathy is a very common ADR of brentuximab vedotin (SmPC Adcetris) while bone pain is a very common ADR of G-CSF, which was protocol-mandated in the BV-AVD arm. Therefore, N-AVD offers a distinct safety profile compared to BV-AVD, with a higher incidence of neutropenia and IMAE but with a lower incidence of peripheral neuropathy compared to BV-AVD.

Grade ≥3 AEs were more common in the N-AVD arm (70.6%) compared to the BV-AVD arm (58.2%), mainly driven by a higher incidence of neutrophil count decreased (51.2% versus 27.8%). However, no differences in the incidence of febrile neutropenia (5.7%, all grade ≥3 in both arms) and AEs within the SOC infections and infestations (37.3% versus 38.2%) were observed. Compared to the integrated safety dataset, the incidence of neutropenia with N-AVD (all grade 61%; grade ≥3 51%) is notably higher than observed in the registrational studies of nivolumab + chemotherapy (all grade 44.6%; grade ≥3 13.6%). As discussed above, a warning for neutropenia in SmPC section 4.4 has been implemented.

The most frequently reported drug-related AEs were in line with the most frequent reported AEs for both arms.

SAEs, deaths and other events of special interest

The most frequently reported SAEs in the N-AVD arm were neutrophil count decreased (7.1%), pyrexia (6.7%), febrile neutropenia (5.7%). The most frequently reported drug-related SAEs were neutrophil count decreased (6.7%), nausea (5.1%) and febrile neutropenia (4.9%). The most frequently reported SAEs in the BV-AVD arm were nausea (8.2%), pyrexia (5.9%), vomiting (5.7%) and febrile neutropenia (5.7%). The most frequently reported drug-related SAEs were nausea (7.3%), febrile neutropenia (5.5%) and vomiting (5.1%). Again, the most striking difference is the higher incidence of neutropenia in the N-AVD arm.

The number of deaths was numerically lower with N-AVD (n=8, 1.6%) compared to BV-AVD (n=17, 3.5%). There were 3 drug-related AEs leading to death, all reported as sepsis in the N-AVD arm and 7 drug-related AEs leading to death in the BV-AVD arm including 4 reported as sepsis.

The most frequent IMAEs were hypothyroidism/thyroiditis (3.9%) and hypothyroidism (3.5%), hepatitis (1.8%) and rash (1.2%). This is consistent with IMAEs observed for the approved indications of nivolumab in combination with chemotherapy. The most frequent IMAEs are therefore adequately described for nivolumab in combination with chemotherapy in SmPC section 4.8.

Drug-related other events of special interest in the N-AVD arm included pancreatitis (n=3, 0.6%), uveitis (n=1, 0.2%), encephalitis (n=1, 0.2%) and rhabdomyolysis/myositis (n=3, 0.6%). Pancreatitis, uveitis and encephalitis are known ADRs for nivolumab in combination with chemotherapy and the frequency is in line with previous studies. Myositis has also been added as ADR for nivolumab in combination with chemotherapy in SmPC section 4.8.

Laboratory findings

Laboratory data were included in the source documents but not reported in the eCRFs and, therefore, no laboratory data were provided. The MAH stated that any observed abnormalities were reported as AEs by the investigator. It is acknowledged that the study was not sponsored by the MAH and performed by the SWOG Cancer Research Group which might hamper data access. However, there is a potential for underreporting.

Safety in special populations

A subgroup analysis in paediatric subjects (≥ 12 to < 18 years; n=120) was performed. Paediatric subject received a weight-based dose of nivolumab (3 mg/kg) for patients < 80kg and a fixed dose of 240mg for patients ≥80kg. AEs more frequently observed in the paediatric population were ALT increased (50.8% versus 37.8%), vomiting (50.8% versus 33.5%), AST increased (45.8% versus 30.2%), pyrexia (33.3% versus 13.3%), anxiety (27.5% versus 4.1%) and cough (25.0% versus 6.9%) for the paediatric versus the total population. Peripheral sensory neuropathy was less frequent in the paediatric population (17.5%) compared to the total population (32.2%). A higher incidence of vomiting, pyrexia, anxiety and cough was also observed in paediatric subjects included in the registrational study for melanoma (CA029070, EMEA/H/C/003985/II/0125/G). In conclusion, although some differences in frequencies were observed, in general the safety profile in paediatric patients was similar to the total population and no new safety signals or toxicities were reported. The description in SmPC section 4.8 is acceptable.

Although safety assessment in the elderly population is hampered by the small number of subjects aged ≥65 years (n=30), a higher frequency of febrile neutropenia was noted in the elderly population and this is reflected in the SmPC section 4.8.

In the ECHELON-1 study with BV-AVD, advanced age was identified as a risk factor for febrile neutropenia in patients with advanced cHL. Similar, in study CA2098UT the incidence of febrile neutropenia was higher for older patients; 16.7% in patients ≥65 years and 5.9% in patients 18 – 64 years and this is reflected in the SmPC to indicate that advanced age was a risk factor for febrile neutropenia. There were no differences between the N-AVD and BV-AVD arm and the incidence within the SOC infections and infestations were similar between age groups.

2.5.2. Conclusions on clinical safety

The overall safety profile of N-AVD was manageable and consistent with the known safety profiles of the therapeutic agents except for a higher frequency of neutropenia but no differences in the clinical relevant outcomes febrile neutropenia and infections. N-AVD offers a distinct safety profile compared to BV-AVD, with a higher incidence of neutropenia and IMAEs but with a lower incidence of peripheral neuropathy compared to BV-AVD.

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 PRAC considered that the risk management plan version 51.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 51.2 with the following content:

Safety concerns

Table 34. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs) Severe infusion reactions (IV only)
Important potential risks	Embryofoetal toxicity Immunogenicity Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment Patients already receiving systemic immunosuppressants before starting nivolumab Long-term safety in adolescent patients ≥12 years of age (IV only)

Pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
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				
None				
Category 3 - Required additional pharmacovigilance activities				

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557) Voluntary PASS	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients ≥ 12 years of age (IV only)	ongoing	1. Submission of protocol[a] : Q4 2023 2. Interim Study Report: Q4 2026 3. Final report of study results: Q4 2033

Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimisation measures: Patient Alert Card
Severe Infusion Reactions (IV only)	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8 Additional risk minimisation measures: None
Embryofoetal toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 Additional risk minimisation measures: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 4.8 Additional risk minimisation measures: None
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimisation measures: Nivo IV SmPC Section 4.4 and 4.8 Nivo SC SmPC Section 4.4 Additional risk minimisation measures: None

Safety Concern	Risk Minimisation Measures
Patients with severe hepatic and/or renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2 Additional risk minimisation measures: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5 Additional risk minimisation measures: None
Long-term safety in adolescent patients ≥ 12 years of age (IV only)	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None

2.7. Update of the Product information

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

2.7.1. User consultation

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

- The proposed indication concerns the same route of administration and has a similar safety profile as the previously approved indications (i.e., key safety messages for the existing and proposed indication are more or less the same).
- The modifications proposed in the PL do not represent major changes. The instructions for dose calculation, preparation, administration, storage and disposal in the currently approved PL remain unchanged.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is:

nivolumab in combination with doxorubicin, vinblastine and dacarbazine (AVD) is indicated for adults and adolescents 12 years of age and older with previously untreated Stage III or IV classical Hodgkin lymphoma.

Classical Hodgkin lymphoma is characterized pathologically by the presence of monoclonal lymphoid cells that may be either mononuclear (Hodgkin cells) or multinucleate (Reed-Sternberg cells). HL is a lymphoid neoplasm which typically affects young adults and presents with painless lymphadenopathy

with or without splenomegaly, fevers, drenching night sweats, weight loss and pruritus. The diagnosis is best established by an excisional lymph node biopsy demonstrating large, atypical lymphoblasts surrounded by a heterogeneous infiltrate of non-neoplastic inflammatory and accessory cells. Patients with Stage I-II disease are considered to have "early stage" HL and are generally treated with short courses (2-4 cycles) of combination chemotherapy followed by involved field RT for some which affords a cure rate of 90-95%. Patients with Stages III-IV disease are considered to have advanced stage HL.

3.1.2. Available therapies and unmet medical need

Early line treatment approaches in the EU for children and adults with cHL typically involve combination chemotherapy, with or without radiotherapy (RT), and may include strategies to tailor subsequent therapies based on response. Differences in treatment between adult and paediatric protocols are largely related to age-specific concerns regarding late effects of alkylating agents (infertility, second malignancy), anthracycline (cardiac toxicity), and RT (bone and soft tissue growth, second malignancy, cardiopulmonary sequalae), with an evolution toward treatment protocols limiting the cumulative doses of the above chemotherapies and limiting radiation doses to 15 to 25 Gy of involved lymph node regions only.

3.1.3. Main clinical studies

Study CA2098UT is a multicentre, randomised, open-label, Phase 3 clinical study in adults and adolescent (age ≥12 and <18 years) subjects with histologically confirmed, newly diagnosed, previously untreated advanced stage (III-IV) cHL (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or NOS).

The primary endpoint was PFS per investigator. The secondary endpoints were overall survival (OS), event-free survival (EFS) and complete metabolic response rate (CMR).

The application provides results for the primary endpoint of investigator-assessed PFS at the pre-specified IA2 based on 51% of events (data cutoff 15-Dec-2022, minimum follow-up 2.4 months). In addition, results with longer follow-up (minimum follow-up of 17.6 months) based on a data cutoff of 24-Mar-2024 and a 3rd data cut was conducted at the 75% PFS information fraction based on the 15-Apr-2025 clinical data cutoff with a minimum follow up of 30.4 months.

3.2. Favourable effects

The primary endpoint of PFS per INV at IA2: HR = 0.42 (95% CI: 0.27, 0.67); stratified log-rank test 1-sided p-value < 0.0001. Difference in PFS maintained with last DCO (15-Apr-2025). The median PFS was not reached in the last DCO (median follow up of 36.5 months).

A high concordance rate (94.5%) between INV-assessed and BICR-assessed PFS was observed and no concern regarding informative censoring of BICR-assessed PFS (i.e., censoring in BICR PFS due to no scans being available after investigator-assessed progression events that is not a BICR-progression events).

The secondary endpoint OS is considered immature with numerically fewer OS events observed in the N-AVD arm (5/496 events) vs the BV-AVD arm (12/498 events) also at the last DCO with a reported OS hazard ratio of 0.47 (95% CI: 0.21, 1.07). This is as expected due to the very long survival and number of treatment options in relapsed setting, including SCT.

EFS per primary definition demonstrated improvement in EFS per INV of N-AVD compared with BV-AVD at 15-Dec-2022 data cutoff (HR = 0.55 (95% CI: 0.38, 0.81)) with consistent results at later DCO.

Increased CMR was observed for N-AVD vs BV-AVD (N-AVD 66.7% vs 55.6% based on the 15-Dec-2022 DCO; 79.0% vs 64.5% based on 24-March-2024 DCO).

With respect to the paediatric patients (≥12 years) the efficacy results showed an improved PFS per INV of N-AVD compared to BV-AVD treatment (24-Mar-2024 data cutoff, HR = 0.34 (95% CI: 0.15, 0.77)). The results for PFS per INV, PFS per BICR, EFS per INV, and CMR in paediatric patients were consistent with the results for the overall population and were in favour of the N-AVD arm.

3.3. Uncertainties and limitations about favourable effects

In principle retreatment with nivolumab could be foreseen as nivolumab is considered 3 times during the treatment course of HL based on its approved indications in this condition. There is currently very little information on the efficacy and safety of retreatment of nivolumab, the MAH is encouraged to evaluate the efficacy of nivolumab in pretreated patients.

3.4. Unfavourable effects

The pivotal dataset consists of 490 patients treated with N-AVD including 120 subjects aged ≥12 – 18 years. The majority of patients (88.6%%) received the intended 6 cycles of nivolumab and this percentage was similar between paediatrics and adults. The number of discontinuations due to adverse events was low (3.9%).

The most common AEs in the N-AVD arm were nausea (70.4%), neutrophil count decreased (61.0%), fatigue (59.0%) and anaemia (52.0%). Grade ≥3 AEs were more common in the N-AVD arm (70.6%) compared to the BV-AVD arm (58.2%), mainly driven by a higher incidence of neutrophil count decreased (51.2% versus 27.8%). No differences in the incidence of febrile neutropenia (5.7%, all grade ≥3 in both arms) and AEs within the SOC infections and infestations (37.3% versus 38.2%) were observed.

The number of deaths was lower with N-AVD (n=8, 1.6%) compared to BV-AVD (n=17, 3.5%). There were three drug-related deaths in the N-AVD arm, all due to sepsis. The most frequent IMAEs were hypothyroidism/thyroiditis (3.9%) and hypothyroidism (3.5%), hepatitis (1.8%) and rash (1.2%). Drug-related other events of special interest in the N-AVD arm included pancreatitis (n=3, 0.6%), uveitis (n=1, 0.2%), encephalitis (n=1, 0.2%) and rhabdomyolysis/myositis (n=3, 0.6%).

AEs more frequently observed in the paediatric population (≥12 – 18 years) were ALT increased (50.8% versus 37.8%), vomiting (50.8% versus 33.5%), AST increased (45.8% versus 30.2%), pyrexia (33.3% versus 13.3%), anxiety (27.5% versus 4.1%) and cough (25.0% versus 6.9%) for the paediatric versus the total population. Peripheral sensory neuropathy was less frequent in the paediatric population (17.5%) compared to the total population (32.2%).

3.5. Uncertainties and limitations about unfavourable effects

G-CSF use was not balanced between treatment arms as prophylactic G-CSF use was mandatory in the BV-AVD arm and not in the N-AVD arm. Therefore, it is uncertain if neutropenic events were caused by nivolumab or the AVD backbone.

Interpretation of the frequencies in the ≥65 years age group is limited due to the small number of subjects (n=30).

3.6. Effects Table

Table 35. Effects Table for nivolumab in combination with AVD for the treatment of adults and adolescents 12 years of age and older with previously untreated Stage III or IV classical Hodgkin lymphoma - Efficacy data cut-off: 15-Dec-2022; Safety data cut-off: 15-APR-2025

Effect	Short description	Unit	N-AVD	BV-AVD	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Time from date of randomisation to date of first observation per investigator assessment of progressive disease according to the 2014 Lugano classification, or death due to any cause, whichever occurs first	Events (%)	28/496 (5.6%)	62/498 (12.4%)	HR = 0.42 (95% CI: 0.27, 0.67); stratified log-rank test 1-sided p-value < 0.0001 The median PFS was not reached in the last DCO. High concordance rate between INV-assessed and BICR-assessed PFS OS data are immature and not type I-error controlled: 9/486 (1.0%) vs 17/483 (3.4%), HR=0.47 (0.10,1.07) for N-AVD and BV-AVD	CA2098UT
Unfavourable Effects						
Neutropenia (grade ≥3)	Reported as AE by investigator, grade ≥3	%	51.2%	27.8%	G-CSF use was not balanced between treatment arms	CA2098UT
IMAEs	Diarrhoea/Colitis	Events (%)	3 (0.6)	0		
	Hepatitis		9 (1.8)	0		
	Pneumonitis		4 (0.8)	5 (1.0)		

Effect	Short description	Unit	N-AVD	BV-AVD	Uncertainties / Strength of evidence	References
	Rash		6 (1.2)	4 (0.8)		
	Hypersensitivity/Infusion Reactions		4 (0.8)	0		
Deaths	Number of deaths		1.6% (N=8)	3.5% (N=17)	Three drug-related deaths in N-AVD arm, all caused by sepsis.	

Abbreviations: AE adverse event; AVD doxorubicin, vinblastine and dacarbazine; BICR: blinded independent review committee; BV brentuximab vedotin; DCO: data cut-off; G-CSF Granulocyte colony stimulating factor; HR: hazard ratio; IMAE: Immune-mediated adverse events OS: Overall Survival; PFS: Progression free survival

Notes: DCO for effects included in the Table are different, i.e. for PFS is 15 Dec 2022 DCO but 15-Apr-2025 for OS and the unfavourable effects.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study CA2098UT has shown superiority of N-AVD versus BV-AVD on PFS supported by secondary endpoints EFS and CMR. The median PFS was not reached at the last DCO, which is understandable given the apparent cure rates above 50%. A difference in PFS rate at the plateau of the KM-curve of app. 10% in favor of N+AVD in the frontline treatment of cHL can be considered a small but clinically relevant difference.

The results for PFS per INV, PFS per BICR, EFS per INV, and CMR in paediatric patients were consistent with the results for the overall population and were in favour of the N-AVD arm.

Results were comparable among the tested subgroups although a multivariate interaction and subgroup analysis investigating the PFS for patients with disease with less favourable prognosis (IPI score 4-7, B symptoms, bulky disease and/or age, stage) is requested for N-AVD vs BV-AVD.

The overall safety profile of N-AVD was manageable and consistent with the known safety profiles of the therapeutic agents except for a higher frequency of neutropenia with no differences in the clinical relevant outcomes febrile neutropenia and infections. N-AVD offers a distinct safety profile compared to BV-AVD, with a higher incidence of neutropenia and IMAEs but with a lower incidence of peripheral neuropathy compared to BV-AVD. Thus, having an alternative treatment option in frontline cHL setting is welcomed especially when associated with a difference in safety profile.

Differences were observed in safety profile of N+AVD vs BV+AVD which might be relevant from a patient preference perspective. The safety profile in adolescents was in general similar to the total population and no new safety signals or toxicities were identified.

3.7.2. Additional considerations on the benefit-risk balance

Not applicable.

3.7.3. Balance of benefits and risks

The benefit-risk balance of nivolumab with doxorubicin, vinblastine and dacarbazine in the applied indication is positive.

3.8. Conclusions

The overall B/R of nivolumab in combination with doxorubicin, vinblastine and dacarbazine for adults and adolescents 12 years of age and older with previously untreated Stage III or IV classical Hodgkin lymphoma, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus 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- Addition of a new therapeutic indication or modification of an approved one	Variation type II	C.I.6.a

Extension of indication to include OPDIVO for the treatment of adults and adolescents 12 years of age and older with previously untreated Stage III or IV classical Hodgkin Lymphoma (cHL), based on results from the pivotal study CA2098UT (SWOG 1826), a Phase 3, randomised, open-label study of nivolumab + doxorubicin/vinblastine/dacarbazine (N-AVD) versus brentuximab vedotin (BV) + AVD (BV-AVD) in patients (age ≥12 years) with newly diagnosed, advanced stage cHL. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 51.2 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following conditions:

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.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the patient card.

- **The patient card** shall contain the following key messages:

- That OPDIVO treatment may increase the risk of:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related nephritis and renal dysfunction
  - Immune-related endocrinopathies
  - Immune-related skin adverse reactions
  - Other immune-related ARs

- Signs or symptoms of the safety concern and when to seek attention from a HCP

- Contact details of the OPDIVO prescriber

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
1. Post authorisation efficacy study (PAES): In order to further elucidate the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab and ipilimumab, the MAH should conduct and submit the results of a randomised, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an appropriate spectrum of PD-L1 expression levels. This study should be conducted according to an agreed protocol.	By 28th February 2027

2. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma, the MAH should submit the OS data from the 2nd IA and the final OS analysis of the Phase 3 CA209274 study in the PD-L1 ≥ 1% population.	By 31st December 2027
3. Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K.	By 31st March 2029
4. Post authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%, the MAH should submit the results of the final OS analysis from study CA20977T, a phase III, randomised, double-blind study.	By 30th June 2027

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0138/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.