27 February 2025
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

OPDIVO

Nivolumab

Procedure no: EMEA/H/C/003985/P46/061

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	30-12-2024	30-12-2024	☐
☐	CHMP Rapporteur Assessment Report	03-02-2025	03-02-2025	☐
☐	CHMP members comments	17-02-2025	17-02-2025	☐
☐	Updated CHMP Rapporteur Assessment Report	n/a	n/a	☐
☒	CHMP adoption of conclusions:	27-02-2025	27-02-2025	☐

LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first line of therapy
ASCT	autologous stem cell transplant
AE	adverse event
BICR	blinded, independent central review
Bv	brentuxumab vedotin
Bv +B	brentuximab vedotin plus bendamustine
cHL	classical Hodgkin lymphoma
CMR	complete metabolic response
CR	complete response
CSR	clinical study report
CTLA-4	cytotoxic T-lymphocyte associated protein 4
EFS	event-free survival
HDCT	high-dose chemotherapy
HL	Hodgkin lymphoma
IRT	Interactive Response Technology
IV	intravenous
IMAE	immune-mediated adverse event
N+Bv	nivolumab + brentuxumab vedotin
ORR	overall response rate
OS	overall survival
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PMR	partial metabolic response
R/R	relapsed/refractory
RT	radiotherapy
SAE	serious adverse event

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1. Introduction

On 26-11-2024, the MAH submitted a completed paediatric study, Study CA209744, in accordance with Article 46 of Regulation (EC) Nº1901/2006, as amended.

A short critical expert overview has also been provided.

Nivolumab is an IgG4 monoclonal antibody that binds to the 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.

2. Scientific discussion

2.1. Information on the development program

Nivolumab (OPDIVO) 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 after 3 or more lines of systemic therapy including ASCT.

Study CA209744 is part of the agreed Nivolumab (OPDIVO) Paediatric Investigation Plan (PIP) covering the conditions of treatment of malignant neoplasms of lymphoid tissue and treatment of malignant neoplasms of the central nervous system (PIP number: EMEA-001407-PIP02-15-M07; latest EMA Decision P/0138/2024, dated 06-May-2024). The submission of these data is intended to fulfil the requirements of Article 46 of Regulation (EC) Nº 1901/2006, which sets out the obligation for marketing authorisation holders (MAHs) to submit any MAH-sponsored study involving the use of an authorised medicinal product in the paediatric population to the competent authority, within six months of its completion.

In addition, submission of the results of Study CA209744 is planned as part of a future variation.

2.2. Information on the pharmaceutical formulation used in the study

Subjects received nivolumab 3 mg/kg as a 30-minute IV infusion, on Day 8 of cycle 1 and then on Day 1 for each subsequent 3-week treatment cycle.

The brentuximab vedotin (Bv) dose was 1.8 mg/kg as a 30-minute IV infusion on Day 1 of every 3-week treatment cycle, and Bv 1.8 mg/kg (Day 1 of each cycle) in combination with bendamustine 90 mg/m2 (Days 1 and 2 of each cycle).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report(s) for Study CA209744.

CA209744 is a Phase 2, open-label study intended to evaluate the efficacy and safety of nivolumab 3 mg/kg + brentuximab vedotin 1.8 mg/kg (hereafter referred to as N+Bv) in pediatric and young adult

subjects with R/R CD30 + cHL after failure of first-line therapy. There were 2 treatment cohorts in this study:

- Cohort R1 for subjects at low risk of relapse and
- Cohort R2 for subjects at standard risk of relapse.

2.3.2. Clinical study

Study CA209744

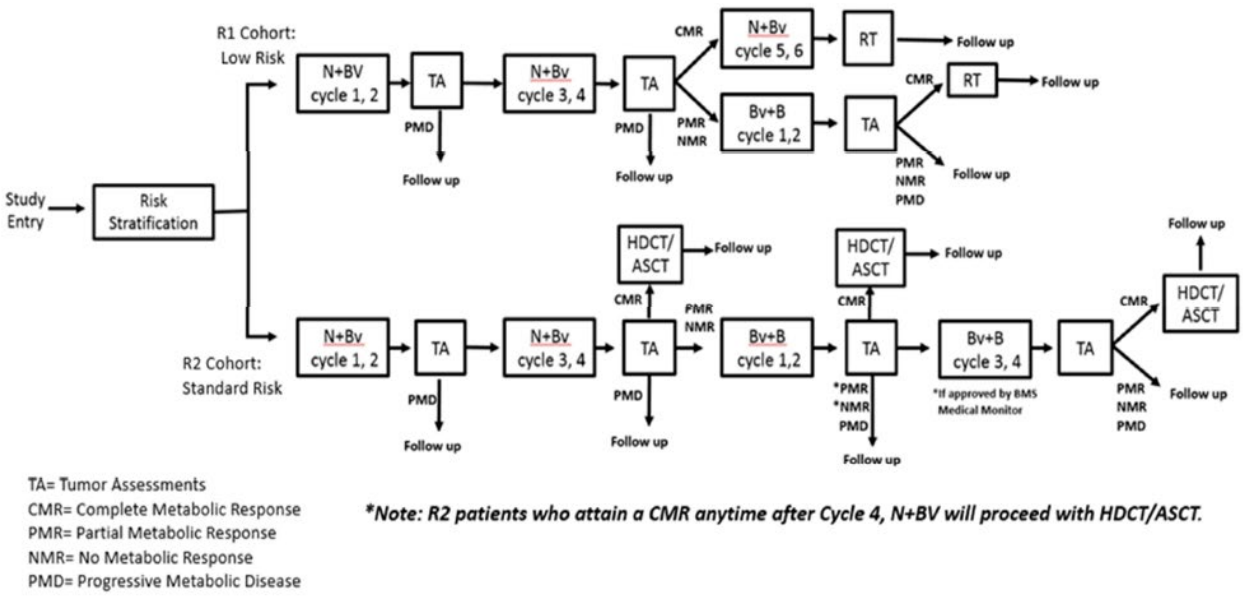
Study CA209744 is a Risk-based, Response-adapted, Phase II Open-Label Trial of Nivolumab + Brentuximab Vedotin (N+ Bv) for Children, Adolescents, and Young Adults (age: 5 to < 30 years) with Relapsed/Refractory (R/R) CD30 + Classic Hodgkin lymphoma (cHL) after Failure of First-line Therapy, followed by Brentuximab Vedotin + Bendamustine (Bv + B) for Participants with a Suboptimal Response.

All subjects entered the Induction Phase and received treatment with N+ Bv. Subjects moved into the Intensification Phase if they received treatment with Bv+B. Subjects moved into the Consolidation Phase if they received radiation therapy (Cohort R1) or HDCT/ASCT (Cohort R2).

The planned study duration included a treatment period of 6 to 8 months and a follow-up period of at least 36 months after completion of treatment for all subjects.

Description

Figure 1. Study Design Schematic



Source: Figure 5.1-1 in the CA209744 Protocol (Appendix 1.1)

The original Protocol for this study was dated 23-Sep-2016. As of the data cut-off date (28-May-2024), there were a total of 4 global revisions; 3 country-specific amendments for Germany, Czech Republic, and the United Kingdom; and 4 administrative letters.

Table 1. Summary of Key Changes to Protocol CA209144

Document (Amendment)/ Date	Summary of Key Changes	Planned Sample Size	Subjects Enrolled/Treated at Time of Protocol Amendment
Original Protocol (23-Sep-2016)	• Not applicable.	100 enrolled 80 treated (40/cohort)	0
Protocol Amendment 01 (01-Mar-2017)	• Added futility rule for Cohort R2. • Clarified that R1 consolidation therapy can include all types of RT per institutional guidelines. • Added up to 2 additional cycles of Bv+B with BMS medical monitor approval for Cohort R2 consolidation therapy delays for consistency with Induction Phase (N+Bv). • Clarified PFS definition for secondary endpoint: start of subsequent anticancer therapy (that is not part of HDCT/ASCT consolidation therapy in Cohort R2) without reported progression or death will be censored at the last tumor assessment prior to initiation of subsequent anticancer therapy. • Added exploratory endpoint assessing efficacy measures using LYRIC 2016 criteria.	100 enrolled 80 treated (40/cohort)	5 enrolled 5 treated (R1:0/0; R2: 5/5)
Protocol Amendment 02 (01-Jun-2017)	• Added CMR rate as co-primary endpoint for Cohort R1 per health authority and study steering committee feedback. CMR is a surrogate endpoint to assess response earlier. • Clarified contraception guidelines to harmonize Protocol and global product labels for brentuximab and bendamustine.	100 enrolled 80 treated (40/cohort)	52 enrolled 49 treated (R1:10/10 R2: 42/39)
Protocol Amendment 03 (26-Mar-2018)	• Added secondary endpoint to evaluate efficacy as assessed by investigators to allow for a comprehensive interpretation of study data. – BICR assessment was used for tumor assessments at study treatment-related decision timepoints to determine further treatment. If investigator assessment was CMR but BICR assessment differed and treatment was discontinued, tumor assessments were collected until investigator-assessed progression.	100 enrolled 80 treated (40/cohort)	77 enrolled 72 treated (R1: 28/28 R2 49/44)
Protocol Amendment 04 (26-Mar-2021)	• Closed recruitment to Cohort R1 due to feasibility issues in accrual. – Reduced number of planned treated subjects from 80 (40 in each cohort) to 72 (R1: n = 28; R2: n = 44) in order to proceed with closing the study and report results in a meaningful timeframe for pediatric subjects. • Added BMS standard Protocol language on COVID-19.	100 enrolled 72 treated (R1: 28; R2: 44)	77 enrolled 72 treated (R1: 28/28 R2: 49/44)

Source: Protocol, Protocol amendments and administrative letters (summary of changes if applicable) in Appendix 1.1.

Methods

Study participants

The enrolled population consisted of males and females, 5 through 30 years of age, with confirmed cHL, excluding nodular lymphocyte-predominant cHL, after failure of or non-response to first-line therapy, at least 1 measurable site of disease using Lugano 2014 criteria (International Working Group criteria), and FDG-PET-avid and bidimensional measurable disease of at least 1.5 cm in longest axis as documented by radiographic technique (CT preferred).

Subjects > 16 years of age must have a Karnofsky performance level ≥50%, and participants ≤16 years of age must have a Lansky performance level ≥50. Subjects who previously received an allogeneic and/or ASCT for cHL were excluded, as were subjects with prior exposure to anti-PD1, anti-PDL1, anti-PD-L2, anti CD137, or anti-CTLA-4 antibodies, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

Treatments

Subjects received nivolumab 3 mg/kg as a 30-minute IV infusion, on Day 8 of cycle 1 and then on Day 1 for each subsequent 3-week treatment cycle. This dose was selected for treatment of all subjects based on the preliminary analysis from Study CA209070 showing similar exposures in paediatric and adult subjects.

The Bv dose (1.8 mg/kg as a 30-minute infusion on Day 1 of every 3-week treatment cycle) used in this study has been shown to be generally well tolerated and is approved for the treatment in adult patients with Hodgkin Lymphoma in both the US and EU. Bv 1.8 mg/kg (Day 1 of each cycle) in combination with bendamustine 90 mg/m2 (Days 1 and 2 of each cycle) was selected for use in this study based on a manageable safety profile reported in a Phase 1/2 clinical study.

Table 2. Study Treatments

Study Treatment	Dose/Route of Administration	Timing of Dose
Nivolumab + Brentuximab Vedotin (21-day cycles) (up to 4-6 cycles, depending upon metabolic response, for Cohort R1 and 4 cycles for Cohort R2)		
Nivolumab	3 mg/kg IV over 30 minutes	• Cycle 1: Day 8 • Cycle 2 and beyond: Day 1 of each cycle, 30 minutes after completion of Bv
Brentuximab vedotin	1.8 mg/kg IV over 30 minutes[a]	• Day 1 of each cycle
Brentuximab Vedotin + Bendamustine (21-day cycles) (up to 2-4 cycles if tumor assessment is PMR/NMR after 4 cycles of N+Bv)		
Brentuximab vedotin	1.8 mg/kg IV over 30 minutes[a]	• Day 1 of each cycle
Bendamustine	90 mg/m^2 IV	• Day 1 of each cycle, 30 minutes after completion of Bv • Day 2 of each cycle

[a] If the participant weighed more than 100 kg, the dose calculation for Bv had to be 100 kg. See local package insert or patient information leaflet for further guidance.

Source: Section 7.1 in the CA209744 Protocol (Appendix 1.1).

Premedication

Subjects treated with N+Bv received prophylactic premedication ≥ 30 minutes prior to study treatment starting at Cycle 2: famotidine (adult: 40 mg IV; paediatric: 0.5 mg/kg IV) and diphenhydramine (adult: 50 mg IV; paediatric: 1 mg/kg IV) or equivalent H2/H1 blocker.

Subjects treated with Bv+B received prophylactic premedication with corticosteroids and antihistamines 30-60 minutes prior to Bv infusion (days when Bv and bendamustine were administered): methylprednisone (adult: 100 mg IV or equivalent; paediatric: 0.8 mg/kg) and diphenhydramine (adult: 50 mg IV or equivalent; pediatric: 1 mg/kg).

Acetaminophen (adult: 650 mg; paediatric: 15 mg/kg) was administered as premedication per investigator discretion.

Dose Modifications

Dose reductions or escalations were not permitted for nivolumab. Dose reductions of Bv were allowed down to 1.2 mg/kg; dose escalations above 1.8 mg/kg were not permitted. Dose modifications for bendamustine were permitted per local package insert or patient information leaflet. Dose delays were permitted for all study treatments. If nivolumab or Bv doses were delayed, the other study treatment was also delayed until combination therapy was resumed.

Objective(s)

Primary Objectives:

- Cohort R1 (Low Risk): To describe the complete metabolic response (CMR) rate prior to Radiation Therapy (RT) and event-free survival (EFS) rate at 3 years, as assessed by blinded independent central review (BICR), using Lugano 2014 response criteria.
- Cohort R2 (Standard Risk): To describe the CMR rate prior to high dose chemotherapy followed by autologous stem cell transplant (HDCT/ASCT) by BICR, using Lugano 2014 response criteria.

Secondary Objectives:

- To assess overall response rate (ORR) (CMR + partial metabolic response [PMR]) using Lugano 2014 criteria of the low risk and standard risk cohorts following 4 cycles of N + Bv by BICR.
- To assess progression-free survival (PFS) rate at 3 years by BICR using Lugano 2014 criteria.
- Duration of Response (DOR) will be evaluated for those participants who achieved PMR or CMR by BICR as well as for those participants who achieved CMR by BICR prior to RT in the low risk cohort and for those participants who achieved CMR prior to HDCT/ASCT in the standard risk cohort.
- To evaluate efficacy as assessed by investigators using Lugano 2014 response criteria.
- To describe the toxicity of N + Bv in combination in paediatric and young adult participants with R/R cHL after failure of first-line treatment.

Outcomes/endpoints

Primary Efficacy Endpoints:

Cohort R1:

- CMR rate by BICR at any time prior to RT

- EFS rate at 3 years.

Cohort R2:

- CMR rate by BICR at any time prior to HDCT/ASCT

The CMR rate is defined as the proportion of all response-evaluable participants who, assessed by the BICR, achieve best response of CMR using Lugano 2014 criteria.

Secondary Efficacy Endpoints:

Both Cohort R1 and R2:

- ORR by BICR following 4 cycles of N+Bv
- PFS rate by BICR at 3 years
- DOR for subjects who achieved PMR or CMR by BICR
- All of the above efficacy endpoints (CMR, ORR, PFS, DOR) by Investigator

Secondary Safety Endpoint:

Serious and non-serious AEs, clinical laboratory tests (haematology, chemistry, urinalysis), vital sign measurements

Sample size

The sample size was not based on any formal statistical testing or power considerations. This study targeted treating initially approximately 40 subjects in each risk cohort. Subsequently due to a change in enrolment projections in Cohort R1, the sample size was modified to reduce the total number of participants from 80 to 72 (total number of treated participants enrolled in Cohort R1 = 28 and Cohort R2 = 44) to be able to proceed with closing the study and reporting the results in a timeframe that could be more meaningful for paediatric participants and treating physicians. Assuming 24 responders out of 28 Cohort R1 participants, the exact 2-sided 90% confidence interval would be 70.23% to 94.97%. Subjects who were not response-evaluable in Cohort R2 were replaced. The width of 90% CIs for CMR rate/ORR in Cohort R2 was provided (Table 3) to illustrate the precision of estimation based on this sample size (assuming different scenarios of observed response).

Table 3. Example of 90% CIs for the Response Rate (ORR or CMR Rate)

Number of Response-evaluable Participants	Number of Responders	Observed Response Rate (%)	Exact 2-sided 90% CI	
			Lower Limit (%)	Upper Limit (%)
40	5	12.50	5.06	24.50
40	10	25.00	14.24	38.71
40	15	37.50	24.73	51.72
40	20	50.00	36.11	63.89
40	25	62.50	48.28	75.27
40	30	75.00	61.29	85.76
40	35	87.50	75.50	94.94
40	40	100.00	92.78	100.00

Source: CA209744 Protocol Amendment 04 (Appendix 1.1)

Randomisation and blinding (masking)

Study CA209744 is as an open-label study.

An aligned risk-stratified algorithm was used to stratify subjects to Cohort R1 (low risk) or Cohort R2 (standard risk) based on relapse-risk category. All subjects were assigned to treatment using an IRT.

Statistical Methods

The rate of CMR per BICR (using Lugano 2014 criteria) at any time prior to HDCT/ASCT was derived from the time-point assessments provided by the BICR and analysed based on the population of response-evaluable subjects. The estimated CMR rate and the exact 2-sided 90% CI are provided.

The EFS function per BICR and the 3-year EFS rate were estimated using the Kaplan-Meier product-limit method when all participants had (whichever was earlier) been followed for at least 3 years, withdrawn consent, or had an EFS event. Its corresponding 90% CI was derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function s(t).

The estimated ORR per BICR and an exact 2-sided 90% CI is provided. The PFS function per BICR and the 3-year PFS rate was estimated using the Kaplan-Meier product-limit method when all participants had been followed for at least 3 years, died, progressed, or withdrawn consent, whichever is earlier. The DOR per BICR was estimated using the Kaplan-Meier product-limit method. In addition to the responders of CMR or PMR (primary analysis), the duration of complete response (DOCR) was also estimated (CMR responders). Time to response is summarized by response type (CMR or PMR, CMR, and PMR). The same analyses described above was performed using investigator assessments as well. The OS was estimated using the Kaplan-Meier product-limit method for Cohorts R1 and R2, respectively.

The following descriptive analyses were conducted for PRO:

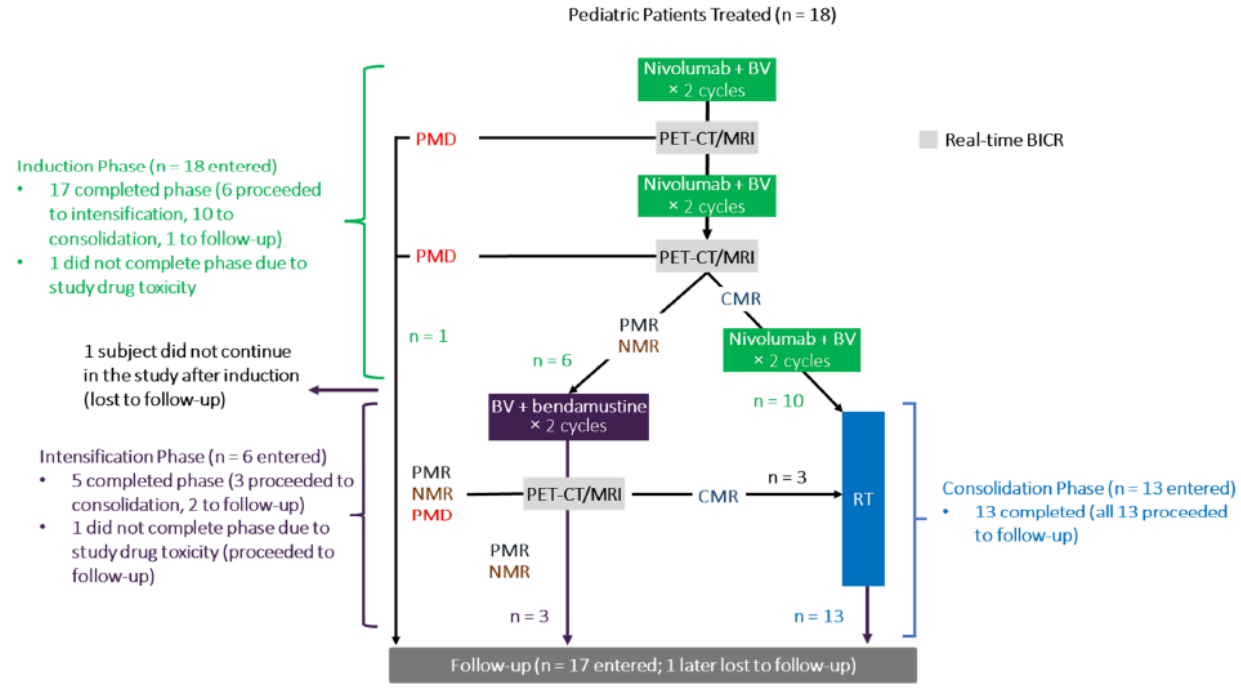
- PRO questionnaire completion rate
- EQ-5D-3L VAS and UI: mean score and mean change from baseline using descriptive statistics and proportion of subjects reporting each response level for each dimension
- FACT-Lym total and subscale scores: mean score and mean change from baseline.

Safety analyses was performed in all treated participants per cohort. Descriptive statistics of safety are presented using NCI CTCAE version 4. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs are tabulated using worst grade per NCI CTCAE criteria by system organ class and MedDRA preferred term.

Results

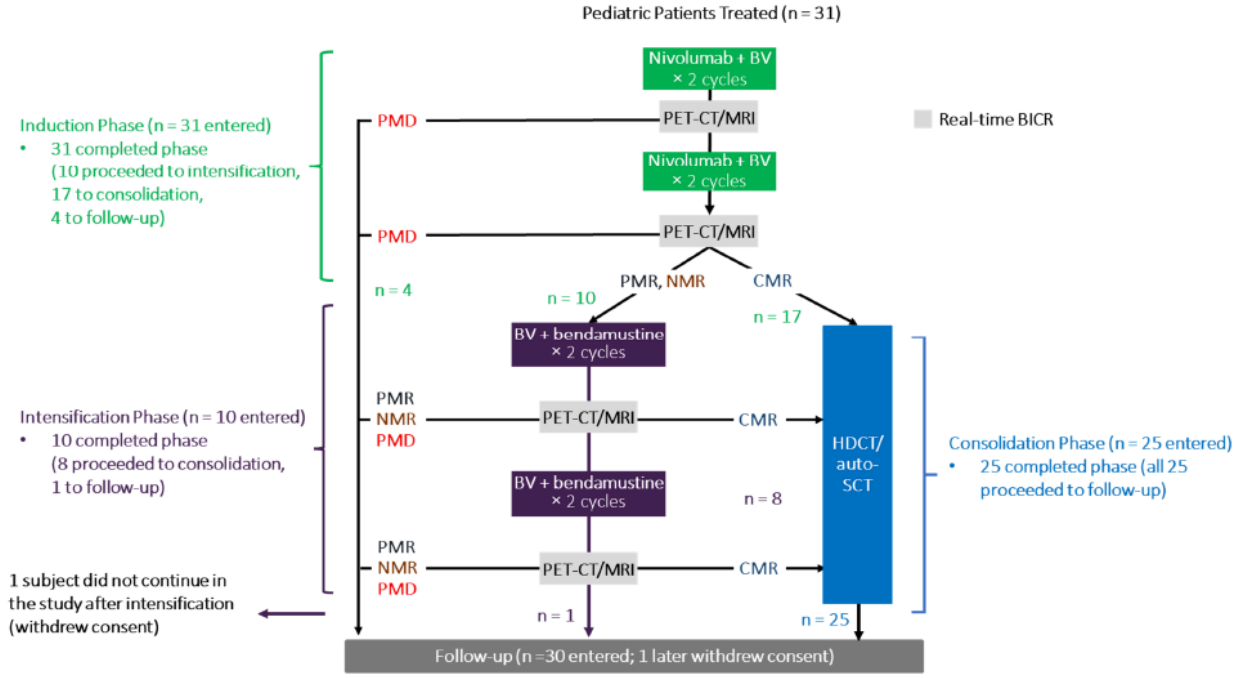
Participant flow

Figure 2. Subject Disposition Cohort R1



Nivolumab 3 mg/kg (day 8 cycle 1; day 1 for others)
BV 1.8 mg/kg day 1 of every cycle
Bendamustine 90 mg/m2 days 1 and 2
Source: refer to CA209744 Primary CSR Table 5.1-2

Figure 3. Subject Disposition Cohort R2



Nivolumab 3 mg/kg (day 8 cycle 1; day 1 for others)
BV 1.8 mg/kg day 1 of every cycle
Bendamustine 90 mg/m^2 days 1 and 2
Source: refer to CA209744 Primary CSR Table 5.1-2

Table 4. Subject Status Summary by Study Phase, All Treated Subjects

	Cohort R1 N = 28	Cohort R2 N = 44	Pooled Cohort N = 72
SUBJECTS ENTERING INDUCTION PHASE (%)	28 (100.0)	44 (100.0)	72 (100.0)
SUBJECTS CONTINUING IN PERIOD (%)	0	0	0
SUBJECTS NOT COMPLETING PERIOD (%)	1 (3.6)	2 (4.5)	3 (4.2)
REASON FOR NOT CONTINUING IN PERIOD (%)			
DISEASE PROGRESSION	0	1 (2.3)	1 (1.4)
STUDY DRUG TOXICITY	1 (3.6)	1 (2.3)	2 (2.8)
SUBJECTS COMPLETED PERIOD (%)	27 (96.4)	42 (95.5)	69 (95.8)
SUBJECTS CONTINUING IN STUDY AFTER INDUCTION PHASE (%)	27 (96.4)	43 (97.7)	70 (97.2)
INTENSIFICATION PHASE	6 (21.4)	11 (25.0)	17 (23.6)
CONSOLIDATION PHASE	19 (67.9)	23 (52.3)	42 (58.3)
FOLLOW-UP	2 (7.1)	8 (18.2)	10 (13.9)
SURVIVAL FOLLOW-UP	0	1 (2.3)	1 (1.4)
SUBJECTS NOT CONTINUING IN STUDY AFTER INDUCTION PHASE (%)	1 (3.6)	1 (2.3)	2 (2.8)
REASON FOR NOT CONTINUING IN STUDY (%)			
SUBJECT WITHDREW CONSENT	0	1 (2.3)	1 (1.4)
LOST TO FOLLOW-UP	1 (3.6)	0	1 (1.4)
SUBJECTS ENTERING INTENSIFICATION PHASE (%)	6 (21.4)	11 (25.0)	17 (23.6)
SUBJECTS CONTINUING IN PERIOD (%)	0	0	0
SUBJECTS NOT COMPLETING PERIOD (%)	1 (16.7)	0	1 (5.9)
REASON FOR NOT CONTINUING IN PERIOD (%)			
STUDY DRUG TOXICITY	1 (16.7)	0	1 (5.9)
SUBJECTS COMPLETED PERIOD (%)	5 (83.3)	11 (100.0)	16 (94.1)
SUBJECTS CONTINUING IN STUDY AFTER INTENSIFICATION PHASE (%)	6 (100.0)	10 (90.9)	16 (94.1)
CONSOLIDATION PHASE	3 (50.0)	9 (81.8)	12 (70.6)
FOLLOW-UP	3 (50.0)	1 (9.1)	4 (23.5)
SUBJECTS NOT CONTINUING IN STUDY AFTER INTENSIFICATION PHASE (%)	0	1 (9.1)	1 (5.9)
REASON FOR NOT CONTINUING IN STUDY (%)			
SUBJECT WITHDREW CONSENT	0	1 (9.1)	1 (5.9)

	Cohort R1 N = 28	Cohort R2 N = 44	Pooled Cohort N = 72
SUBJECTS ENTERING CONSOLIDATION PHASE (%)	22 (78.6)	32 (72.7)	54 (75.0)
SUBJECTS CONTINUING IN PERIOD (%)	0	0	0
SUBJECTS NOT COMPLETING PERIOD (%)	0	0	0
SUBJECTS COMPLETED PERIOD (%)	22 (100.0)	32 (100.0)	54 (100.0)
SUBJECTS CONTINUING IN STUDY AFTER CONSOLIDATION PHASE (%)	22 (100.0)	32 (100.0)	54 (100.0)
FOLLOW-UP	22 (100.0)	32 (100.0)	54 (100.0)
SUBJECTS NOT CONTINUING IN STUDY AFTER CONSOLIDATION PHASE (%)	0	0	0
FOLLOW-UP			
SUBJECTS CONTINUING TO BE FOLLOWED IN THE STUDY (%)	27 (96.4)	42 (95.5)	69 (95.8)
SUBJECTS NOT CONTINUING TO BE FOLLOWED IN THE STUDY (%)	1 (3.6)	2 (4.5)	3 (4.2)
REASON FOR NOT CONTINUING TO BE FOLLOWED IN THE STUDY (%)			
SUBJECT WITHDREW CONSENT	0	2 (4.5)	2 (2.8)
LOST TO FOLLOW-UP	1 (3.6)	0	1 (1.4)

Percentages based on subjects entering period.
Source: Table S.R1.2.2.1

Recruitment

Subjects were enrolled at 34 sites in 8 countries (United States [15 sites], France [6 sites], Italy [5 sites], Germany, Netherlands, United Kingdom (2 sites each), Ireland, and Spain [1 site each]).

The median follow-up duration for all treated subjects was 64.95 weeks and the minimum follow-up was 40.7 months.

Table 5. Key Dates and Follow-up

First Subject First Visit Date	28-Mar-2017	
Last Subject First Visit Date	16-Dec-2020	
Clinical Cutoff Date (LPLV)	28-May-2024	
DBL Date	08-July-2024	
Median follow-up time, months	**All Treated Subjects**	**Treated Pediatric Subjects**
Cohort R1	64.95	64.95
Cohort R2	78.03	78.95
Minimum follow-up time, months	**All Treated Subjects**	**Treated Pediatric Subjects**
Cohort R1	40.7	42.5
Cohort R2	72.2	72.2

Baseline data

In Cohort R1, most of the subjects had Stage IIA disease at the study entry; while in Cohort R2, most subjects had Stage IIA, IIB, or IVA disease. The mean Karnofsky and Lansky performance status was > 95% in both cohorts. The time from end of prior therapy to relapse was ≥12 months for most subjects in Cohort R1, while it was <12 months in most subjects in Cohort R2.

Number analysed

Table 6. Analysis Populations

Population, n	Cohort R1	Cohort R2	Total
Enrolled: All subjects who signed an ICF.	28	44	72
Treated: Subjects who received at least 1 dose of study drug.			
All Treated subjects	28	44	72
Treated Pediatric subjects	18	31	49
Response-evaluable: All treated subjects who reach 1 of the following endpoints: PMR or CMR at any time, or completion of 6 cycles of therapy (4 cycles of N+Bv and ≥ 2 cycles of Bv+B). Participants who come off early for toxicity without a CMR or PMR are evaluable.			
All Treated subjects (BICR/Investigator)	28	44	72
Treated Pediatric subjects (BICR/Investigator)	18	31	49
Immunogenicity: All N+Bv-treated subjects with baseline and ≥ 1 post-baseline assessment for ADA			
All Treated subjects	Nivolumab: 25 Brentuximab: 24	Nivolumab: 40 Brentuximab: 41	
Treated Pediatric subjects	Nivolumab: 16 Brentuximab: 15	Nivolumab: 28 Brentuximab: 28	
Biomarker: Biomarker quantifiable subjects with matched samples			
All Treated subjects	28	44	72
Treated Pediatric subjects	18	31	49
Patient-reported Outcomes: All treated subjects ≥ 12 years of age			
All treated subjects	25	40	

Relevant Protocol Deviations

Table 7. Relevant Protocol Deviations – All Treated Subjects, Cohorts 1 and 2

	Cohort R1	Cohort R2
Subjects with at least one deviation	2 (7.1)	3 (6.8)
At Entrance		
Subject without documented classical Hodgkins lymphoma	0	0
Subject not at age range >= 5 and <= 30 years old	0	0
Treatment naive subject or subject who received more than one prior CHL treatment	0	0
Not relapsed nor refractory subject	0	0
Subject without measurable disease and no FDG avid to tumor	0	0
Subject who previously received stem cell transplant for CHL	0	0
On-Treatment		

	Cohort R1	Cohort R2
Subject receiving concurrent prohibited therapy	1 (3.6)	0
Subject received more than pre-planned treatment duration	1 (3.6)	3 (6.8)

Efficacy results

Primary Endpoints:

- A total of 88.9% (90% CI: 69.0, 98.0) of paediatric subjects at low risk of relapse (Cohort R1) and 90.3% (90% CI: 76.8, 97.3) of subjects at standard risk of relapse (Cohort R2) achieved CMR per BICR prior to consolidation.
- The 3-year EFS rate in Cohort R1 was 79.8% (90% CI: 55.6, 91.7). 15 paediatric subjects (83.3%) were censored for EFS per BICR (on the date of last tumour assessment on-study or last assessment prior to subsequent anti-cancer therapy).

Secondary Endpoints:

- High rates of PFS and ORR per BICR following 4 cycles of N + Bv (>90%) were observed in both Cohort R1 and Cohort R2. Efficacy assessments by investigator were comparable to those by BICR.

Exploratory Endpoint:

- The 3-year OS (90%CI) rate was 100.0% (100.0, 100.0) in Cohort R1 and 96.7% (83.9, 99.3) in Cohort R2. Median OS was not reached in either Cohort.

The 5-year OS rates (90% CI) were 100% (100.0, 100.0) and 97.6% (88.0, 99.5) among all treated subjects in Cohorts R1 and R2, respectively, with similar results observed within each cohort for treated paediatric subjects.

Table 8. Summary of Efficacy in Cohorts R1 and R2, All Treated and Treated Pediatric Subjects

	Cohort R1 Low Risk Cohort		Cohort R2 Standard Risk Cohort	
	All Treated Subjects (n = 28)	**Treated Pediatric Subjects (n = 18)**	**All Treated Subjects (n = 44)**	**Treated Pediatric Subjects (n = 31)**
Primary Endpoints				
CMR prior to consolidation per BICR, n (%)[a]	26 (92.9)	16 (88.9)	39 (88.6)	28 (90.3)
90% CI	(79.2, 98.7)	(69.0, 98.0)	(77.6, 95.4)	(76.8, 97.3)
EFS rate at 3-yr per BICR (90% CI), %	87.5 (70.6, 95.0)	79.8 (55.6, 91.7)	-	-
Secondary Endpoints				

	Cohort R1 Low Risk Cohort		Cohort R2 Standard Risk Cohort	
	All Treated Subjects (n = 28)	**Treated Pediatric Subjects (n = 18)**	**All Treated Subjects (n = 44)**	**Treated Pediatric Subjects (n = 31)**
ORR per BICR following 4 cycles of N+Bv, n (%)[b]	27 (96.4)	17 (94.4)	41 (93.2)	29 (93.5)
90% CI	84.1, 99.8	76.2, 99.7	83.3, 98.1	81.1, 98.8
PFS rate at 3-yr per BICR (90% CI), %	95.2 (77.7, 99.1)	91.7 (63.7, 98.3)	91.1 (78.4, 96.5)	91.8 (75.9, 97.4)
DOR per BICR				
n events/n responders (%)[c]	3/28 (10.7)	3/18 (16.7)	3/43 (7.0)	2/31 (6.5)
Median, mo (min, max)	NA (0.0, 54.1)	NA (0.0, 54.1)	NA (0.0, 55.3)	NA (1.3, 55.3)
CMR prior to consolidation per Inv, n (%)	25 (89.3)	15 (83.3)	38 (88.4)	28 (90.3)
90% CI	74.6, 97.0	62.3, 95.3	77.1, 95.3	76.8, 97.3
EFS rate at 3-yr per Inv (90% CI), %	88.5 (72.8, 95.4)	82.4 (60.5, 92.8)	-	-
ORR per Inv following 4 cycles of N+Bv, n (%)	28 (100.0)	18 (100.0)	40 (90.9)	29 (93.5)
90% CI	89.9, 100.0	84.7, 100.0	80.4, 96.8	81.1, 98.8
PFS rate at 3-yr per Inv (90% CI), %	95.8 (80.2, 99.2)	93.3 (69.9, 98.7)	88.1 (74.8, 94.6)	88.2 (72.0, 95.3)
DOR per Inv				
n events/n responders (%)	3/28 (10.7)	3/18 (16.7)	4/43 (9.3)	3/31 (9.7)
Median, mo (min, max)	NA (0.0, 64.4)	NA (0.0, 54.1)	NA (1.2, 55.3)	NA (1.3, 55.3)
Exploratory Endpoint				
OS rate at 5-yr (90% CI), %	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	97.6 (88.0, 99.5)	96.7 (83.9, 99.3)

Minimum follow-up was ≥ 40 months for Cohort R1 and ≥ 70 months for Cohort R2. Median follow-up was ≥ 64 months for Cohort R1 and ≥ 78 months for Cohort R2.

[a] The denominator is the number of response-evaluable subjects. All treated subjects/treated pediatric subjects were response-evaluable.

[b] The denominator is the number of subjects who were evaluable after 4 cycles of N+Bv. All treated subjects/treated pediatric subjects were evaluable 4 cycles of N+Bv.

[c] The denominator is the number responders. All-treated subjects/treated pediatric subjects were responders.

Subsequent Anti-cHL Therapy

A low number of subjects in Cohort R1 and most subjects in Cohort R2 received subsequent anti cHL therapy. The most common therapy was radiotherapy in Cohort R1 and systemic therapy in Cohort R2.

Table 9. Subsequent anti-cHL Therapy Summary, All Treated Subjects

	Number of Subjects (%)		
	Cohort R1 N = 28	Cohort R2 N = 44	Pooled Cohort N = 72
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%)	5 (17.9)	31 (70.5)	36 (50.0)
SURGERY (%)	0	2 (4.5)	2 (2.8)
RADIOTHERAPY (%)	4 (14.3)	9 (20.5)	13 (18.1)
CURATIVE	4 (14.3)	1 (2.3)	5 (6.9)
PALLIATIVE	0	0	0
OTHER	0	8 (18.2)	8 (11.1)
AUTOLOGOUS STEM CELL TRANSPLANT NOT PART OF R2 CONSOLIDATION (%)	0	12 (27.3)	12 (16.7)
SYSTEMIC THERAPY (%)	2 (7.1)	22 (50.0)	24 (33.3)
REASON FOR THERAPY REGIMEN			
DOCUMENTED PROGRESSION OF DISEASE	1 (3.6)	3 (6.8)	4 (5.6)
CLINICAL DETERIORATION WITHOUT DOCUMENTED PROGRESSION	0	0	0
MAINTENANCE THERAPY WITHOUT DISEASE PROGRESSION OR CLINICAL DETERIORATION	1 (3.6)	10 (22.7)	11 (15.3)
OTHER	0	4 (9.1)	4 (5.6)
NOT REPORTED	0	6 (13.6)	6 (8.3)
BENDAMUSTINE	2 (7.1)	2 (4.5)	4 (5.6)
BRENTUXIMAB VEDOTIN	2 (7.1)	13 (29.5)	15 (20.8)
CARBOPLATIN	0	1 (2.3)	1 (1.4)
CARMUSTINE	0	7 (15.9)	7 (9.7)
CISPLATIN	0	3 (6.8)	3 (4.2)
CYTARABINE	0	11 (25.0)	11 (15.3)
DEXAMETHASONE	0	2 (4.5)	2 (2.8)
ETOPOSIDE	0	10 (22.7)	10 (13.9)
FOTEMUSTINE	0	1 (2.3)	1 (1.4)
GEMCITABINE	0	2 (4.5)	2 (2.8)
IFOSFAMIDE	0	2 (4.5)	2 (2.8)

	Number of Subjects (%)		
	Cohort R1 N = 28	Cohort R2 N = 44	Pooled Cohort N = 72
LOMUSTINE	0	1 (2.3)	1 (1.4)
MELPHALAN	0	9 (20.5)	9 (12.5)
NIVOLUMAB	0	1 (2.3)	1 (1.4)
PREDNISOLONE	0	1 (2.3)	1 (1.4)
STEM CELL RESCUE	0	1 (2.3)	1 (1.4)
VINORELBINE	0	2 (4.5)	2 (2.8)

(1) Radiotherapy which are part of R1 consolidation and autologous stem cell transplant which are part of R2 consolidation are not included into pooled cohort.
(2) For Cohort R1 radiotherapy are not part of R1 consolidation.
Source: Table S.R1.3.6.1

Safety results

Extent of exposure

In both cohorts, the mean number of doses, cumulative dose, and relative dose intensity for nivolumab, brentuximab, and bendamustine in treated pediatric subjects was similar to those in all treated subjects.

Table 10. Cumulative Dose and Relative Dose Intensity Summary, All Treated Subjects

Induction Phase	Cohort R1		Cohort R2	
	Nivolumab N = 28	Brentuximab Vedotin N = 28	Nivolumab N = 44	Brentuximab Vedotin N = 44
NUMBER OF DOSES RECEIVED				
MEAN (SD)	5.4 (1.1)	5.4 (1.1)	4.1 (0.7)	4.1 (0.6)
MEDIAN (MIN - MAX)	6.0 (2 - 6)	6.0 (2 - 6)	4.0 (1 - 6)	4.0 (2 - 6)
CUMULATIVE DOSE				
MEAN (SD)	16.27 (3.31)	9.78 (2.00)	12.33 (2.09)	7.34 (1.03)
MEDIAN (MIN - MAX)	17.89 (6.0 - 18.6)	10.78 (3.6 - 11.3)	11.99 (3.1 - 17.8)	7.19 (3.7 - 10.7)
RELATIVE DOSE INTENSITY				
>= 110%	0	0	0	0
>= 90% TO < 110%	26 (92.9)	27 (96.4)	40 (90.9)	39 (88.6)
>= 70% TO < 90%	2 (7.1)	1 (3.6)	4 (9.1)	5 (11.4)
>= 50% TO < 70%	0	0	0	0
< 50%	0	0	0	0

Intensification Phase	Cohort R1		Cohort R2	
	Brentuximab Vedotin N = 6	Bendamustine N = 6	Brentuximab Vedotin N = 11	Bendamustine N = 11
NUMBER OF DOSES RECEIVED				
MEAN (SD)	2.0 (0.0)	3.8 (0.4)	2.5 (0.8)	5.1 (1.6)
MEDIAN (MIN - MAX)	2.0 (2 - 2)	4.0 (3 - 4)	2.0 (2 - 4)	4.0 (4 - 8)
CUMULATIVE DOSE				
MEAN (SD)	3.55 (0.05)	339.28 (32.75)	4.53 (1.54)	458.20 (158.85)
MEDIAN (MIN - MAX)	3.57 (3.5 - 3.6)	344.82 (278.3 - 372.4)	3.54 (3.3 - 7.4)	368.48 (326.2 - 752.2)
RELATIVE DOSE INTENSITY				
>= 110%	0	0	0	0
>= 90% TO < 110%	6 (100.0)	5 (83.3)	9 (81.8)	9 (81.8)
>= 70% TO < 90%	0	1 (16.7)	2 (18.2)	2 (18.2)
>= 50% TO < 70%	0	0	0	0
< 50%	0	0	0	0

Overall Phase	Cohort R1		
	Nivolumab N = 28	Brentuximab Vedotin N = 28	Bendamustine N = 6
NUMBER OF DOSES RECEIVED			
MEAN (SD)	5.4 (1.1)	5.9 (0.8)	3.8 (0.4)
MEDIAN (MIN - MAX)	6.0 (2 - 6)	6.0 (2 - 6)	4.0 (3 - 4)
CUMULATIVE DOSE			
MEAN (SD)	16.27 (3.31)	10.54 (1.38)	339.28 (32.75)
MEDIAN (MIN - MAX)	17.89 (6.0 - 18.6)	10.80 (3.6 - 11.3)	344.82 (278.3 - 372.4)
RELATIVE DOSE INTENSITY			
>= 110%	0	0	0
>= 90% TO < 110%	26 (92.9)	27 (96.4)	5 (83.3)
>= 70% TO < 90%	2 (7.1)	1 (3.6)	1 (16.7)
>= 50% TO < 70%	0	0	0
< 50%	0	0	0

Overall Phase	Cohort R2		
	Nivolumab N = 44	Brentuximab Vedotin N = 44	Bendamustine N = 11
NUMBER OF DOSES RECEIVED			
MEAN (SD)	4.1 (0.7)	4.8 (1.3)	5.1 (1.6)
MEDIAN (MIN - MAX)	4.0 (1 - 6)	4.0 (2 - 8)	4.0 (4 - 8)
CUMULATIVE DOSE			
MEAN (SD)	12.33 (2.09)	8.47 (2.34)	458.20 (158.85)
MEDIAN (MIN - MAX)	11.99 (3.1 - 17.8)	7.31 (3.7 - 14.8)	368.48 (326.2 - 752.2)
RELATIVE DOSE INTENSITY			
>= 110%	0	0	0
>= 90% TO < 110%	40 (90.9)	35 (79.5)	9 (81.8)
>= 70% TO < 90%	4 (9.1)	9 (20.5)	2 (18.2)
>= 50% TO < 70%	0	0	0
< 50%	0	0	0

Units for Nivolumab and Brentuximab Vedotin are mg/kg, for Bendamustine - mg/m2.
Source: Table S.R1.4.1.1

The overall safety profile of N + Bv in Cohort R1 and Cohort R2 (all treated subjects and treated paediatric subjects) was manageable and consistent with the known safety profiles of the individual components. No new safety signals or toxicities were identified.

- 1 death was reported in the treated paediatric population in Cohort R2; the cause of death was reported as disease.
- The overall frequencies (all causality and drug related) of AEs, SAEs, and AEs leading to discontinuation of study treatment were similar between all treated subjects and treated paediatric subjects in both cohorts.
- In Cohort R1, the most frequently (≥25% subjects) reported all-causality AEs were headache, nausea, pyrexia, and ALT increased in the all-treated subjects while nausea, headache, and pyrexia were the most frequently reported AEs in the treated paediatric subjects. In Cohort R2, the most frequently (≥ 25%) reported all-causality AEs were nausea, diarrhoea, and pyrexia in the all-treated and treated paediatric subjects.
- In Cohort R1, pyrexia was the only SAE that was reported in > 1 subject in the all-treated and treated paediatric subjects. In Cohort R2, the SAEs that were reported in > 1 subject were pyrexia and hypersensitivity in the all-treated subjects while hypersensitivity was reported in the treated paediatric subjects.
- In Cohort R1, Grade 3-4 AEs reported in > 1 subject were AST increased (3 subjects) and ALT increased (2 subjects) in all treated subjects while no Grade 3-4 AEs were reported in > 1 subject in the treated paediatric subjects. In Cohort R2, Grade 3-4 AEs reported in > 1 subject were neutropenia (3 subjects) and infusion-related reaction (2 subjects) in the all-treated subjects while neutropenia (3 subjects) was reported in the treated paediatric subjects.
- Select AEs and IMAEs were mostly Grade 1-2 and were manageable.
- All drug-related select AEs and IMAEs were reported to have resolved prior to the clinical cutoff date.
- Laboratory abnormalities (haematology, liver, kidney, and thyroid function tests, and electrolytes) were primarily Grade 1-2 in severity and were consistent across all treated and treated paediatric population.

Table 11. Safety Summary – All Treated Subjects and Treated Pediatric Subjects in Cohorts R1 and R2

	No. of Subjects (%)			
	Cohort R1		Cohort R2	
	All Treated Subjects (n = 28)	Treated Pediatric Subjects (n = 18)	All Treated Subjects (n = 44)	Treated Pediatric Subjects (n = 31)
Deaths	0	0	1 (2.27%)	1 (3.22%)
Primary Reason for Death				
Disease[a]	0	0	1 (2.27%)	1 (3.22%)

	Adverse Event Grades							
Safety Parameter	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality AEs	26 (92.9)	8 (28.6)	18 (100.0)	4 (22.2)	42 (95.5)	18 (40.9)	29 (93.5)	13 (41.9)
Drug-related AEs	22 (78.6)	7 (25.0)	14 (77.8)	4 (22.2)	32 (72.7)	10 (22.7)	24 (77.4)	8 (25.8)
All-causality SAEs	8 (28.6)	4 (14.3)	5 (27.8)	2 (11.1)	9 (20.5)	6 (13.6)	5 (16.1)	2 (6.5)
Drug-related SAEs	6 (21.4)	3 (10.7)	4 (22.2)	2 (11.1)	5 (11.4)	3 (6.8)	3 (9.7)	1 (3.2)
All-causality AEs leading to discontinuation of study treatment	2 (7.1)	1 (3.6)	2 (11.1)	1 (5.6)	1 (2.3)	1 (2.3)	0	0
Drug-Related AEs leading to discontinuation of study treatment	2 (7.1)	1 (3.6)	2 (11.1)	1 (5.6)	1 (2.3)	1 (2.3)	0	0
Drug-related Select AEs, by Category								
Endocrine	0	0	1 (5.6)	0	1 (2.3)	0	1 (3.2)	0
Gastrointestinal	5 (17.9)	1 (3.6)	3 (16.7)	1 (5.6)	7 (15.9)	0	6 (19.4)	0
Hepatic	8 (28.6)	2 (7.1)	6 (33.3)	0	4 (9.1)	1 (2.3)	2 (6.5)	1 (3.2)
Pulmonary	0	0	0	0	1 (2.3)	0	0	0
Renal	1 (3.6)	0	1 (5.6)	0	0	0	0	0
Skin	8 (28.6)	3 (10.7)	6 (33.3)	3 (16.7)	12 (27.3)	0	8 (25.8)	0
Hypersensitivity/Infusion Reaction	8 (28.6)	0	5 (27.8)	0	13 (29.5)	2 (4.5)	9 (29.0)	0
All-causality IMAEs within 100 Days of Last Dose, by Category								
Pneumonitis	0	0	0	0	1 (2.3)	0	0	0
Diarrhea/Colitis	0	0	0	0	0	0	0	0
Hepatitis	0	0	0	0	0	0	0	0
Adrenal insufficiency	0	0	0	0	0	0	0	0
Hypothyroidism/ thyroiditis	1 (3.6)	0	0	0	1 (2.3)	0	1 (3.2)	0
Diabetes mellitus	0	0	0	0	0	0	0	0
Nephritis/renal dysfunction	1 (3.6)	0	1 (5.6)	0	0	0	0	0
Rash	3 (10.7)	1 (3.6)	2 (11.1)	1 (5.6)	6 (13.6)	0	3 (9.7)	0
Hypersensitivity	2 (7.1)	0	2 (11.1)	0	4 (9.1)	1 (2.3)	3 (9.7)	0
Hyperthyroidism	2 (7.1)	0	1 (5.6)	0	0	0	0	0
Hypophysitis	0	0	0	0	0	0	0	0
All-causality OESI within 100 Days of Last Dose, by Category								
	0	0	0	0	0	0	0	0

a The subject had disease progression at the time of death; however, the site reported "disease" as the reason for death.
MedDRA Version: 27.0; CTC Version: 4.0

Clinical Laboratory Evaluations

Hematology

Cohort R1

Grade 3 or 4 hematologic abnormalities reported in treated subjects or treated pediatric subjects included:

- All treated subjects: hemoglobin (1 subject), lymphocytes (2 subjects), absolute neutrophil count (3 subjects).
- Treated pediatric subjects: hemoglobin (1 subject), lymphocytes (1 subject).

A shift from Grade 0/1/2 at baseline to Grade 3/4 post-baseline was observed for the following hematology parameters:

- All treated subjects: hemoglobin (1 subject), absolute neutrophil count (3 subjects), lymphocytes (2 subjects each).
- Treated pediatric subjects (Table S.R1.7.25.2): hemoglobin (1 subject) and lymphocytes (1 subject).

Cohort R2

Grade 3 or 4 hematologic abnormalities reported in treated subjects or treated pediatric subjects included:

- All treated subjects: platelet count (1 subject), leukocytes (3 subjects), lymphocytes (8 subjects), and absolute neutrophil count (5 subjects).
- Treated pediatric subjects: platelet count (1 subject), leukocytes (3 subjects), lymphocytes (7 subjects), and absolute neutrophil count (5 subjects).

A shift from Grade 0/1/2 at baseline to Grade 3/4 post-baseline was observed for platelet count (1 subject), leukocytes (3 subjects), lymphocytes (4 subjects), absolute neutrophil count (5 subjects) in all treated subjects and treated pediatric subjects.

Serum Chemistry

Liver Function Tests

Cohort R1

Grade 3 or 4 hepatic abnormalities of AST and ALT (2 subjects each) were reported in all-treated subjects. None of the treated pediatric subjects had Grade 3 or 4 hepatic abnormalities.

A total of 8 (28.6%) all-treated subjects and 3 (16.7%) treated pediatric subjects reported ALT or AST increased > 3× ULN and none of these subjects had concurrent elevation in bilirubin > 2× ULN.

Cohort R2

Grade 3 or 4 hepatic abnormalities of AST and ALT (2 subjects each) were reported in all-treated and treated pediatric subjects.

A total of 5 (11.4%) all-treated subjects and 4 (12.9%) treated pediatric subjects reported ALT or AST increased > 3× ULN and none of these subjects had concurrent elevation in bilirubin > 2× ULN.

Kidney Function Tests

Cohorts R1 and R2

Abnormalities in creatinine (increases from baseline) were Grade 1 or Grade 2 in severity and no Grade 3 or 4 increased creatinine levels were reported in all treated subjects or treated pediatric subjects.

Thyroid Function Tests

Cohort R1

Table 12. Summary of Laboratory Abnormalities in Specific Thyroid Tests (SI Units) – All Treated Subjects in Cohort R1

Abnormality (%)	Cohort R1 N = 28
TSH > ULN	6 (21.4)
TSH > ULN	
WITH TSH <= ULN AT BASELINE	5 (17.9)
TSH > ULN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	1 (3.6)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	4 (14.3)
WITH FT3/FT4 TEST MISSING (A)(B)	1 (3.6)
TSH < LLN	4 (14.3)
TSH < LLN	
WITH TSH >= LLN AT BASELINE	4 (14.3)
TSH < LLN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	3 (10.7)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	1 (3.6)
WITH FT3/FT4 TEST MISSING (A)(B)	0

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date.
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.
Source: Table S.R1.7.31.2

Cohort R2

Table 13. Summary of Laboratory Abnormalities in Specific Thyroid Tests (SI Units) – All Treated Subjects in Cohort R2

Abnormality (%)	Cohort R2 N = 44
TSH > ULN	8 (18.2)
TSH > ULN	
WITH TSH <= ULN AT BASELINE	4 (9.1)
TSH > ULN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	0
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	5 (11.4)
WITH FT3/FT4 TEST MISSING (A)(B)	3 (6.8)
TSH < LLN	1 (2.3)
TSH < LLN	
WITH TSH >= LLN AT BASELINE	1 (2.3)
TSH < LLN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	1 (2.3)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	0
WITH FT3/FT4 TEST MISSING (A)(B)	0

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date.
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from
only one of the two tests and no value from the other test.

Immunogenicity

In Cohort R1, none of the subjects were ADA-positive at baseline while in Cohort R2, 2 subjects were ADA positive for nivolumab, including 1 pediatric subject at baseline. Post-baseline, among all treated subjects in Cohorts R1 and R2, a majority (~96% and 59% respectively) were brentuximab ADA

positive while a smaller proportion (36%, and ~13% respectively) were nivolumab ADA positive with a similar trend observed within each cohort for the pediatric subjects.

All subjects with ADAs to brentuximab had neutralizing antibodies while none of the subjects with ADAs to nivolumab had neutralizing antibodies. Despite the higher brentuximab ADA and neutralizing antibody incidences, the overall frequency of hypersensitivity and infusion related reactions in the study was small and the combination of nivolumab and brentuximab vedotin was able to induce a CMR before consolidation in >90% of patients.

Table 14. Anti-Drug Antibody Assessments, Cohort R1

	All-Treated Subjects		**Treated Pediatric Subjects**	
Subject ADA Status (%)	**Nivolumab ADA N=25**	**Brentuximab ADA N=24**	**Nivolumab ADA N=16**	**Brentuximab ADA N=15**
Baseline ADA Positive	0	0	0	0
ADA Positive	9 (36.0)	23 (95.8)	6 (37.5)	14 (93.3)
Persistent Positive (PP)	0	6 (25.0)	0	4 (26.7)
Not PP- Last Sample Positive	3 (12.0)	4 (16.7)	2 (12.5)	4 (26.7)
Other Positive	6 (24.0)	13 (54.2)	4 (25.0)	6 (40.0)
Neutralizing Positive	0	23 (95.8)	0	14 (93.3)
ADA Negative	16 (64.0)	1 (4.2)	10 (62.5)	1 (6.7)

Baseline ADA Positive: A subject with baseline ADA-positive sample.

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (≥) than baseline positive titer) at any time after initiation of treatment.

Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart; Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint.

Other Positive: Not PP but some ADA-positive samples with the last sample being negative.

Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline.

ADA Negative: A subject with no ADA-positive sample after initiation of treatment.

Table 15. Anti-Drug Antibody Assessments, Cohort R2

	All-Treated Subjects		**Treated Pediatric Subjects**	
Subject ADA Status (%)	**Nivolumab ADA N=40**	**Brentuximab ADA N=41**	**Nivolumab ADA N=28**	**Brentuximab ADA N=28**
Baseline ADA Positive	2 (5.0)	0	1 (3.6)	0
ADA Positive	5 (12.5)	24 (58.5)	4 (14.3)	16 (57.1)
Persistent Positive (PP)	0	6 (14.6)	0	4 (14.3)
Not PP- Last Sample Positive	1 (2.5)	5 (12.2)	1 (3.6)	4 (14.3)
Other Positive	4 (10.0)	13 (31.7)	3 (10.7)	8 (28.6)
Neutralizing Positive	0	24 (58.5)	0	16 (57.1)
ADA Negative	35 (87.5)	17 (41.5)	24 (85.7)	12 (42.9)

2.3.3. Discussion on clinical aspects

Study CA209744 is a risk-based, response-adapted, Phase 2, open-label trial of nivolumab + brentuximab vedotin (N +Bv) for children, adolescents, and young adults with relapsed/refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab + bendamustine (Bv + B) for participants with a suboptimal response.

The R1 cohort (for subjects at low risk of relapse) received N+Bv for 2 cycles (6 weeks) followed by tumour assessments (TA). Participants with radiographic progression, assessed by the Investigator at cycle 2 of N+Bv, taken off the study treatment and entered follow-up. All other participants received 2 additional cycles of N+Bv study treatment (total 4 cycles = 12 weeks).

Participants who developed a complete metabolic response (CMR), as assessed by BICR, after a total of 4 cycles (12 weeks) of N+Bv, received 2 additional cycles of N+Bv treatment (for a total of 6 cycles [18 weeks]), followed by Radiotherapy (RT).

The R2 cohort (for subjects at standard risk of relapse) received N+Bv for 2 cycles (6 weeks), followed by TA. Participants with radiographic progression, assessed by the Investigator at cycle 2 of N+Bv, were taken off from study treatment and entered follow-up (unless treatment beyond progression is indicated). All other participants received 2 additional cycles of N+Bv study therapy (total 4 cycles = 12 weeks).

Baseline disease characteristics of all treated paediatric subjects were consistent with those of a paediatric patient population with R/R cHL. In Cohort R1, most paediatric subjects (61.1%) had Stage IIA disease at study entry; while in Cohort R2, overall higher disease stages were reported at study entry, with 29.0% of subjects assessed as Stage IVA. The mean Karnofsky and Lansky performance status was > 95% in both cohorts. The time from end of prior therapy to relapse was ≥12 months for most paediatric subjects in Cohort R1, while it was < 12 months in most paediatric subjects in Cohort R2.

The median age of paediatric subjects was 16.0 years in Cohort R1 and 15.0 years in Cohort R2. The majority of subjects (77.6%) were from Europe or the United Kingdom.

Most subjects were in the age group of ≥ 5 years to <18 years and of White race. In Cohort R1, most of the subjects were female while in Cohort R2, most of the subjects were male.

The study protocol has been amended 4 times. Most notably, Amendment 2 which added the co-primary endpoint CMR rate, and Amendment 4 which considered reducing the number of accrued R1 participants from 40 to 28 and closing recruitment in the R1 cohort due to feasibility issues encountered in accrual. The original size of the R1 cohort was estimated at approximately 40 participants.

In Study CA209744, participants received nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion on day 1 of each treatment cycle every 3 weeks, until progression, unacceptable toxicity, withdrawal of consent or study termination, whichever comes first.

The selected dose was based on a previous study of nivolumab involving paediatric participants (CA209070). The preliminary analysis showed that paediatric participants (6-12 years) have similar exposure to adults.

Brentuximab vedotin is generally well tolerated in paediatric patients at a dose of up to 1.8 mg/kg every 3 weeks. Five participants aged 12-17 with cHL were enrolled in the pivotal Phase 2 trial that led to the FDA approval and there were no common severe toxicities or premature discontinuation of therapy related to an AE.

With regard to the study results, the efficacy of N + Bv in subjects with cHL who progressed or relapsed after first-line treatment failure was demonstrated in both standard-risk and low-risk patients. Results demonstrated high rates of durable responses in both cohorts in all-treated and paediatric subjects. CMR for the low risk group is considered a surrogate endpoint to provide short-term impact on response to assess response earlier, in addition to EFS rate at 3 years that provides important efficacy insight on the longer-term clinical benefit.

CMR rates by BICR before transitioning to consolidation therapy were high in both all-treated (92.9% R1 cohort and 88.6% R2 cohort) and paediatric subjects (88.9% R1 cohort and 90.3% R2 cohort). In addition, high CMR rates by Investigator assessment prior to consolidation therapy were observed in all-treated (89.3% R1 cohort and 88.4 R2 cohort) and paediatric subjects (83.3% R1 cohort and 90.3% R2 cohort).

Similarly to the reported high ORR per BICR following 4 cycles of N+Bv (96.4% R1 cohort and 93.2% R2 cohort in all-treated subjects and 94.4% R1 cohort and 93.5% R2 cohort in treated paediatric subjects), other endpoints support the primary endpoint. DOR per BICR (10.7% R1 cohort and 7% R2 cohort in all-treated subjects and 16.7% R1 cohort and 6.5% R2 cohort in treated paediatric subjects), EFS rate at 3-years per Investigator (88.5% R1 cohort and 82.4% R2 cohort in all-treated subjects), PFS rate at 3-years per BICR (92.5% R1 cohort and 91.1% R2 cohort in all-treated subjects and 91.7% R1 cohort and 91.8% R2 cohort in treated paediatric subjects) and the 5-years OS rates were 100% and 97.6% among all- treated subjects in Cohorts R1 and R2, respectively, with similar results observed within each cohort for treated paediatric subjects.

The CA209744 study was conducted in 10 countries worldwide (although only 8 of these were able to recruit participants) with 75 centres activated in total; however, only 20% of all centres recruited R1 participants. Although the R1 and R2 cohorts began recruitment at the same time (March 2017, the study start date), R2 was closed in May 2018 as the target number of participants was reached (44 subjects), based on the revised protocol. R1 enrolled only 28 participants, confirming the rarity of this disease.

The overall safety profile of the combination treatment of N + Bv in Cohort R1 and Cohort R2 for both all-treated subjects and treated paediatric subjects were manageable and consistent with the known safety profiles of the therapeutic agents. No new safety signals were identified. There was a low frequency of hematologic toxicity, and none of the hematologic treatment related AEs led to treatment discontinuation and there were no Grade 5 hematologic treatment related AEs reported.

No deaths were reported in Cohort R1. One death was reported in the treated paediatric population in Cohort R2. The subject completed the induction, intensification, and consolidation (ASCT) phases, and then progressed < 12 months after the first study drug dose and died 505 days after the last dose of study drug. The subject had disease progression at the time of death.

No new safety signals were identified. There was a low frequency of haematological toxicity, and none of the treatment-related haematological AEs led to treatment discontinuation.

In the cohort 1, the most frequently (≥25% subjects) reported all-causality AEs were headache, nausea, pyrexia, and ALT increased in the all-treated subjects while nausea, headache, and pyrexia were the most frequently reported AEs in the treated paediatric subjects. Grade 3-4 AEs reported in > 1 subject were AST increased (3 subjects) and ALT increased (2 subjects) in the all-treated subjects. None of the Grade 3-4 AEs were reported in > 1 subject in the treated paediatric population.

In the cohort 2, the most frequently (≥25%) reported all-causality AEs were nausea, diarrhoea, and pyrexia in the all-treated and treated paediatric subjects. Grade 3-4 AEs reported in > 1 subject were

neutropenia (3 subjects) and infusion-related reaction (2 subjects) in the all-treated subjects while neutropenia (3 subjects) was reported in the treated paediatric subjects.

The overall frequencies of SAEs in the cohort 1 were similar between all-treated subjects and treated paediatric subjects. Pyrexia was the only SAE that was reported in > 1 subject in the all-treated and treated paediatric subjects. None of the Grade 3-4 SAEs were reported in > 1 subject.

The overall frequencies of SAEs (all causality and drug related) in the cohort 2 were similar between all-treated subjects and treated paediatric subjects. The SAEs that were reported in > 1 subjects were pyrexia and hypersensitivity in the all-treated subjects while hypersensitivity was reported in the treated paediatric subjects. None of the Grade 3-4 SAEs were reported in > 1 subject in the all-treated and treated paediatric subjects.

3. CHMP overall conclusion and recommendation

In accordance with Article 46 of the regulation (EC) No. 1901/2006, the MAH has submitted a final study report for Study CA209744. Study CA209744 is a Phase II study of nivolumab + brentuximab vedotin for paediatric subjects, adolescents, and young adults with relapsed/refractory CD30+ classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab + bendamustine for participants with a suboptimal response.

Study CA209744 is part of the agreed nivolumab Paediatric Investigation Plan (PIP) covering the conditions of treatment of malignant neoplasms of lymphoid tissue and treatment of malignant neoplasms of the central nervous system (PIP number: EMEA-001407-PIP02-15-M07; latest EMA Decision P/0138/2024, dated 06-May-2024).

Based on the study objectives, the efficacy of N + Bv in subjects with cHL who progressed or relapsed after first-line treatment failure was demonstrated in both standard-risk and low-risk patients. Safety results were consistent with the know safety profile of the individual components. There are no issues arising from assessment of this completed study that otherwise require further regulatory action at this time. The MAH is planning to submit the results of study CA209744 as part of a future variation.