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SCIENCE MEDICINES HEALTH

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EMADOC-1700519818-2843503
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMA/VR/0000282199

Note

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

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List of abbreviations

ADA	antidrug antibody
AE	adverse event
ASCT	autologous stem cell transplant
BICR	blinded independent central review
Bv	Brentuximab vedotin
Bv + B	Brentuximab vedotin + Bendamustine
cHL	classical Hodgkin lymphoma
CMR	complete metabolic response
COVID 19	coronavirus Disease 2019
CR	complete response
CRF	case report form
CSP	Clinical Safety Program
CSR	Clinical Study Report
CT	computerized tomography
DHAP	Dexamethasone, High-dose cytarabine (Ara-C), and Cisplatin (Platinol)
DMC	Data Monitoring Committee
DOR	duration of response
DOCR	duration of complete response
EBV	Epstein-Barr virus
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFS	event-free survival
ELISA	Enzyme-Linked Immunosorbent Assay
EPIC	Etoposide, Prednisolone, Ifosfamide, and Cisplatin/Carboplatin
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSFV	First Subject First Visit
GDP	Gemcitabine, Dexamethasone, and Cisplatin
GCP	Good Clinical Practice
GV	Gemcitabine and Vinorelbine
HDCT/ASCT	high dose chemotherapy (followed by) autologous stem cell transplant
HIPAA	Health Insurance Portability Accountability Act

HRQoL	Health-Related Quality of Life
ICE	Ifosfamide, Carboplatin, and Etoposide
ICF	informed consent form
IEC	Independent Ethics Committee
IGEV	Ifosfamide, gemcitabine and vinorelbine
IMAE	Immune-mediated adverse events
IV	Ifosfamide and Vinorelbine
IV	Intravenous
IP	investigational product
IRB	Institutional Review Board
IRR	Infusion-Related Reactions
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantitation
LSLV	Last Subject Last Visit
MMAE	monomethyl auristatin E
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
N + Bv	Nivolumab + Brentuximab vedotin
NMR	no metabolic response
OESI	other events of special interest
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	Pharmacodynamics
PMD	progressive metabolic disease
PMR	partial metabolic rate
PRO	Patient-reported outcome
QoL	quality of life
qPET	quantitative positron emission tomography
RCT	Randomised clinical study
R/R	Relapsed/Refractory

RT	Radiotherapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSH	thyroid stimulating hormone
VAS	Visual Analogue Scale

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 30 June 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 for OPDIVO to include treatment of patients paediatric and adults, with relapsed/refractory classical Hodgkin Lymphoma, based on results from study CA209744; a phase 2, open-label study of nivolumab + brentuximab vedotin for children, adolescents, and young adults with R/R CD30+ classical Hodgkin lymphoma after failure of first-line therapy, followed by brentuximab vedotin + bendamustine for participants with a suboptimal response. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 44.0 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.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Mol Co-Rapporteur: Not applicable

Timetable	Actual dates
Submission date	30 Jun 2025
Start of procedure:	19 Jul 2025
CHMP Rapporteur Assessment Report	12 Sep 2025
PRAC Rapporteur Assessment Report	19 Sep 2025

Timetable	Actual dates
PRAC members comments	24 Sep- 2025
PRAC Outcome	02 Oct 2025
CHMP members comments	06 Oct 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	09 Oct 2025
Request for supplementary information (RSI)	16 Oct 2025
CHMP Rapporteur Assessment Report	05 Jan 2026
PRAC Rapporteur Assessment Report	06 Jan 2026
PRAC members comments	08 Jan 2026
Updated PRAC Rapporteur Assessment Report	09 Jan 2026
PRAC Outcome	15 Jan 2026
CHMP members comments	19 Jan 2026
Updated CHMP Rapporteur Assessment Report	22 Jan 2026
Opinion	29 Jan 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).

Claimed therapeutic indication

Opdivo in combination with brentuximab vedotin is indicated for the treatment of adult and paediatric patients 5 years of age and older with relapsed or refractory classical Hodgkin lymphoma after one prior line of therapy.

Epidemiology

The crude incidence of HL in the European Union is 2.3, the mortality 0.4 cases/100 000/year. Slightly more men than women are diagnosed with HL. cHL accounts for ~95% of all HL cases (ESMO Guideline, 2018). Hodgkin Lymphoma has a bimodal distribution with the first peak between ages ~15-35 and the second peak being ~55 years old and older (Varughese et al, 2023), with young adults most often affected (ESMO Guideline, 2018).

Biological features

The malignant Hodgkin and Reed Sternberg (HRS) cells of cHL express CD15 and CD30 surface antigens, but usually not typical B cell markers such as surface immunoglobulin, CD20, CD79a, or the common leukocyte antigen, CD45. Although it has been described that HRS cells universally express CD30, heterogeneous expression and even CD30-negative cHL cases have been described (Sarwar et al, 2023). Assessment of CD30 expression is complicated by the lack of a consistent definition of positive CD30 expression and no known clinically meaningful cutoff between CD30 "positive" and "negative" IHC values (Jagadeesh et al, 2022; Gru et al, 2022).

The malignant 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

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.

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).

In adult (age ≥ 18 years) treatment guidelines (NCCN guideline Hodgkin Lymphoma), it is recommended that most patients with R/R cHL receive HDCT/ASCT, unless they are not a candidate due to insufficient fitness for chemotherapy, transplant ineligibility, or other reasons. Second-line re-induction systemic therapy is recommended (with checkpoint inhibitor-based therapy preferred for those with no prior exposure to and no contraindications to a checkpoint inhibitor), followed by HDCT/ASCT, with or without RT. Brentuximab vedotin (Bv) (as monotherapy or in combination regimens) is also noted as an option for R/R disease in appropriate patients. Maintenance therapy with Bv after HDCT/ASCT can be considered for patients at high risk of relapse. NCCN guidelines include nivolumab (N) + Bv as a recommendation (Category 2A) for adult patients with R/R cHL based on study SGN35-025. According to the most recent EU adult treatment guidelines (ESMO Guideline 2025), patients should receive salvage chemotherapy followed by ASCT. Further consolidating treatment with Bv after HDCT/ASCT is recommended in patients presenting with defined poor risk factors. Re-induction salvage chemotherapies such as DHAP, IGEV, or ICE can be given before HDCT/ASCT and

guidelines note that in some patients single-agent Bv may be sufficient as salvage before HDCT/ASCT. Some patients may also be considered for RT before HDCT/ASCT.

In paediatric guidelines (patients ≤ 18 years) (NCCN guideline Paediatric Hodgkin Lymphoma) systemic salvage re-induction therapy is administered for all patients. In highly favourable-risk patients only, re-induction therapy may be accompanied by RT, with subsequent monitoring and additional treatment only if needed. All other patients are assessed after salvage re-induction. If Deauville score 1-3 is achieved with first salvage re-induction treatment, the patient may proceed to HDCT/ASCT as consolidation, ± RT, ± maintenance chemotherapy. If a patient has Deauville score 4-5 after first salvage re-induction treatment, subsequent salvage therapy (i.e., a re-induction regimen not previously used) should be offered in an effort to achieve CR before proceeding to consolidation. The preferred reinduction regimen according to the NCCN guideline Paediatric Hodgkin Lymphoma lists Bv + nivolumab ± bendamustine as preferred option and other recommended options include targeted therapy and immunotherapy-based regimens (Bv combined with bendamustine, gemcitabine, or nivolumab, or single-agent nivolumab, or single-agent pembrolizumab), gemcitabine-based regimens (GV and IGEV), ifosfamide-/etoposide-based regimens (ICE, IV, and bortezomib+IV), and platinum-based regimens (DHAP, EPIC, and GDP). The EU paediatric guideline (Daw et al 2020) differentiates between low risk (RT consolidation) and standard risk patients (HDCT/ASCT consolidation). Low risk is defined as early relapse after a maximum 4 cycles of first line chemotherapy or late relapse after a maximum of 6 cycles of first line chemotherapy and ALL of the following: stage at relapse is I-III, no prior RT or relapse only outside prior RT field and no excessive RT fields required in salvage (Daw et al 2020). The aim of re-induction salvage chemotherapy is to achieve a CMR (defined as Deauville score 1-3 or qPET < 1.3) prior to consolidation. Daw, et al. note that the optimal salvage treatment has not been defined in children and adolescents, as there are no randomized trials defining the best regimen.

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 Bv or after 3 or more lines of systemic therapy including ASCT.

2.1.3. The development programme

The pivotal study (CA209744) for this application 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.

Originally, the MAH planned to perform an RCT as part of the paediatric investigation plan. However, this study was later removed from the PIP as the MAH considered that, based on the promising data of study CA209744, it was not justified to conduct an additional randomised study as the phase 2 study could provide for the evidence needed for a benefit/risk assessment.

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

Nivolumab is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk for the environment. As a protein, nivolumab (BMS-936558) is exempt from submitting 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 therefore 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 Number Study Design	Primary Endpoint(s) or Key Efficacy Endpoint(s)	No. Subjects Treated/ Evaluated for Efficacy	Population	Regimen and Dose	Study Status
Pivotal study					
CA209744 Phase 2, risk-based, response-adapted, open label study of nivo + Bv in children, adolescents, and young adults with R/R cHL after failure of 1L therapy, followed by Bv + bendamustine for patients with suboptimal response	In Cohort R1 (Low Risk of relapse): • CMR rate prior to RT, per BICR, using Lugano 2014 response criteria • EFS rate at 3 years, per BICR using Lugano 2014 response criteria In Cohort R2 (Standard Risk of relapse): • CMR rate prior to HDCT/ASCT, as assessed by BICR, using Lugano 2014 response criteria	Cohort R1: All treated (N = 28) Treated paediatric (N = 18) Cohort R2: All treated (N = 44) Treated paediatric (N = 31)	Paediatric and young-adult subjects with R/R cHL, after failure or non-response to 1L therapy	**Induction Phase** N+Bv (21-day cycles) (up to 4-6 cycles, depending on metabolic response, for Cohort R1 and 4 cycles for Cohort R2) **Intensification Phase** Bv+Bendamustine (21-day cycles) (up to 2-4 cycles if tumour assessment is PMR/NMR after 4 cycles of N+Bv) **Consolidation Phase** Radiation therapy (Cohort R1) or HDCT/ASCT (Cohort R2)	***Complete*** Primary closeout DCO 09-Sep-2019 Updated results DCO 28-May-2024
Supportive study					
SGN35-025 A phase 1/2 study evaluating brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy	Complete response rate	91 (all treated analysis set) Part 1 n=6 Part 2 n=55 Part 3 n=30	Patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy	Part 1 and 2 (staggered dosing): N+Bv (21-day cycles) up to four cycles Part 3 (same-day dosing): N+Bv (21-day cycles) up to four cycles	***Complete*** Study report date 22-Aug-2022

The pivotal study for this submission is CA209744, an open-label, Phase 2 study that evaluated the efficacy and safety of intravenous nivolumab 3 mg/kg + brentuximab vedotin 1.8 mg/kg given Q3W in paediatric and young adult patients with R/R cHL after failure of 1L therapy. Subjects were assigned to

1 of 2 treatment cohorts based on risk: Cohort R1 for subjects at low risk of relapse and Cohort R2 for subjects at standard risk of relapse.

2.3.2. Pharmacokinetics

Methods

PK and immunogenicity bioanalytical methods are described in bioanalytical study reports included in the CSR for study CA209744 (submitted in procedure EMA/H/C/003985/P46/061).

All bioanalytical assays used for analysis of nivolumab, brentuximab vedotin, and MMAE in study CA209744 have been previously submitted for Opdivo and Adcetris: for nivolumab (Method ICD 416), brentuximab vedotin (Validation Report 7646-127 and Addenda) and MMAE (Validation Report 7646-130 and amendments). Incurred sample reanalyses were acceptable.

The same (neutralising) ADA analytical assays were used for nivolumab (Method ICDIM 140 and Method 15400) and brentuximab vedotin (Methods ECL-0123 and ICDIM 227) as described in earlier applications for Opdivo and Adcetris.

The nivolumab popPK model including 275 paediatric subjects (EMEA/H/C/003985/II/0125/G) has been used to compare nivolumab exposures in paediatric and adult subjects with cHL.

Pharmacokinetic data collection

In study CA209744, sparse PK data were collected i.e. at day 8 first cycle prior to nivolumab infusion and pre-dose concentrations at cycle 2, 3, and 4.

Results

Comparison of observed nivolumab concentrations in R1 and R2 Cohorts in CA209744

Following the availability of Cohort R1 concentration-time data in CA209744, a descriptive comparison of observed pre-dose nivolumab concentrations following the administration of nivolumab 3 mg/kg + brentuximab vedotin 1.8 mg/kg IV Q3W between Cohorts R1 (low risk) and R2 (standard risk) was conducted. Geometric mean pre-dose nivolumab concentrations were similar (difference in geometric mean ≤10.5%) between Cohort R1 and Cohort R2 (**Table 1**).

Table 1. **Summary of the observed nivolumab exposures in Cohort R1 and R2 of Study CA209744**

Observed Nivolumab Exposures	Cohort R1 Geometric Mean, □g/mL (%CV)[N]	Cohort R2 Geometric Mean, □g/mL (%CV)[N]	Difference in Geometric Mean % (R1-R2)/R2
C2D1 Predose	18.2 (27.4%) [24]	19.8 (21.9%) [41]	-8.4%
C3D1 Predose	24.6 (30.1%) [25]	27.5 (25.3%) [41]	-10.5%
C4D1 Predose	31.9 (29.4%) [25]	33.3 (23.6%) [43]	-4.3%

Comparison of observed nivolumab and brentuximab vedotin concentrations in CA209744 in various age cohorts.

Descriptive statistics of nivolumab concentrations (C2D1, C3D1, and C4D1) per age category (<12, 12-<18, ≥18 years) for study CA209744 are provided in **Table 2.** Comparable nivolumab exposures were observed between the age categories.

Table 2. Summary statistics for Ctrough nivolumab concentrations by visit and age - all treated patients, pooled population [Cohorts R1 and R2 combined]

Visit	Summary	< 12 Years	12 to < 18 Years	>= 18 Years	All Ages
CYCLE 2 DAY 1	N	5	37	21	63
	MEAN	19.740	19.636	20.481	19.926
	SD	3.625	4.691	5.392	4.812
	MEDIAN	21.200	19.900	19.500	19.900
	MIN	14.60	7.54	8.10	7.54
	MAX	23.20	29.40	27.50	29.40
	CV	18.362	23.887	26.328	24.151
	GEO MEAN	19.454	18.984	19.682	19.251
CYCLE 3 DAY 1	N	6	39	21	66
	MEAN	28.317	27.408	28.129	27.720
	SD	6.854	8.322	6.377	7.534
	MEDIAN	29.250	27.500	26.700	27.150
	MIN	17.30	5.42	17.60	5.42
	MAX	35.40	41.30	41.10	41.30
	CV	24.206	30.363	22.669	27.178
	GEO MEAN	27.535	25.656	27.442	26.380
CYCLE 4 DAY 1	N	6	41	21	68
	MEAN	31.417	34.380	34.095	34.031
	SD	6.109	9.185	8.620	8.719
	MEDIAN	31.150	36.200	32.200	33.400
	MIN	23.80	14.80	18.80	14.80
	MAX	42.30	50.80	49.90	50.80
	CV	19.445	26.716	25.281	25.620
	GEO MEAN	30.951	32.939	33.036	32.788

NA = Not Applicable
Samples were taken pre-dose.

Descriptive statistics of brentuximab vedotin concentrations (C2D1, C3D1, and C4D1) per age category (<12, 12-<18, ≥18 years) for study CA209744 are provided in **Table 3**. Subjects with brentuximab vedotin concentrations <LLOQ were not included.

Table 3. Summary Statistics for Brentuximab Vedotin Concentrations by Visit and Age - All Treated Patients, Pooled Population [Combined Cohorts R1 and R2]

Visit	Summary	< 12 Years	12 to < 18 Years	>= 18 Years	All Ages
CYCLE 2 DAY 1	N	3	27	15	45
	MEAN	438.280	419.854	294.773	379.389
	SD	483.841	401.230	243.119	358.130
	MEDIAN	312.560	296.893	238.904	296.893
	MIN	29.71	16.65	69.38	16.65
	MAX	972.57	1424.46	834.41	1424.46
	CV	110.395	95.564	82.477	94.397
	GEO MEAN	208.246	202.626	208.791	205.034
CYCLE 3 DAY 1	N	2	27	16	45
	MEAN	963.627	551.317	404.864	517.570
	SD	411.096	541.695	391.974	493.937
	MEDIAN	963.627	393.309	214.625	368.404
	MIN	672.94	13.69	52.90	13.69
	MAX	1254.32	1995.78	1446.28	1995.78
	CV	42.661	98.255	96.816	95.434
	GEO MEAN	918.736	276.626	265.045	287.381
CYCLE 4 DAY 1	N	3	29	16	48
	MEAN	707.540	740.348	665.182	713.242
	SD	563.330	652.013	515.034	593.858
	MEDIAN	974.856	530.479	727.546	717.350
	MIN	60.32	16.57	16.76	16.57
	MAX	1087.45	2286.90	1535.46	2286.90
	CV	79.618	88.069	77.428	83.262
	GEO MEAN	399.884	407.273	389.539	400.815

NA = Not Applicable
Samples were taken pre-dose.

PopPK predicted PK parameters of nivolumab in paediatric and adult patients with cHL

The full model was a two-compartment, zero-order IV infusion and time-varying CL (sigmoidal-Emax function) with a proportional residual error model, with random effects on CL, VC, VP, and Emax and correlation of random effects between CL and VC. The effect of body weight and cHL on CL was evaluated separately for adults and paediatrics. Parameter estimates for full popPK model are presented in **Table 4**.

Table 4. Parameter estimates of the nivolumab population pharmacokinetic full model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e,f]
Fixed Effects				
CL [mL/h]	θ_1	0.0118	5.20E-04 (4.40)	0.0109 - 0.0132
VC [L]	θ_2	4.19	0.0643 (1.53)	4.06 - 4.31
Q [L/h]	θ_3	0.0345	0.00345 (9.99)	0.0277 - 0.0449
VP [L]	θ_4	2.37	0.138 (5.83)	2.01 - 2.68
$CL_{BBWTadult}$	θ_7	0.632	0.0645 (10.2)	0.489 - 0.736
CL_{AGE}	θ_8	0.121	0.0481 (39.6)	0.00123 - 0.200
CL_{BGFR}	θ_9	0.0844	0.0446 (52.9)	-0.00851 - 0.183
CL_{SEX}	θ_{10}	-0.164	0.0293 (17.9)	-0.229 - -0.118
CL_{PS}	θ_{11}	0.135	0.0253 (18.8)	0.0818 - 0.182
CL_{RAAA}	θ_{12}	0.0551	0.0546 (99.1)	-0.0643 - 0.155
CL_{RAAS}	θ_{13}	-0.0944	0.0641 (67.9)	-0.244 - 0.0280
VC_{BBWT}	θ_{14}	0.708	0.0549 (7.75)	0.598 - 0.814
VC_{SEX}	θ_{15}	-0.138	0.0278 (20.2)	-0.192 - -0.0821
$CL_{adultCHL}$	θ_{16}	-0.244	0.0376 (15.4)	-0.335 - -0.180
CL_{PedCHL}	θ_{17}	-0.265	0.0840 (31.7)	-0.568 - -0.189
CL_{OTH}	θ_{18}	0.100	0.0370 (36.9)	0.0270 - 0.182
CL_{EMAX}	θ_{19}	-0.402	0.0621 (15.5)	-0.547 - -0.266
CL_{T50}	θ_{20}	1.22E+03	117 (9.63)	954 - 1.51E+03
CL_{HILL}	θ_{21}	2.29	0.654 (28.6)	1.48 - 7.00
$V1_{BBWTPed}$	θ_{22}	1.17	0.196 (16.7)	0.316 - 1.91
$CL_{BBWTPed}$	θ_{23}	0.787	0.172 (21.8)	0.238 - 1.28
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.103 (0.321)	0.0091 (8.83)	0.0787 - 0.115
ZVC [-]	$\omega_{2,2}$	0.0798 (0.283)	0.0110 (13.8)	0.0604 - 0.102
ZVP [-]	$\omega_{3,3}$	0.317 (0.563)	0.0539 (17.0)	0.169 - 0.382
ZEMAX [h]	$\omega_{4,4}$	0.0686 (0.262)	0.0207 (30.2)	0.0281 - 0.105
ZCL:ZVC	$\omega_{1,2}$	0.0485 (0.535)	0.0064 (13.2)	0.0332 - 0.0539
Residual Error				
RESERR[f]	$\sigma_{1,1}$	1.00 (1.00)		1.00 - 1.00
PERR [-]	θ_6	0.207	0.00561 (2.71)	0.195 - 0.217

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

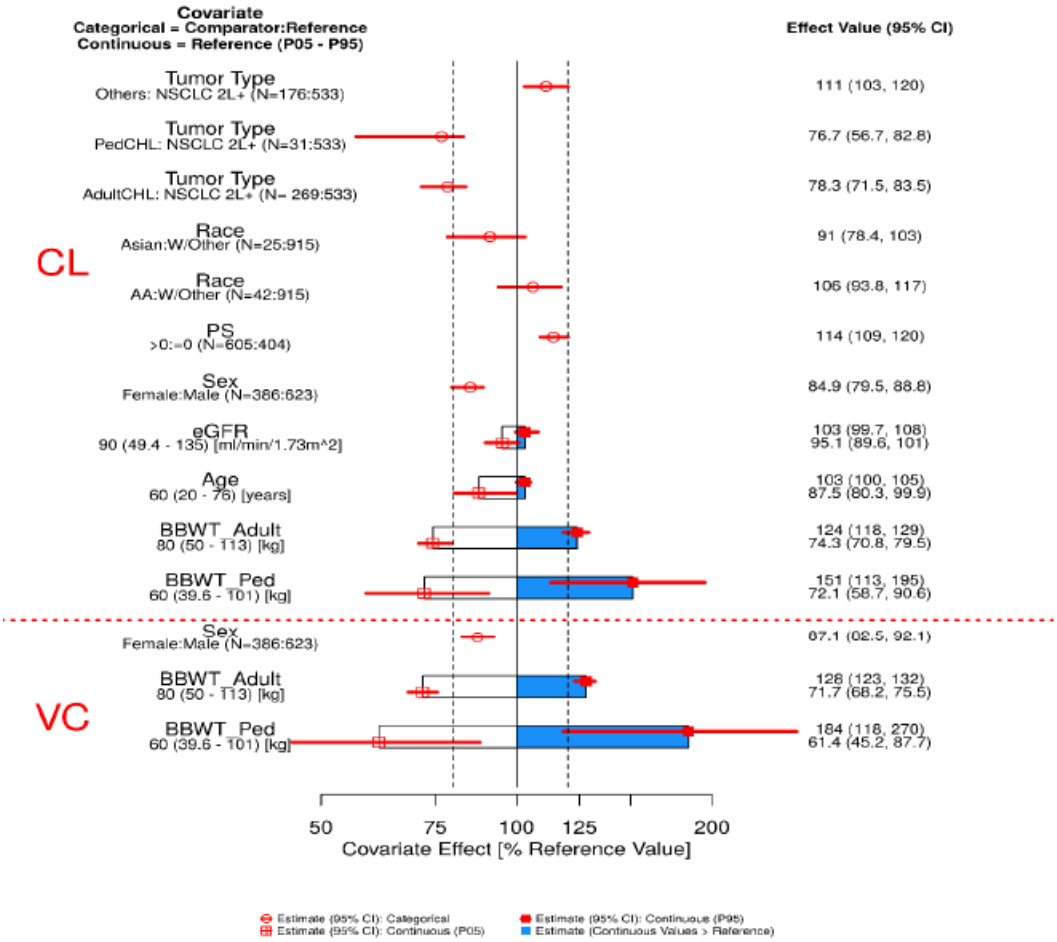
[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

[f] Confidence Interval values are taken from bootstrap calculations (1000 successful out of a total of 1000)

Note: *CL0REF is the typical value in a reference subject with NSCLC, receiving nivolumab monotherapy as 2L+, male and weighing 80 kg adult or 60 kg paediatric subject. VCREF, QREF, and VPREF are typical values in a reference subject weighing 80 kg (adult) or 60 kg (paediatric). These reference values represent the approximate median values in the popPK analysis dataset.*
Note: *Eta shrinkage (%): ETA_CL: 15.4; ETA_VC: 23.4; ETA_EMAX: 47.5; EPS shrinkage (%): 15.2.*
Note: *OTH (OTHERS) includes subjects with melanoma, renal cell carcinoma (RCC), prostate cancer (PC), and colorectal cancer (CRC)*

The effects of covariates on PK model parameters are shown in **Figure 1**.

Figure 1. Covariate effects on nivolumab pharmacokinetic model parameters (full nivolumab popPK model)



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is male, white/other race, BW = 80 kg adult or 60 kg pediatric subject, PS = 0, eGFR = 90 mL/min/1.73 m2, with NSCLC as tumor type and received nivolumab monotherapy as 2L+. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.

The exposure metrics (Cmin, Cmax, and Cavg after first or fourth dose) were predicted from the full model for paediatric and adult subjects with cHL (**Table 5**). In Study CA209744 R2 Cohort, the exposures achieved in paediatrics with 3 mg/kg Q3W dosing were ~13% lower relative to the corresponding exposures achieved in adults receiving the same dosing regimen. The difference in trough concentration and average concentration was marginal, ranging from -1.3% -to 5.7% (in geometric means) for paediatrics subjects with cHL as compared to adults.

Table 5. Geometric Mean exposure for nivolumab in paediatric and adult subjects with cHL

Summary Exposure	Geometric Mean, µg/mL (%CV)			Difference in Geometric Mean %	
	Pediatric cHL 3 mg/kg Q3W (N=31, G1[a])	Adult cHL 3 mg/kg Q3W (N=13, G2[b])	Adult cHL 3 mg/kg Q2W (N=256, G3[c])	(G2-G1)[d]	(G3-G1)[e]
Cmax1	48.7 (10.3)	55.5 (14.9)	59.2 (13.6)	-12.3	-17.7
Cavg1	23 (12.7)	24.4 (16.9)	30.1 (17.4)	-5.74	-23.6
Cmin1	15.3 (16.5)	15.5 (20.7)	21.1 (21.3)	-1.29	-27.5
Cmax4	76.3 (12.4)	83.6 (18.2)	103 (16.9)	-8.73	-25.9
Cavg4	43.3 (16.3)	45.2 (21.6)	65.2 (20.1)	-4.2	-33.6
Cmin4	29.6 (20.2)	30.4 (28.4)	49 (22.7)	-2.63	-39.6

[a] Pediatric subjects with cHL from Study CA209744 R2 Cohort, treated with 3 mg/kg Q3W

[b] Adult subjects with cHL from Study CA209744 R2 Cohort, treated with 3 mg/kg Q3W

[c] Adult subjects with cHL from studies CA209039 and CA209205, treated with 3 mg/kg Q2W

[d] Percent difference in geometric mean of 3 mg/kg Q3W (adults, G2) relative to 3 mg/kg Q3W (pediatrics, G1)

[e] Percent difference in geometric mean of 3 mg/kg Q2W (adults, G3) relative to 3 mg/kg Q3W (pediatrics, G1)

Immunogenicity

Results of anti-drug antibody assessments are shown in **Table 6** (cohort R1) and **Table 7** (cohort R2).

Table 6. Anti-Drug Antibody Assessments, Cohort R1

	All-Treated Subjects		Treated Paediatric Subjects	
Subject ADA Status (%)	**Nivolumab ADA N=25**	**Brentuximab vedotin ADA N=24**	**Nivolumab ADA N=16**	**Brentuximab vedotin 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)

Table 7. Anti-Drug Antibody Assessments, Cohort R2

	All-Treated Subjects		Treated Paediatric Subjects	
Subject ADA Status (%)	**Nivolumab ADA N=40**	**Brentuximab vedotin ADA N=41**	**Nivolumab ADA N=28**	**Brentuximab vedotin 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)

	All-Treated Subjects		Treated Paediatric Subjects	
Subject ADA Status (%)	**Nivolumab ADA N=40**	**Brentuximab vedotin ADA N=41**	**Nivolumab ADA N=28**	**Brentuximab vedotin ADA N=28**
Neutralizing Positive	0	24 (58.5)	0	16 (57.1)
ADA Negative	35 (87.5)	17 (41.5)	24 (85.7)	12 (42.9)

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.

2.3.3. Discussion on clinical pharmacology

The basis of this extension of indication for the treatment of adult and paediatric patients 5 years of age and older with relapsed or refractory classical Hodgkin lymphoma after one prior line of therapy with nivolumab in combination with brentuximab vedotin is Study CA209744. Study CA209744 is an open-label, Phase 2 study that evaluated the efficacy and safety of intravenous nivolumab 3 mg/kg + brentuximab vedotin 1.8 mg/kg given Q3W in paediatric and young adult patients with R/R cHL after failure of 1L therapy. Pharmacokinetics was an exploratory endpoint in study CA209744 and only sparse data i.e. Ctrough values were collected. The Ctrough values at the first day of the 2nd cycle (19.0 µg/mL), which was 14 days after the first administration, was comparable with the historical Ctrough values of 3 mg/kg Q2W in adult subjects with cHL (20.2 µg/mL; EMEA/H/C/003985/II/0012) suggesting that the pharmacokinetics were comparable in this paediatric/young adult population as in the adult population with cHL. Nivolumab Ctrough values in study CA209744 were comparable in subjects < 12 years, 12-<18, and ≥18 years of age.

Posology justification

The posology of brentuximab vedotin was selected as this is the approved posology in adults and also used in a study in 587 patients 2 to 21 years with previously untreated Hodgkin's lymphoma demonstrating that 1.8 mg/kg Q3W is efficacious and safe in this population even though brentuximab vedotin and MMAE exposures are 23-38% lower in subjects 2-12 year compared to adolescents and adults (Castellino et al., NEJM, 2022, Locatelli et al 2018, Zhang et al, 2024).

The nivolumab dose of 3 mg/kg was selected because it was the initially approved IV dose across many adult indications including for cHL. The Q3W schedule was chosen to align with that of brentuximab vedotin schedule. Nivolumab Q3W dosing is also approved in combination with ipilimumab treatment. The MAH simulated nivolumab exposures of nivolumab 3 mg/kg Q3W in paediatric (5 to 11 years) and adolescent (12 to 17 years) subjects with HL across a range of body weights using, as requested, the 'paediatric' popPK model (EMEA/H/C/003985/II/0125/G). Simulated paediatric exposures were compared to simulated 5%-95% nivolumab exposures following 3 mg/kg Q3W treatment in adults with cHL. PopPK analysis indicated that pharmacokinetics of nivolumab in combination with brentuximab vedotin were comparable to pharmacokinetics of nivolumab monotherapy in adults with cHL. Hence it is considered acceptable to use the nivolumab pharmacokinetic data in adults from cHL from other studies to estimate the adult exposure range. The MAH used the 5%-95% popPK simulated nivolumab exposures following 3 mg/kg Q3W treatment in adults with cHL as target range. Selection of 5%-95% of nivolumab exposures in adults with cHL as

target range implicitly assumes a similar benefit-risk at 5% exposures as at 95% percentile exposures, in other words assumes flat exposure-efficacy and efficacy-safety relationships at this dosing regimen. Based on the flat dose efficacy/safety relationships of nivolumab monotherapy over the dose range 1-10 mg/kg for melanoma and RCC, supported by the dose proportional pharmacokinetics and dose independent receptor occupancy over the dose range 0.3-10 mg/kg, the 5%-95% nivolumab exposure target range based on 3 mg/kg Q3W treatment for adults can be accepted.

Simulated nivolumab exposures are similar in adolescents and adults as the body weight ranges overlap and body weight is the most important co-variate. Simulated nivolumab exposures are lower in the paediatric subjects between 5 and 11 years for the lowest body weight groups 10-20 kg and 20-30 kg, which are predicted closer to the 5th percentile of adult exposures. Similarly, as for brentuximab vedotin, in paediatric patients with lower body weight mean nivolumab exposures are ~25-35% lower in subjects 10-30 kg compared to adults. A lower exposure of monoclonal antibodies, which have a cellular receptor as target, can be expected in subjects with lower body-weight when using a power function with an exponent of 0.75 on clearance consistent with allometric principles while dosing on a mg/kg basis (Temrikar et al., 2020, Edlund et al., 2015). Overall, a lower nivolumab exposure is expected in subjects 10-30 kg compared to adolescents and adults. A higher nivolumab dose than 3 mg/kg in subjects 10- 30 kg could provide a better match of nivolumab exposures with adolescents and adults. On the other hand, the expected lower nivolumab exposures in subjects 10-30 kg dosed 3 mg/kg Q3W are still in the effective exposure range established for nivolumab monotherapy. Therefore, nivolumab 3 mg/kg Q3W in combination with brentuximab vedotin 1.8 mg/kg Q3W is considered acceptable for subjects >5 years with cHL.

Immunogenicity

More than 25% of the subjects in study CA209744 had brentuximab vedotin Ctrough levels < 50 ng/mL. Subjects < 18 years, subjects with low risk of relapse and subjects with persistent anti-brentuximab vedotin ADAs had more often all brentuximab vedotin Ctrough values < 50 ng/mL. Nevertheless, efficacy was comparable is subjects with low brentuximab vedotin Ctrough levels and subjects with "normal" brentuximab vedotin Ctrough levels; the 4-year EFS rate in cohort R1 was high also in subjects with low brentuximab vedotin concentrations. Drug-related hepatic AEs and hypersensitivity/infusion AEs are increased in subjects with brentuximab vedotin < 50 ng/mL concentrations. A confounding factor might be the persistent anti-brentuximab ADAs, which also lead to increased hypersensitivity/infusion AEs and this is already described in the SmPC.

The incidence of ADA positivity and neutralising antibodies against brentuximab vedotin as reflected in the SmPC is much higher than historically reported for brentuximab vedotin despite that the same bioanalytical assays have been used to evaluate ADAs and neutralising ADAs as have been used in the applications for brentuximab vedotin. The MAH suggested that upregulation of the body's immune response by nivolumab might explain the higher incidences. An increase in incidence of ADAs of nivolumab in combination with ipilimumab has been observed and concomitant use with immunosuppressive agents is known to lower the incidence of ADAs. This argumentation is plausible and CHMP recommended that immunogenicity needs to be followed in future studies when nivolumab is combined with antibodies.

The MAH also evaluated the occurrence of IRR in subjects with ADA persistent positivity: 4 out of 12 subjects with persistent ADAs had IRR while 8 out 60 subjects without persistent ADAs had IRR. Although the numbers are small, the occurrence of IRR is higher in the persistent positive group, which is consistent with earlier observations for brentuximab vedotin and is already described in the SmPC.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetic data from study CA209244 are considered supportive for this extension of indication. The dosing regimen of nivolumab 3 mg/kg Q3W in combination with brentuximab vedotin 1.8 mg/kg Q3W has been sufficiently justified for subjects with cHL of 5 years of age and older.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were submitted. Nivolumab was administered 3 mg/kg Q3W based on the monotherapy dosing of nivolumab in adults for various tumour types (including cHL). Dosing of nivolumab 3 mg/kg was timed at Q3W to align with the Q3W frequency of Bv dosing.

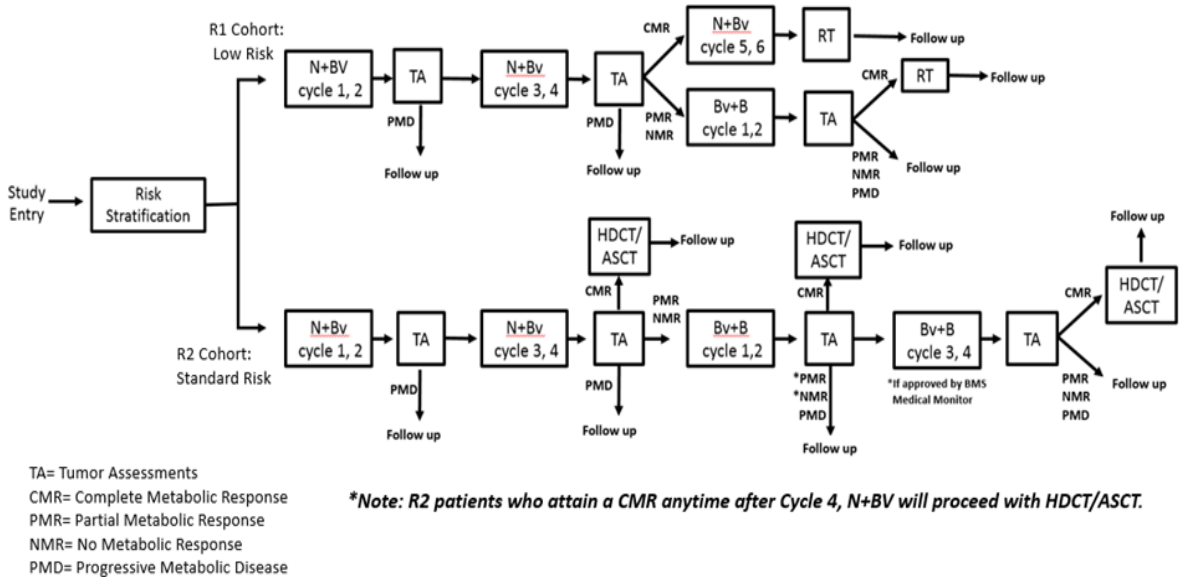
Brentuximab vedotin was administered 1.8 mg/kg Q3W. This is the CHMP approved posology for adults with relapsed or refractory HL. Brentuximab vedotin is not approved for paediatric patients.

2.4.2. Main study

CA209744: Risk-based, response-adapted, Phase II 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 study design is depicted in **Figure 2.**

Figure 2. Study CA209744 design schematic



Methods

Study participants

Inclusion criteria

1. Signed Written Informed Consent
    a. Participants must have signed and dated an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.
    b. Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
    c. For participants unable to give their written consent, in accordance with local regulations, one or both parents, a guardian, or a legally acceptable representative must be informed of the study procedures and must document permission by signing the informed consent form approved for the study prior to clinical study participation.
    d. Each participant must be informed about the nature of the study to the extent compatible with his or her understanding. Should a participant become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a participant who is a minor or unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.
    e. Minors who are judged to be of an age of reason as determined by local requirements should also give their assent. The assent should be documented based on local requirements. Continued assent should be documented when important new information becomes available that is relevant to the participant's assent.
2. Type of Participant and Target Disease Characteristics
    a. Participants must have measurable disease, documented by pathological and radiographic criteria
        i. Participants with pathologically confirmed cHL, excluding nodular lymphocyte-predominant HL, after failure or non-response to first-line therapy.
            1. Relapsed disease is defined as achieving a CR to previous therapy but then progressing 3 months or more after completion of that therapy.
            2. Refractory disease is defined as never achieving a CR to previous therapy or achieving a CR but then progressing within 3 months of completion of that therapy.
        ii. At least 1 measurable site of disease according to the Lugano 2014 criteria (International Working Group criteria).

iii. Participants must have FDG-PET-avid and bidimensional measurable disease of at least 1.5 cm in longest axis as documented by radiographic technique (CT preferred).

b. Performance Level: Karnofsky ≥ 50 for participants > 16 years of age or Lansky ≥ 50 for participants ≤ 16 years of age. Participants who are unable to walk because of paralysis, but who are in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

c. Evaluable tumour tissue (archived or new biopsy) must be provided to the central laboratory as formalin-fixed paraffin-embedded (FFPE) tumour block or slides. In order to be treated, the sample must meet the minimum quality requirements, as determined by the central laboratory during the screening period.

3. Age and Reproductive Status

a. Males and Females, ages 5 to 30 years, inclusive.

b. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

c. Women must not be breastfeeding.

d. WOCBP must agree to follow instructions for 2 methods of contraception or complete abstinence (listed in Appendix 4) for the duration of treatment with investigational drugs (all IMPs) and for an additional 6 months post-treatment completion.

e. Males who are sexually active with WOCBP must agree to follow instructions for 2 methods of contraception or complete abstinence for the duration of treatment with investigational drugs (all IMPs) and for an additional 6 months posttreatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f. Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

4. Physical and Laboratory Test Findings

a. Screening laboratory values must meet the following criteria:

i. Adequate bone marrow function defined as the following:

1. For participants without known bone marrow involvement:

a. Peripheral absolute neutrophil count (ANC) ≥ 750/mm3.

b. Platelet count ≥ 75,000/mm3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrolment). Participants with known bone marrow metastatic disease will be eligible for study provided they meet the platelet counts following transfusion, however they will not be eligible for assessment of hematologic toxicity.

2. For participants with known bone marrow involvement:

a. Participants with cytopenias secondary to known bone marrow involvement are eligible regardless of ANC or platelet counts.

b. Participants may be enrolled and receive transfusions provided they are not known to be refractory to red cell or platelet transfusions. Participants with bone marrow involvement will not be evaluated for hematologic toxicity regardless of ANC or platelet counts at the time of diagnosis.

ii. Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m2 or a serum creatinine based on age/gender.

iii. Adequate hepatic function as evidenced by the following:

1. Total bilirubin ≤ 1.5 x upper limit of normal (ULN).
2. SGPT (alanine aminotransferase [ALT]) ≤ 3 x ULN. For the purpose of this study, the ULN for SGPT is 45 U/L.

5. Prior Anti-tumour Therapy

a. Participants must have received first-line anti-cancer therapy that failed

b. Participants must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy prior to signing consent.

c. Myelosuppressive chemotherapy: At least 14 days after the last dose of myelosuppressive chemotherapy.

d. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for short-acting growth factor. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the BMS Medical Monitor.

e. Biologic (anti-neoplastic agent): At least 3 half-lives after the last dose of a biologic agent.

f. Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody.

g. Bleomycin: At least 28 days must have elapsed since the most recent dose of bleomycin, to allow adequate time to detect evidence of bleomycin-related pulmonary toxicity.

<u>Exclusion criteria</u>

1) Medical Conditions

a. Participants with an immunodeficiency that existed prior to diagnosis, such as primary immunodeficiency syndromes, organ transplant recipients, and participants on current systemic immunosuppressive agents are not eligible.

b. Active cerebral/meningeal disease related to the underlying malignancy.

c. History of progressive multifocal leukoencephalopathy (PML).

d. Pre-existing neuropathy of ≥ Grade 2.

e. Any active Grade 3 or higher (per Common Terminology Criteria for Adverse Events [CTCAE] version 4) viral, bacterial or fungal infection prior to the first dose of brentuximab vedotin; routine antimicrobial prophylaxis is permitted.

f. Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

g. Other serious underlying medical condition that, in the opinion of the investigator, would impair the ability to receive or tolerate the planned treatment and follow-up.

h. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

i. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

2) Prior/Concomitant Therapy

a. Participants who received more than one line of anti-cancer therapy or are treatment naive are not eligible.

b. Previously received an allogeneic and/or autologous SCT for HL.

c. Participants who have received a prior solid organ transplantation are not eligible.

d. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study medication. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

e. Prior exposure to anti-PD1, anti-PDL1, anti-PD-L2, anti-CD137 or anti- CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

f. Prior radiation therapy within 3 weeks, or chest radiation ≤ 12 weeks prior to first dose of study drug(s).

g. Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cHL).

h. Prior exposure to bendamustine.

i. Live vaccine (< 4 weeks prior to the start of study treatment).

3) Physical and Laboratory Test Findings

a. Any positive test for hepatitis B or C virus indicating acute or chronic infection, and/or detectable virus.

4) Allergies and Adverse Drug Reaction

a. History of allergy or hypersensitivity to study drug components.

b. Participants with serious or uncontrolled medical disorders that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

5) Other Exclusion Criteria

a. Prisoners or participants who are involuntarily incarcerated.

b. Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

There were 2 treatment cohorts: Cohort R1 for subjects at low risk of relapse and Cohort R2 for subjects at standard risk of relapse (**Table 8**).

Table 8. Risk stratification algorithm

Stage at Initial Diagnosis	Time to Relapse (from end of therapy)	B Symptoms or Extranodal Disease at Relapse, Extensive Disease where RT was Contraindicated at Relapse, or Relapse in a Prior Radiation Field	Relapse Risk Category
IA, IIA	≥ 12 months	No	Cohort R1 Low Risk
	3-12 months (≤ 3 cycles and no RT)	No	
IB, IIB, IIIA	> 12 months	No	
All Others			Cohort R2 Standard Risk

Treatments

The study treatment is shown in **Table 9**.

Table 9. Study treatments in CA209744

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 tumour 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 subject 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.

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; paediatric: 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.

Discontinuation of treatment

Nivolumab was permanently discontinued in case of disease progression and in case of prespecified drug-related adverse events. Furthermore, in most cases treatment was discontinued if dose delays lasting > 6 weeks occurred.

Objectives

Cohort R1 (low risk): To describe the CMR rate prior to RT and EFS rate at 3 years.

Cohort R2 (standard risk): To describe the CMR rate prior to HDCT/ASCT.

Outcomes/endpoints

Cohort R1 (low risk) co-primary endpoint

- CMR rate per BICR: Proportion of response-evaluable subjects who achieved a best response of CMR using Lugano 2014 criteria prior to consolidation.
- EFS rate at 3 years per BICR: Time from the date of first treatment to the earliest occurrence of composite events, including:
    - HDCT/ASCT
    - Disease progression per Lugano 2014 criteria
    - Failure to achieve CMR after 4 cycles of N+Bv and 2 cycles of Bv+B
    - Secondary malignancy
    - Death due to any cause

Cohort R2 (standard risk) primary endpoint

- CMR rate per BICR: Proportion of response-evaluable subjects who achieved a best response of CMR using Lugano 2014 criteria prior to HDCT/ASCT, that is, any time after first 4 cycles of treatment prior to consolidation.

Secondary endpoints (both cohort R1/R2)

- ORR per BICR using Lugano 2014 criteria
- PFS rate at 3 years per BICR using Lugano 2014 criteria

- DOR per BICR using Lugano 2014 criteria
- Toxicity/safety (incidence of AEs, SAEs, AEs leading to discontinuation of study treatment, select AEs, Immune-mediated adverse events (IMAEs), deaths, and clinical laboratory abnormalities)
- Investigators assessment
    - Cohort R1: CMR rate prior to RT, EFS at 3 years
    - Cohort R2: CMR rate prior to HDCT/ASCT
    - Cohort R1/R2: ORR after 4 cycles of N+Bv, PFS rate at 3 years, DOR

Exploratory endpoints (both cohort R1/R2)

- Overall Survival
- Biomarker levels (baseline PD-L1 expression and EBV status association with tumour response)
- Biomarkers in peripheral blood (changes in immune cells counts of memory B-cells and T-cells, and vaccinated antibody concentrations over time)
- PK (nivolumab, brentuximab vedotin)
- Immunogenicity (frequency of positive anti-drug antibodies and neutralizing antibodies for nivolumab and brentuximab vedotin)
- Patient-reported outcomes (EQ-5D-3L and FACT-Lym)
- ORR and EFS in different risk factors subgroups based on performance status, time from diagnosis to relapse/refractory disease, extranodal disease at the time of ASCT and chemosensitivity association with EFS and ORR
- LYRIC 2016 for efficacy assessment (CMR rate, EFS, PFS, ORR, DOR per BICR using LYRIC 2016 criteria)

Sample size

The sample size was not based on any formal statistical testing or power considerations, but precision of a 90% CI was considered (+/-14% around 50% response and +/-10% around 75% response). This study targeted treating initially approximately 40 subjects in each risk cohort. In protocol amendment 4 (26-Mar-2021) the recruitment of Cohort 1 was closed due to feasibility issues. 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.

Randomisation and blinding

This was an open-label single-arm study.

Statistical methods

R1 Cohort

The best response of a subject by BICR over the induction and intensification periods prior to receiving the consolidation radiotherapy, or subsequent anti-cancer therapy if applicable, are summarised. The estimated CMR rate and the exact 2-sided 90% CI will be provided. In addition to the Response-Evaluable Participants (primary analysis), the analysis of CMR rate will be carried out for treated population as well (secondary analysis).

The EFS function per BICR and the 3-year EFS rate were estimated using the Kaplan-Meier product-limit method when all participants have (whichever is 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).

In addition to the treated population, the EFS per BICR analysis were carried out for the following subgroup: Participants who achieved CMR, went into RT, and did not receive HDCT/ASCT.

The same analyses described above for R1 was performed using investigator assessments as well. The same analyses described above was performed using LYRIC 2016 (BICR only) as exploratory analyses.

R2 Cohort

The best response of a subject by BICR over the induction and intensification periods prior to receiving the consolidation HDCT/ASCT, or subsequent anti-cancer therapy if applicable, was summarised. The estimated CMR rate and the exact 2-sided 90% CI was provided. In addition to the Response-Evaluable Participants (primary analysis), the analysis of CMR rate was carried out for treated population as well (secondary analysis).

The same analyses described above for R2 was performed using investigator assessments as well. The same analyses described above was performed using LYRIC 2016 (BICR only) as exploratory analyses.

An interim analysis was performed when all subjects in R2 were response evaluable to estimate the primary (CMR prior to HDCT/ASCT) and secondary (ORR, PFS, DoR and safety) endpoints with a minimum follow-up of 68 weeks. The timing was when all patients in R2 were response evaluable (reached CMR prior to HDCT/ASCT, entered follow-up or withdrawn consent).

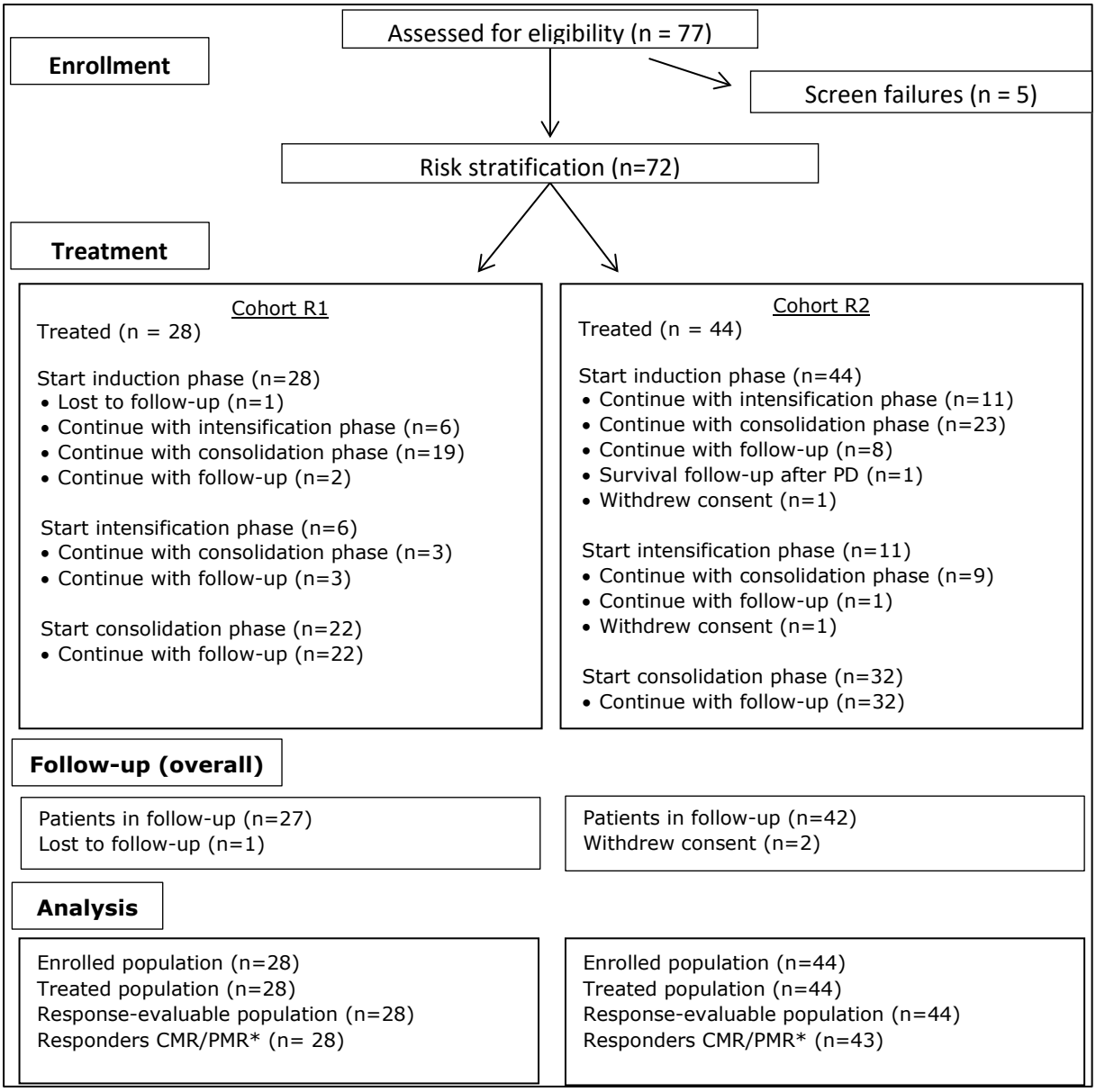
Both cohorts

Duration of response was defined as the time from first response (CMR or PMR) to the date of an EFS event in R1 (see Outcomes/Endpoints) and to the date of an PFS event (documented progression or death). Participants who started subsequent therapy that was not part of the HDCT/ASCT were censored at the last tumour assessment prior to start of subsequent therapy.

Results

Participant flow

Table 10. Participant flow in study CA209744



* "Responders CMR/PMR" is the denominator used for DoR analyses and refers to the number of participants in each cohort who achieved a CMR or PMR at any time (not necessarily prior to Consolidation, or after 4 cycles of Nivo+Bv as Induction therapy).

Recruitment

Study start date: 28-March-2017 (First patient first visit).

Data cut-off date for final report: 28-May 2024.

Conduct of the study

The original Protocol for this study was dated 23-Sep-2016. There was a total of 4 global revisions, which are described in **Table 11**.

Table 11. Key changes to protocol CA209744

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 tumour 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 tumour assessments at study treatment-related decision timepoints to determine further treatment. If investigator assessment was CMR but BICR assessment differed and treatment was discontinued, tumour 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	100 enrolled 72 treated (R1: 28; R2: 44)	77 enrolled 72 treated (R1: 28/28 R2: 49/44)

Document (Amendment) /Date	Summary of Key Changes	Planned Sample Size	Subjects Enrolled/ Treated at Time of Protocol Amendment
	results in a meaningful timeframe for paediatric subjects. • Added BMS standard Protocol language on COVID-19.		

There were 5 patients with a relevant protocol deviation. In cohort R1, one subject received concurrent prohibited therapy and one subject received more than the pre-planned treatment duration. In cohort R2, three patients received more than the pre-planned treatment duration.

In cohort R1, there were 31 important protocol deviations mainly related to trial procedures not performed per protocol. In cohort R2, there were 45 important protocol deviations mainly related to trial procedures and informed consent (lost informed consent forms, updated informed consent forms not signed).

Baseline data

Demographics are presented in **Table 12**. Baseline characteristics are presented in **Table 13**.

Table 12. Demographics in study CA209744 – All treated population

	Cohort R1		Cohort R2	
	Total (n=28)	**Paediatrics (n=18)**	**Total (n=44)**	**Paediatrics (n=31)**
Age *median (range)*	17 (6 – 27)	16 (6 – 17)	16 (9 – 30)	15 (9 – 17)
Children (5 – 11)	3 (10.7)	3 (16.7)	4 (9.1)	4 (12.9)
Adolescents (12 – 17)	15 (53.6)	15 (83.3)	27 (61.4)	27 (87.1)
Adults (≥18)	10 (35.7)	0	13 (29.5)	0
Sex *n (%)*				
Male	10 (35.7)	5 (27.8)	29 (65.9)	18 (58.1)
Female	18 (64.3)	13 (72.2)	15 (34.1)	13 (41.9)
Race *n (%)*				
White	25 (89.3)	16 (88.9)	41 (92.3)	28 (90.3)
Black/African American	1 (3.6)	1 (5.6)	1 (2.3)	1 (3.2)
Asian	1 (3.6)	1 (5.6)	0	0
Native Hawaiian or other pacific islander	0	0	1 (2.3)	1 (3.2)
Other	1 (3.6)	0	1 (2.3)	1 (3.2)
Country *n (%)*				
Europe	20 (71.4)	13 (72.2)	32 (72.7)	25 (80.6)
US	8 (28.6)	5 (27.8)	12 (27.3)	6 (19.4)

Table 13. Baseline characteristics in study CA209744 - All treated population

	Cohort R1		Cohort R2	
	Total (n=28)	**Paediatrics (n=18)**	**Total (n=44)**	**Paediatrics (n=31)**
Ann Arbor Stage initial diagnosis *n (%)*				
IA	2 (7.1)	2 (11.1)	0	0
IB	0	0	0	0
IIA	20 (71.4)	13 (72.2)	5 (11.4)	5 (16.1)
IIB	2 (7.1)	0	16 (36.4)	11 (35.5)
IIIA	4 (14.3)	3 (16.7)	2 (4.5)	2 (6.5)
IIIB	0	0	5 (11.4)	1 (3.2)
IVA	0	0	5 (11.4)	4 (12.9)
IVB	0	0	11 (25.0)	8 (25.8)
Ann Arbor Stage study entry *n (%)*				
IA	6 (21.4)	3 (16.7)	2 (4.5)	1 (3.2)
IB	0	0	0	0
IIA	18 (64.3)	11 (61.1)	11 (25.0)	7 (22.6)
IIB	0	0	10 (22.7)	7 (22.6)
IIIA	4 (14.3)	4 (22.2)	5 (11.4)	2 (6.5)
IIIB	0	0	0	0
IVA	0	0	11 (25.0)	9 (29.0)
IVB	0	0	5 (11.4)	5 (16.1)
Time from end of prior therapy to relapse				
< 3 months	0	0	16 (36.4)	13 (41.9)
3 – 12 months	5 (17.9)	5 (27.8)	18 (40.9)	14 (45.2)
≥12 months	23 (82.1)	13 (72.2)	10 (22.7)	4 (12.9)
Response to prior line of therapy *n (%)*				
Relapsed	27 (96.4)	17 (94.4)	20 (45.5)	14 (45.2)
Refractory	1 (3.6)	1 (5.6)	24 (54.5)	17 (54.8)
Karnofsky *median (range)*	100 (70 – 100)	100 (70 – 100)	100 (80 – 100)	100 (90 – 100)
Lansky *median (range)*	100 (80 – 100)	100 (80 – 100)	100 (70 – 100)	100 (70 – 100)
Deauville by BICR at baseline *n (%)*				
4	6 (21.4)	4 (22.2)	6 (13.6)	3 (9.7)
5	22 (78.6)	14 (77.8)	38 (86.4)	28 (90.3)
Extra lymphatic involvement at baseline				
Yes	4 (14.3)	2 (11.1)	4 (9.1)	2 (6.5)
No	22 (78.6)	15 (83.3)	38 (86.4)	28 (90.3)
Not reported	2 (7.1)	1 (5.6)	2 (4.5)	1 (3.2)

Lymphoma involvement in bone marrow at baseline *n (%)*				
Yes	0	0	5 (11.4)	2 (6.5)
No	28 (100)	18 (100)	39 (88.6)	29 (93.5)
Prior anti-CHL therapy	28 (100)	18 (100)	44 (100)	31 (100)
ABV/COPP	0	0	4 (9.1)	3 (9.7)
ABVD	5 (17.9)	2 (11.1)	4 (9.1)	1 (3.2)
ABVE	1 (3.6)	1 (5.6)	2 (4.5)	1 (3.2)
ABVE-PC	2 (7.1)	1 (5.6)	6 (13.6)	3 (9.7)
OEPA	1 (3.6)	1 (5.6)	6 (13.6)	5 (16.1)
OEPA/COPDAC	12 (42.9)	8 (44.4)	20 (45.5)	17 (54.8)
Other	7 (25.0)	5 (27.8)	2 (4.5)	1 (3.2)

In total 18 subjects (64.3%) in Cohort R1 and 32 subjects (72.7%) in Cohort R2 underwent prior surgery related to cancer. In total 2 subjects (7.1%) in cohort R1 and 16 subjects (36.4%) in cohort R2 received prior radiotherapy.

Numbers analysed

The primary analysis was performed on the treated population (cohort R1 n=28; cohort R2 n=44).

Outcomes and estimation

A summary of the efficacy results is provided in **Table 14**. The median follow-up was ≥ 64 months for cohort R1 and ≥ 78 months for cohort R2.

Table 14. **Efficacy results in study CA209744**

	Cohort R1 Low Risk Cohort		**Cohort R2 Standard Risk Cohort**	
	All Treated Subjects (n = 28)	**Treated Paediatric Subjects (n = 18)**	**All Treated Subjects (n = 44)**	**Treated Paediatric 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)
95% CI	(76.5, 99.1)	(65.3, 98.6)	(75.4, 96.2)	(74.2, 98.0)
EFS rate at 3-yr per BICR	87.5	79.8	-	-
90% CI	(70.6, 95.0)	(55.6, 91.7)		
95% CI	(65.9, 95.8)	(49.4, 93.0)		
Secondary Endpoints				
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)
95% CI	(81.7, 99.9)	(72.7, 99.9)	(81.3, 98.6)	(78.6, 99.2)

	Cohort R1 Low Risk Cohort		Cohort R2 Standard Risk Cohort	
	All Treated Subjects (n = 28)	**Treated Paediatric Subjects (n = 18)**	**All Treated Subjects (n = 44)**	**Treated Paediatric Subjects (n = 31)**
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 paediatric 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 paediatric subjects were evaluable 4 cycles of N+Bv.
[c] The denominator is the number responders. All treated subjects/treated paediatric subjects were responders.

Primary endpoints

Cohort R1 (co-primary endpoint)

- In total 26/28 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 92.9% (95% CI: 76.5, 99.1). In the paediatric population, 16/18 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 88.9% (95% CI: 65.3, 98.6). Two paediatric patients had a PMR. The paediatric patients with a PMR were 6 years and 17 years of age. Consolidation with radiotherapy was achieved in 79% of all treated patients and 72% of paediatric patients.
- The 3-year EFS rate by BICR was 87.5% (95%CI: 65.9, 95.8) in all treated subjects and 79.8% (95%CI: 49.4, 93.08) in the treated paediatric subjects. There was one paediatric patient (age 16 years) with disease progression. Two paediatric patients failed to achieve CMR after 4 cycles of N+Bv and 2 cycles of Bv+B.

The KM-curves are shown in **Figure 3** (total population) and **Figure 4** (paediatric population). Consolidation with ASCT was achieved in 73% of all treated patients and 81% of paediatric patients.

Figure 3. Kaplan-Meier Plot of Event Free Survival per BICR in study CA209744 - Cohort R1- All Treated Subjects

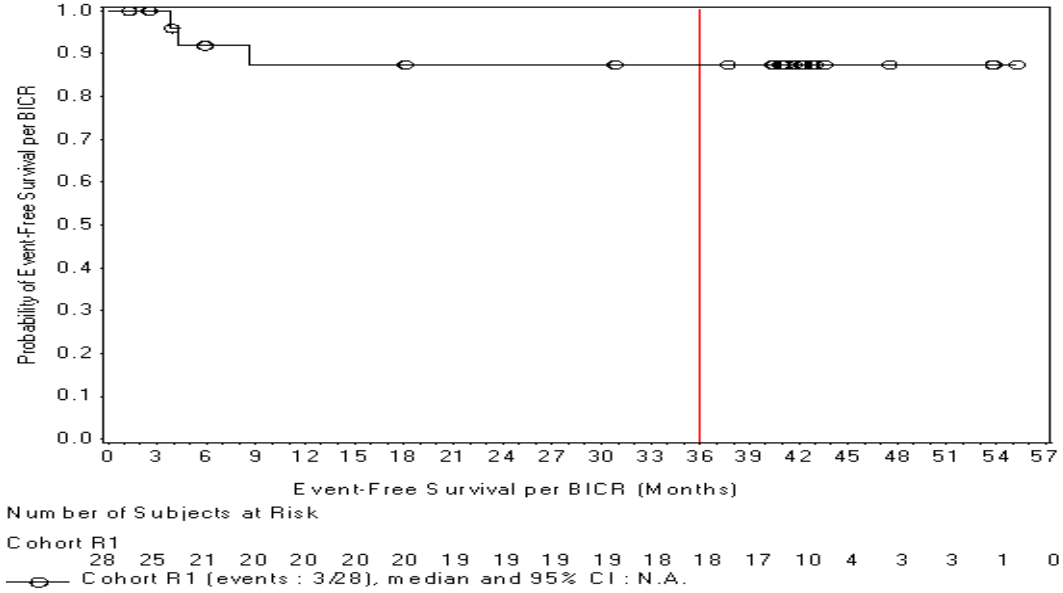
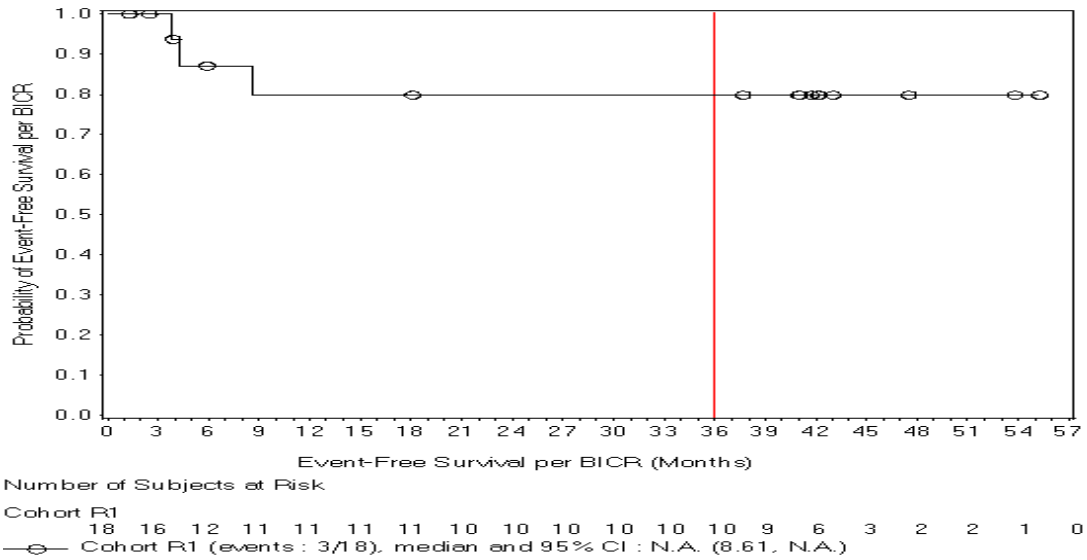


Figure 4. Kaplan-Meier Plot of Event Free Survival per BICR in study CA209744 - Cohort R1- Treated Paediatric Subjects



Cohort R2

- In total 39/44 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 88.6% (95% CI: 75.4, 96.2). In the paediatric population, 28/31 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 90.3% (95% CI: 74.2, 98.0). Three paediatric patients had a best metabolic response of PMR prior to consolidation. The paediatric patients with a PMR were 10 years, 16 years and 16 years of age. One adult had a best metabolic

response of PMR prior to consolidation and one adult patient had no metabolic response prior to consolidation.

Secondary endpoints

ORR per BICR after 4 cycles of N+Bv

Cohort 1: In the total population, the ORR was 96.4% (23 patients CMR; 4 patients PMR; 1 patient NMR). In the paediatric population the ORR was 94.4% (13 patients CMR; 4 patients PMR; 1 patient NMR).

Cohort 2: In the total population, the ORR was 90.9% (33 patients CMR; 8 patients PMR; 2 patients NMR; 1 patient NR). In the paediatric population the ORR was 93.5% (23 patients CMR; 6 patients PMR; 2 patients NMR).

PFS rate at 3 years per BICR using Lugano 2014 criteria

Cohort 1: The 3-year PFS rates (90% CI) per BICR (Lugano 2014 criteria) was 95.2% (77.7, 99.1). There was one paediatric patient with disease progression.

Cohort 2: The 3-year PFS rates (90% CI) per BICR (Lugano 2014 criteria) was 91.1% (78.4, 96.5). There were three patients with disease progression; two paediatric patients and one adult.

DOR per BICR using Lugano 2014 criteria

As the majority of the responders did not have an event, the median DOR was not observed (data not shown).

Investigators assessment

The CMR rates, EFS, ORR and PFS per investigator assessment were similar to the assessment by BICR (**Table 14**).

Exploratory endpoints

Overall Survival

The 5-year OS rate (90% CI) was 100% (100.0, 100.0) in cohort R1 as there were no OS events. The 5-year OS rate (90% CI) was 97.6% (88.0, 99.5) in cohort R2 with one paediatric patient with an OS event 21.6 months after first dose.

ORR and EFS in different risk subgroups

In Cohort R1, no statistically significant difference was observed in the EFS between subjects with PS (Lansky/Karnofsky≥ 90 and those with PS < 90 (p-value = 0.3323) in all-treated subjects.

In Cohort R2, no statistically significant difference was observed in the ORR between all treated subjects with and without extranodal disease (p-value = 0.8422) and between subjects who were refractory to the initial line of therapy and those who relapsed (p-value = 0.1822).

Biomarker results

In cohort R1, 22 out of 26 patients (91.7%) had a baseline PD-L1 expression of ≥40% of which 20 patients (90.9%) obtained a CMR and 2 patients (9.1%) a PMR. Two patients had a non-quantifiable PD-L1 expression at baseline; both patients achieved CMR.

In cohort R2, 41 out of 44 patients (97.6%) had a baseline PD-L1 expression of ≥40% of which 37 patients (90.2%) obtained a CMR and 3 patients (7.3%) a PMR. There were two subjects without PD-L1 quantifiable at baseline; both patients achieved CMR. In one patient baseline PD-L1 expression was <10%. This patient had a best metabolic response of PMR.

CD30 expression was not measured in study CA209744.

EBV status was missing at baseline in 66% (cohort R1) and 71% (cohort R2) of patients. In each cohort, 1 patient was EBV positive. Both patients achieved CMR.

Patient reported outcomes

Cohort R1: The mean (SD) baseline value for FACT-Lym Overall Score was 140.86 (18.35) in all treated subjects. The mean (SD) change from baseline in the FACT-Lym Overall Score was 1.05 (11.98) at week 6 and -1.46 (13.99) at week 12. The mean (SD) baseline value for EQ-5D-3L VAS score was 69.61 (29.00) in all treated subjects. The mean (SD) change from baseline in the EQ-5D-3L Utility Index scores was 2.50 (44.74) at Week 6 and 1.42 (39.23) at Week 12. Questionnaire completion rates were low after week 12.

Cohort R2: The mean (SD) baseline value for FACT-Lym Overall Score was 130.95 (21.89) in all treated subjects. The mean (SD) change from baseline in the FACT-Lym Overall Score was 6.62 (16.90) at week 6 and 13.36 (17.23) at week 12. The mean (SD) baseline value for EQ-5D-3L VAS score was 57.95 (32.45) in all treated subjects. The mean (SD) change from baseline in the EQ-5D-3L Utility Index scores was 12.10 (23.21) at Week 6 and 29.00 (28.66) at week 12. Questionnaire completion rates were low after week 12.

Subsequent therapy

Subsequent anti-cHL therapy after consolidation is shown in **Table 15**. 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 15. Subsequent treatment in study CA209744.

	Cohort R1 Total (n=28) n (%)	**Cohort R2 Total (n=44) n (%)**
Subjects with any subsequent therapy	5 (17.9)	31 (70.5)
Surgery	0	2 (4.5)
Radiotherapy*	4 (14.3)	9 (20.5)
ASCT*	0	12 (27.3)
Systemic therapy	2 (7.1)	22 (50.0)
Reason for systemic therapy		
PD	1 (3.6)	3 (6.8)
Clinical deterioration without PD	0	0
Maintenance without PD/clinical	1 (3.6)	10 (22.7)
Other	0	4 (9.1)
Not reported	0	6 (13.6)
Type of systemic therapy		
Bendamustine	2 (7.1)	2 (4.5)
Brentuximab vedotin	2 (7.1)	13 (29.5)
Carboplatin	0	1 (2.3)

Carmustine	0	7 (15.9)
Cisplatin	0	3 (6.8)
Cytarabine	0	11 (25.0)
Dexamethasone	0	2 (4.5)
Etoposide	0	10 (22.7)
Fotemustine	0	1 (2.3)
Gemcitabine	0	2 (4.5)
Ifosfamide	0	2 (4.5)
Lomustine	0	1 (2.3)
Melphalan	0	9 (20.5)
Nivolumab	0	1 (2.3)
Prednisolone	0	1 (2.3)
Stem cell rescue	0	1 (2.3)
Vinorelbine	0	2 (4.5)

**RT not part of R1 consolidation, ASCT not part of R2 consolidation*

Ancillary analyses

To provide contextualization of the observed efficacy, a search of the literature and www.clinicaltrials.gov was performed. Results included data on use of chemotherapy and novel regimens.

- Details on patient population were summarised as available; namely, whether subjects were relapsed or refractory to 1L therapy (early vs late relapse noted where possible).
- Most studies enrolled either all adults or adult and paediatric subjects, but all comprised some patients < 30 years and a few comprised only paediatric subjects.
- Definition of CMR per Deauville score was not provided in most publications. Several state that CR was based on radiographical evidence and a few that CMR was per Lugano criteria (2014). Studies were performed over a broad date range, so presumably evolving CMR criteria were used over time, in accordance with practice guidelines at the time of study start.
- The results excluded studies in which the population mostly included subjects in later lines of relapse (3L+/ much more heavily pre-treated), review articles in which it was not possible to determine specific patient characteristics like age and relapsed/refractory status, and studies that mainly enrolled patients with haematology malignancies other than cHL.

Table 16. Summary of Chemotherapy Regimens in 2L Salvage R/R cHL - Literature Review

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
Chemotherapy-based salvage regimens					
Cisplatin-based regimens					
ESHAP (etoposide, methyl-prednisolone, high-dose cytarabine, cisplatin)	Pts received 3 courses of ESHAP. Those suitable for AHT were then given high-dose chemo with CBV+AHT; responding, non-AHT-suitable	22	5 refractory; 17 relapsed (10 in first relapse; 7 in ≥ second relapse)	Median: 34 yrs Range: 18-66 yrs	• 73% ORR (9 [41%] CRs; 7 [32%] PRs). • 9 pts received CBV+AHT. • OS and DFS were 35% and 27% at 3 years, respectively.

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
	patients completed 6 ESHAP courses.				
DHAP (cytarabine, cisplatin, dexamethasone)	Pts received 2 cycles of DHAP; those with PR or CR after 2 cycles of DHAP received sequential HDCT.	102	16% primary progressive/ refractory disease; 42% had late relapse, 29% early relapse, 12% multiple relapsed	Median: 34 yrs Range: 21-64 yrs	• 89% ORR (21% CR; 68% PR).
ASHAP (doxorubicin, methyl-prednisolone, high-dose cytarabine, cisplatin)	Pts received 2 cycles of ASHAP; responders underwent stem cell collection, then underwent 1 more chemo cycle before HDCT+ASCR.	56	7 refractory; 33 in first relapse, 10 in second relapse	Median: 29 yrs Range: 18-56 yrs	• 70% ORR (19 [34%] CR; 20 [36%] PR). • At 4 years, OS was 41% and EFS was 36%.
Ifosfamide/etoposide-based regimens					
ICE (ifosfamide, carboplatin, etoposide)	2 cycles of ICE, then stem cell collection, then HDCT+ASCR for any patients with response + IFRT before HDCT for bulky disease or residual disease after chemo.	65	22 refractory ; 43 in relapse (unknown number in first relapse)	Median: 27 yrs Range 12-59 yrs (4 pts < 20 yrs)	• 88% ORR (26% CR). • EFS at median fu of 43 mos was 82% for those in CR after ICE and 59% for those in PR or minor response (at least 25% reduction in tumor bulk) after ICE.
IVE (ifosfamide, etoposide, epirubicin)	IVE for 3 cycles followed by HDCT+ASCR (at physician discretion).	51	13 refractory; 26 in first relapse, 9 in 2+ relapse	Median: 34 yrs Range: 16-53 yrs	• 84% ORR (31 [61%] CR; 4 [8%] good PR; 8 [16%] PR). • 31 went to ASCT; These pts had a median survival of 46 mos. • With median follow-up of 24 mos., 26 pts were alive and in continuous remission.
IEP-ABVD (cisplatin, etoposide, ifosfamide - doxorubicin, bleomycin, vinblastine, dacarbazine)	2 to 3 cycles of IEP alternating with 1 to 2 cycles of ABVD supplemented in part by 1 to 2 cycles of CCNU, etoposide, and prednimustine. RT was given to involved areas (individualized doses). Later in study, additional HDCT+ASCT was introduced for pts with unfavourable prognosis.	176	Group 1 (refractory disease, 51 pts) Group 2 (early relapse within 1 yr of 1L completion, 57 pts) Group 3 (late relapse, 68 pts)	Median: 14.7 yrs Range: 4.3-24.5 yrs	• DFS and OS after 10 years were 62% and 75%, respectively (SE, 4% each). • Of 176 patients, 73 had second events after a median of 1.1 years (61 progressions, 4 deaths, 8 SMN). • 44 patients died after a median of 1.7 years.
Gemcitabine-based regimens					
IGEV (ifosfamide, gemcitabine, vinorelbine, prednisolone)	Included 4 cycles of IGEV; Patients in CR or PR after 4 cycles went on to	91	36 refractory; 28 pts early relapse, 27 late relapse.	Median: 30 yrs Range: 17-59 yrs	• 81.3% ORR (53.8% CR; 27.5% PR). • 3-year PFS and OS rates were 52.98% and 70.03%, respectively, for the entire series.

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
	single or tandem HDCT+ASCR.		Most patients (76.9%) had received only 1 regimen, with a range from 1 to 4.		
BeGEV (bendamustine, gemcitabine, vinorelbine)	BeGEV for 4 cycles; pts with CR/PR moved on to HDCT+ASCR.	59	27 refractory; 22 early relapse, 10 late relapse (all relapsed were first relapse)	Median: 33 yrs Range: 18-68 yrs	• 83% ORR (73% CR; 10% PR). • With a median follow-up of 29 months, the 2-year PFS and OS rates for the total population were 62.2% and 77.6%, respectively, and were 80.8% & 89.3% for pts receiving ASCR.
GDP (gemcitabine, dexamethasone, cisplatin)	2-6 cycles of GDP; pts with any response could then move on to HDCT+ASCR.	23	6 refractory; 8 early relapse, 9 late relapse	Median: 36.5 yrs Range: 19-57 yrs	• 69.5% ORR (4 [17%] CRs; 12 [52%] PRs); the remaining 7 pts had stable disease, and no patient progressed on treatment • All pts proceeded on to HDCT + ASCR. • Response was defined per Cheson, et al. 1999 criteria.[1]
GVD (gemcitabine, vinorelbine, liposomal doxorubicin)	2-6 cycles of GVD (with 2 dose levels in Phase 1).	91	40 pts had relapsed after SCT; 40 pts had relapsed after 1 line of treatment	Median: 33 yrs Range: 19-83 yrs	• 70% ORR (19% CR). • 4-year EFS and OS rates in transplant-naive pts treated with GVD followed by ASCT were 52% and 70%, and in the pts in whom prior transplant failed, these were 10% and 34%, respectively.

Table 17. Summary of Novel Regimens in 2L Salvage R/R cHL - Literature Review

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
Brentuximab vedotin (Bv)-based salvage regimens					
Bv single agent (adult and paediatric)	Bv (1.8 mg/kg) was given for 4 cycles. Patients then proceeded to AHCT, if eligible, with or without additional salvage therapy, based on remission status after Bv.	37	65% primary refractory; 35% relapsed (no info on relapse timing)	Median: 34 yrs Range: 11-67 yrs	• 68% ORR (13 [35%] CRs; 12 [32%] PRs). • 86% were able to proceed to AHCT, with 24 patients (65%) in CR at time of AHCT. 13 pts in CR, 4 in PR, and 1 with SD (49%) received AHCT without salvage combination chemotherapy.
Bv single agent (adult and paediatric)	Bv (1.8 mg/kg) for 2 cycles. Pts in CR after 2 cycles received 2 additional cycles Bv (1.8 mg/kg); pts with SD or PR received Bv 2.4 mg/kg for 2 cycles. All pts went directly to AHCT or received additional pre-AHCT therapy (at discretion of Inv) based on	56	61% primary refractory; 39% relapsed (no info on relapse timing)	Median: 32 yrs Range: 11-67 yrs	• 75% ORR (43% CR). • 50 pts proceeded to AHCT (28 without post-Bv chemo). 13 pts received consolidative post-AHCT therapy with either RT, Bv, or a PD-1 inhibitor. • After AHCT, the 2-year PFS and OS were 67% and 93%, respectively. 2-year PFS among patients in CR at the time of AHCT was 71% compared with 54% in patients not in CR. 2-year PFS in patients who proceeded to AHCT directly after receiving Bv alone was 77%.

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
	remission status after 2L Bv.				
Bv single agent (paediatric)	Bv (1.8 mg/kg) for up to 16 cycles.	16 (with cHL)	31% refractory; 63% relapsed; 6% unknown	Median: 15 yrs Range: 12.5-16.5 yrs	• 47% ORR (33% CR). • Median PFS = 3.8 months; median EFS = 2.1 months; OS rate at 24 months = 61.4%.
Bv-bendamustine	Bv (1.8 mg/kg) + Benda for 2-6 cycles, followed by Bv mono (1.8 mg/kg) or HDCT+ASCR.	55	28 refractory; 10 early relapse, 17 late relapse	Median: 36 yrs Range: 19-79 yrs	• 92.5% ORR (73.6% CR). 40 patients underwent ASCT. • After a median of 20.9 months of follow-up, the estimated 2-year PFS was 69.8% and 62.6% for pts who received ASCT and all pts, respectively.
Bv-ESHAP	3 cycles of ESHAP, with Bv administered on Day -1 of each cycle (final Bv dose = 1.8 mg/kg); responders then had ASCT, followed by 3 cycles of Bv.	66	40 primary refractory; 16 early relapse and 10 late relapse (all after first-line chemo)	Median: 36 yrs Range: 18-66	• 91% ORR (70% CR) before transplant. 60 patients were transplanted with no graft failure. Post-transplant response was CR in 49 patients (82%) and PR in 6 (10%). • After a mean follow-up of 27 months, the 30-month TTF was 74%, PFS 71%, and OS 91%.
Bv-ICE	2 cycles of Bv (1.5 mg/kg) + ICE.	45	29 refractory; 8 early relapse, 8 late relapse	Median: 31 yrs Range: 28-45 yrs	• Of 43 evaluable pts, 91% ORR (74% CR) after 2 cycles. 19 pts proceeded directly to ASCT after 2 cycles. • With median follow-up of 3.1 years, estimated 2-yr PFS was 80.4% and OS was 97.8%.
Bv-DHAP	Bv (1.8 mg/kg) + DHAP for 3 cycles, followed by HDCT+ASCR.	12	2 refractory; 10 in first relapse	Median: 30.5 yrs Range: 21-56 yrs	• 100% ORR (92% CMR).
Bv-IGEV	1-2 cycles of IGEV + Bv (1.8 mg/kg) followed by HDCT+ASCR.	28	12 refractory, 16 relapsed (no info on relapse timing)	Median: 25 yrs Range: 15-49 yrs	• 96% ORR (71% CMR; 25% PMR); Deauville up to 3 was considered CMR. • Post HDCT, the estimated 2-year PFS and 2-year OS were 87.1% and 73.5%, respectively.
Bv-ibrutinib	Bv (1.8 mg/kg) intravenously every 3 weeks and ibrutinib 560 mg PO daily (420 mg PO daily in the lead-in cohort). Prior Bv was allowed if patients were not refractory.	39	Pts with ≥ 1 prior LOT were eligible. Median prior lines = 2 (range: 1-7); 17 pts had only 1 prior line of treatment. 21% had prior Bv.	Median: 33 yrs Range: 17-71 yrs	• 64% ORR (33% CR). CR rate was per Lugano 2014. • Median DoR was 25.5 mos. • 13 pts received autologous transplant and 2 received allogenic transplant for consolidation after response. • Due to toxicity, Bv-ibrutinib not recommended for further development.
Bv-gemcitabine	Each 21-day cycle consisted of 1000 mg/m² intravenous gemcitabine on days 1 and 8 and intravenous Bv on Day 1 at 1.4 mg/kg or 1.8 mg/kg.	46	29 primary refractory; 9 early relapse (< 6 mos); 7 Stage III or IV with relapse >6 mos. after initial treatment.	Median: 17.6 yrs Range: 15.3-18.6 yrs	• 74% ORR (57% CR per protocol criteria [Deauville 1 or 2]). • Note: 4 additional pts with SD or PR per protocol criteria were Deauville 3 or lower on central review and thus would be considered CRs per 2014 response criteria (published after study AHOD1221 opened for recruitment) - under these criteria, CR would be 67%.

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
Checkpoint inhibitor (CPI)/ anti-PD-1-based salvage regimens					
Nivolumab single-agent or in combination with ICE (**NICE**)	PET-adapted design (Cohort A): 240 mg Nivo Q2W for up to 6 cycles; Pts in CR after C6 proceeded to AHCT, whereas pts with PD at any point or not in CR after C6 received NICE.	34 (Nivo mono) 9 (NICE)	19 primary refractory; 24 relapsed (all had 1 previous line of treatment)	Median: 35 yrs Range: 18-70 yrs	• After nivolumab: 81% ORR (71% CR). • After NICE: 100% ORR (89% CR). • At the end of protocol therapy, the ORR and CR rates were 93% and 91%, overall. CR rate was per 2014 Lugano classification. • 33 patients were bridged directly to AHCT, including 26 after Nivo alone. • 2-year PFS and OS in all treated patients (n=43) were 72% and 95%, respectively. Among 33 patients who bridged directly to AHCT, the 2-year PFS was 94%.
NICE	Non-PET adapted design (Cohort B): 240 mg Nivo followed by 2-3 cycles of NICE. (*All had high-risk disease [primary refractory cHL, relapse within 1 year of completing 1L therapy, B symptoms at relapse, extranodal disease at relapse, or 1L Bv use*]).	35	21 primary refractory; 14 relapsed (all had 1 previous line of treatment)	Median: 30 yrs Range: 19-70 yrs	• 100% ORR (86% CR). CR rate was per 2014 Lugano classification. • 2-year PFS and OS were 88% and 100%, respectively. 32 patients proceeded to ASCT directly after NICE; 2-year post-ASCT PFS and OS were 94% and 100%, respectively.
Low dose nivolumab (LD-Nivo) as single-agent, LD-Nivo+Bv, or LD-Nivo+chemo	LD-Nivo was given in 40, 100, and 140 mg fixed doses Q2W.	23	12 refractory; 11 relapsed (all had 1 previous line of treatment)	Median: 27 yrs Range: 20-30 yrs	• 73% ORR (43% CR and 30% PR); median dose of nivolumab was 0.78 mg/kg (range: 0.62-1.11) and the median number of cycles until response was 6 (range: 2-9). • 1-yr PFS and OS were 89.4% and 94.4%, respectively. • During follow-up, 18 pts received transplantation (11 auto; 6 allo). No stat. signif. differences in survival or response were seen between nivo combinations or doses.
Other novel salvage regimens					
Panobinostat + ICE (P-ICE)	Phase 1 (dose-finding); 3 cohorts, ie, Pano-ICE (10 mg), Pano-ICE (20 mg), and Pano-ICE (30 mg). Phase 2: Pano-ICE (30 mg).	Phase 1: 29 evaluable Phase 2: 11 treated with P-ICE and evaluable	Phase 1: 13 primary refractory; 9 relapsed < 1yr, 6 relapsed > 1 yr Phase 2: 7 primary refractory; 1 relapsed < 1 yr, 3 relapsed > 1 yr	All subjects were 18+ years old.	• In Phase 1: 86% ORR (72% CR). 4-yr OS was 82%. • In Phase 2: CR in 9/11 (82%) in P-ICE arm; all pts with CR proceeded to auto-HSCT except 1 (due to insurance issues). In Phase 2, no difference was seen in FFS at 18 mos. compared to ICE alone. Due to high rates of Gr. 4 heme. tox with P-ICE, limited efficacy benefit, and emergence of other less toxic agents (Bv and anti-PD-1s), further development of panobinostat in combination with ICE was terminated.

Therapy	Regimen	Number of Patients	Relapsed/ refractory status	Age (median and range)	Efficacy Results (as available in publication)
Bortezomib + ICE (B-ICE)	Bortezomib on days 1 and 4, ifosfamide on day 1, carboplatin on day 1, and etoposide on days 1-3. Treatment Q14D (up to 6 courses) in absence of progression or unacceptable toxicity. *(All had received a 1L standard anthracycline-containing regimen, such as ABVD, Stanford V, or BEACOPP).*	10 (B-ICE)	6 refractory; 4 relapsed (no info on relapse timing)	All subjects were 18+ years old.	• 70% ORR (30% CR). • PFS rate at 12 mos. was 50%; OS rate at 24 mos. was 70%.

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 18. Summary of Efficacy for trial CA209744

Title: Risk-based, response-adapted, Phase II 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.		
Study identifier	CA209744; CheckMate 744; EudraCT 2016-002347-41; NCT02927769	
Design	Phase II, single arm, open-label	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	3 years not applicable not applicable
Hypothesis	Exploratory: • Cohort R1 (low risk): To describe the CMR rate prior to RT and EFS rate at 3 years. • Cohort R2 (standard risk): To describe the CMR rate prior to HDCT/ASCT.	

Treatments groups	Cohort R1 *tumour assessment after each 2 cycles; end of study treatment in case of disease progression*		Induction: N+Bv (4 cycles; +2 cycles if CMR) Intensification: • CMR no intensification • PMR/NMR Bv+B (2 cycles) Consolidation (if CMR): radiotherapy
	Cohort R2 *tumour assessment after each 2 cycles; end of study treatment in case of disease progression*		Induction: N+Bv (4 cycles) Intensification: • CMR no intensification • PMR/NMR: Bv+B (2 – 4 cycles) Consolidation (if CMR): HDCT/ASCT
Endpoints and definitions	Cohort R1 Co-Primary endpoint	CMR EFS	CMR rate per BICR using Lugano 2014 criteria EFS rate at 3 years per BICR (time to HDCT/ASCT, disease progression, failure to achieve CMR after 4 cycles of N+Bv and 2 cycles of Bv+B, secondary malignancy, Death due to any cause)
	Cohort R2 Primary endpoint	CMR	CMR rate per BICR using Lugano 2014 criteria prior to HDCT/ASCT
	Secondary endpoint	ORR	ORR per BICR using Lugano 2014 criteria after 4 cycles N+Bv
	Secondary endpoint	DOR	DOR per BICR using Lugano 2014 criteria
	Secondary endpoint	PFS	PFS rate at 3 years per BICR using Lugano 2014 criteria
	Exploratory endpoint	OS	Overall Survival
Database lock	Interim CSR 09-Sep-2018; closeout CSR 28-May-2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Treated participants (all participants who received at least 1 dose of study treatment) *Treated population was identical to the enrolled population*		
	Treatment group	Cohort R1	Cohort R2

Descriptive statistics and estimate variability	Number of subject	28	44
	CMR	26 (92.9%) 95% CI (76.5, 99.1)	39 (88.6%) 95% CI (75.4, 96.2)
	EFS (3-year rate)	87.5% 95% CI (65.9, 95.8)	NA
	ORR (after 4 cycles N+Bv)	27 (96.4%)	41 (93.2%)
	DOR mo, median (min-max)	NA (0.0 – 54.1)	NA (0.0 – 55.3)
	PFS (3-year rate)	95.2 90% CI (77.7, 99.1)	91.1 90% CI (78.4, 96.5)
	OS (5-year rate)	100 90% CI (100, 100)	97.6 90% CI (88.0, 99.5)
Notes	Median follow-up was ≥ 64 months for cohort R1 and ≥ 78 months for cohort R2.		

Supportive study

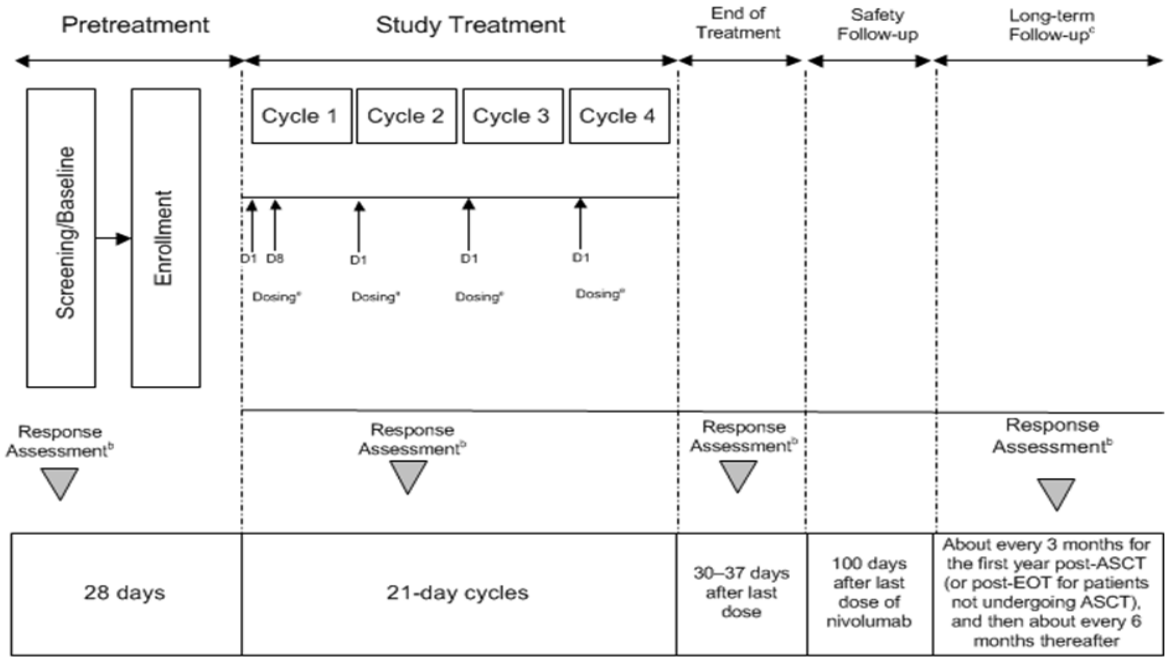
Since CA209744 evaluated the efficacy and safety of N+Bv in paediatric and young-adult patients (5-30 years) only, data from study SGN35-025 were provided in support of the proposed indication including adults without an age restriction.

SGN35-025 is a phase 1/2 study evaluating brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy.

Adults with biopsy-proven primary refractory (i.e., not achieving a CR or progression <3 months after CR) or relapsed Hodgkin lymphoma (HL; progression ≥3 months after CR) were included. Patients were required to have an ECOG score of 0-1 and to be eligible to undergo ASCT. Patients with prior salvage therapy for R/R cHL (including radiotherapy), prior Bv (parts 1/2 only) or immuno-oncology therapy, or prior autologous or allogeneic stem cell transplantation were excluded.

The study was conducted in 3 parts. Parts 1 and 2 used a staggered dosing regimen, with brentuximab vedotin (1.8 mg/kg) on cycle 1, day 1 and nivolumab (3 mg/kg) on cycle 1 day 8 (**Figure 5**). For Cycle 2 and all subsequent cycles, both brentuximab vedotin and nivolumab were administered on Day 1. Part 3 was later added via an amendment. In part 3, brentuximab vedotin and nivolumab were dosed on the same day. In all 3 parts patients were treated for up to four 21-day cycles. Response assessment was performed at cycle 2 and after cycle 4. If patients had progressive disease at cycle 2, they were not eligible for further treatment on study.

Figure 5. Study SGN35-025 design: Staggered dosing in Cycle 1 (Parts 1 and 2)



a Each cycle consists of 21-days. At Cycle 1, 1.8 mg/kg brentuximab vedotin is administered on Day 1, followed by 3 mg/kg nivolumab on Day 8. At subsequent cycles, 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab are both administered on Day 1.

b Response assessment performed at Screening/Baseline, between Days 15–21 at Cycle 2, and at EOT. CT only at Cycle 2 to assess for progressive disease. CT/PET at Screening/Baseline, EOT (23–37 days post last dose of study drug), and during long-term follow-up until a patient has achieved CmR by PET assessment; once a patient has achieved CmR by PET assessment, responses will be followed by CT scans of diagnostic quality only.

c All patients who receive at least one dose of brentuximab vedotin will have long-term follow-up assessments at the following time points post-ASCT (or for patients who do not undergo ASCT, post-EOT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months, and then per institutional standard thereafter. A final safety visit will be performed 100 days after the last dose of nivolumab and after the EOT to assess for potential immune-mediated adverse events. Patients will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

The primary objectives of the study were:

- To assess the safety profile of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL (primary endpoint type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities).
- To assess the antitumor activity of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL (primary endpoint CR rate following the completion of study treatment; investigator assessment).

Sample size

The sample size needed to provide adequate power to test the primary endpoint is at least 53. With this sample size a one-sided exact binomial test at level α=0.05 will reject the null hypothesis of a CR rate less than or equal to 30% approximately 90% of the time when the true CR rate is 50%. For the given parameters the null will be rejected when 22 or more CRs are observed (i.e., CR rate ≥41.5% is observed).

For the safety assessment of the combination treatment, a sample size of 55 patients will provide a 94% chance of observing at least one occurrence of an adverse event with a true event rate of 5%.

For Part 3, no formal hypothesis test was specified. The sample size of 30 patients was chosen to allow adequate precision of estimates for response rates and safety data. For example, if 63% (19/30) of

patients have a CR, then the 95% exact CI is (44%, 80%). The sample size of 30 patients was sufficient to perform exploratory biomarker analyses.

Results

Participants and exposure

Of the 105 subjects screened, a total of 93 subjects were enrolled at 12 study sites in the USA. A total of 91 subjects (98%) received at least 1 dose of study treatment in this study, of which 61 subjects (98%) were treated in Parts 1 and 2 (staggered dosing regimen) (6 subjects in Part 1 and 55 subjects in Part 2) and 30 subjects (97%) treated into Part 3 (same-day dosing regimen).

The median number of doses administered of brentuximab vedotin and nivolumab were both 4.0 doses (range: 1 to 4) for all treated subjects. The relative dose intensity for brentuximab vedotin and nivolumab were 100% (range: 75 to 102) and 109.1% (range: 66 to 120) for all treated subjects, respectively.

Baseline data

The median age of all subjects treated in this study was 34.0 years (range: 18 to 69) including 39 patients aged ≤30 years. Of the 91 subjects treated, 56% were female and 44% were male. A majority were white (85%) and not Hispanic or Latino (81%). Subjects entering the study were generally ambulatory and able to perform normal activities without assistance as indicated by an ECOG performance status of 0 (64%) and 1 (35%) for most subjects.

Of 91 subjects treated in the study, 70 (77%) were diagnosed with nodular sclerosing HL, 9 (10%) with mixed cellularity HL, 4 (4%) with lymphocyte-rich HL, 3 (3%) with nodular sclerosing HL (syncytial variant), and 5 (5%) with unknown initial HL disease diagnosis. Fifty-two subjects had Stage II (57%) or III (18%) disease at initial diagnosis. Thirty-eight subjects had primary refractory disease, defined as subjects who did not achieve a CR or who relapsed within 3 months of completing frontline therapy. Relative to frontline therapy, 30% of subjects had relapsed ≤1 year ago, 29% of subjects had relapsed more than 1 year ago, and 42% had primary refractory disease.

Subjects were pretreated with a median of 1 prior cancer related systemic therapies (range: 1 to 3) including radiation. The median time from initial HL diagnosis to first dose was 13.0 months (range: 5 to 132).

Outcomes and estimation

The median follow-up time from first dose was 52.6 months (range: 1.8 to 72.0) and 50.1 months (range: 0.0 to 69.0) from end of treatment for all treated subjects in the study. The efficacy outcomes are presented in **Table 19**. The median duration of CR and the median duration of objective response (DOR) were not reached for any part of this study.

Table 19. Efficacy outcomes SGN35-025. DCO 19-Nov-2021

	Part 1 (n=6)	**Part 2 (n=55)**	**Part 3 (n=30)**	**Part 1&2 (n=61)**	**Total (n=91)**
Best clinical response *n (%)*					
CMR/CR	4 (67)	33 (60)	24 (80)	37 (61)	61 (67)
PMR/PR	2 (33)	10 (18)	4 (13)	12 (20)	16 (18)
NMR/SD	0	5 (9)	1 (3)	5 (8)	6 (7)

PMD/PD	0	6 (11)	1 (3)	6 (10)	7 (8)
NE	0	1 (2)	0	1 (2)	1 (1)
ORR (CR + PR) *n (%)*	6 (100)	43 (78)	28 (93)	49 (80)	77 (85)
Median DOR *mo (min, max)*	NA (0, 69.3)	NA (0, 61.9)	NA (0, 50.4)	NA (0, 69.3)	NA (0, 69.3)
PFS (3-year rate) *% (95%CI)*	100 (100,100)	91 (74, 97)	91 (70, 98)	92 (77, 97)	92 (81, 96)

Most patients proceeded to ASCT in part 1 (n=6, 100%), part 2 (n=36, 65%) and part 3 (n=25, 83%). Of the 67 patients that underwent per-protocol ASCT, best responses to study treatment prior to ASCT in these patients included 56 patients with CR, 10 with PR, and 1 with stable disease (SD). The median PFS post-ASCT was not reached. The estimated PFS rate after 36 months (3 years) is shown in **Table 19**.

Post-hoc subgroup analyses were performed in patients aged 18 – 30 and >30 years. In patients aged 18 – 30 years, the CMR was 76.9% and the ORR was 87.2%. In patients aged >30 years, the CMR was 59.6% and the ORR was 82.7%. The median PFS and OS were not reached in both age categories.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Design

The MAH conducted a risk-based, response-adapted phase 2 open-label single-arm trial (study CA209744*)* to evaluate the efficacy and safety of nivolumab in combination with brentuximab vedotin in children, adolescents and young adults with relapsed/refractory cHL after failure of first-line therapy. No scientific advice was requested on the study protocol. The MAH initially had planned to perform an RCT which was part of the paediatric investigation plan. However, this study was later removed from the PIP as the MAH considered that, based on the promising data of the phase 2 study, it was not justified to conduct an additional randomised study as the phase 2 study could provide for the evidence needed for a benefit/risk assessment. Furthermore, feasibility issues were anticipated as the combination was already included in the NCCN guidelines. The MAH also argued that the conduct of an RCT was unfeasible due to the heterogeneity of possible 2L options as well as the rarity of the population studied. The heterogeneity of 2L treatment options is acknowledged, however an RCT in the adult setting is considered feasible. Reference is made to RCTs conducted in the 3L setting with Keytruda (KEYNOTE-204) and brentuximab vedotin (AETHERA).

Study population

Patients aged 5 to 30 years, with pathologically confirmed cHL (nodular lymphocyte predominant HL excluded) after failure or non-response to first-line therapy and at least 1 measurable site of disease were eligible for inclusion. The age limits are in line with the peak incidence of cHL in paediatrics, adolescents and young adults (AYA). Although the lower limit of 5 years is somewhat arbitrary, the incidence of cHL and especially relapsed/refractory cHL <5 years is very low. There is an unmet medical need in this age population, as there is no clear consensus on the management of AYA and they are often treated as either paediatric or adult patients. The US NCCN paediatric guideline includes AYA patients up to the age of 39 years (NCCN guideline Paediatric Hodgkin Lymphoma). This is in line with the distinct disease biology in the paediatric and AYA age group compared to older adults, for example age-related differences in mutational burden have been observed (Kelly et al, 2023). Especially for the AYA population a lower treatment intensity and a reduction of long-term complications is important as these patients have decades of life left to live. The targeted age group in

the pivotal study is therefore endorsed, as limited exposure to chemotherapy and a potential transplant-free treatment regimen are considered clinically relevant for this population.

In total 79 patients were screened and 72 were enrolled. All enrolled patients were treated. Cohort R1 enrolled 28 patients, including 18 paediatric patients. The paediatric patients were mainly adolescents (n=15) with only 3 children aged 5 – 11 years. Cohort R2 enrolled 44 patients, including 31 paediatric patients. Also in this cohort the paediatric patients were mainly adolescents (n=27) with 4 children aged 5 – 11 years. The number of young children is limited but considered acceptable because of the rarity of the disease in young children. The aim of the PIP was to include at least 5 low-risk and 20 standard-risk paediatric patients, which was achieved (EMEA-001407-PIP02-15-M05).

Baseline disease characteristics showed a heterogeneous study population with more favourable disease characteristics (lower disease stage, late relapse) in cohort R1 compared to cohort R2 in line with the criteria used for risk stratification.

Overall, the study population is small and the robustness of the observed results is limited by the uncontrolled nature of the study. Most planned subgroup analysis could not be performed due to insufficient data.

Patients who received >1 line of anticancer therapy were excluded. Furthermore, patients with prior exposure to anti-PD(L)1/2 or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways were excluded and this is reflected in the SmPC. Overall, the in- and exclusion criteria are considered acceptable. However, after the pivotal study completed enrolment, brentuximab vedotin was approved for first-line treatment of cHL (EMA/CHMP/125287/2025). Therefore, nowadays patients may have had prior exposure to brentuximab vedotin in the first line. Data on response rates upon retreatment in R/R cHL are limited but suggestive of lower response rates as those obtained with initial use (Bartlett et al, 2014; Fukuhara et al, 2020; Sano et al, 2025; Sureda et al, 2025). Down-regulation of CD30 expression can occur during brentuximab vedotin treatment and lower response rates are reported with retreatment.

Treatment schedule

Induction treatment consisted of nivolumab in combination with brentuximab vedotin. Brentuximab vedotin is EU approved in adults and was therefore used off-label in paediatric patients. Paediatric studies with brentuximab vedotin as monotherapy in relapsed/refractory HL (e.g. NCT01492088; n=17) and in the first-line setting in combination with AVD (e.g.NCT02979522; n=59) have been conducted The combination of brentuximab vedotin and doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (https://clinicaltrials.gov/study/NCT02166463) is approved by the FDA with a weight-based posology of 1.8 mg/kg for brentuximab vedotin for paediatric patients. This is the same as the approved adult dose and a dose of 1.8 mg/kg was used in the pivotal study CA209744. There is some clinical experience with nivolumab in paediatrics as nivolumab is approved in adolescents from 12 years of age for melanoma.

Treatment in the 2L setting usually consists of combination treatment, but monotherapy with both anti-PD1 (Geoerger et al, 2020; Chen et al, 2017) and brentuximab vedotin (Plattel et al, 2021) can also be effective. Based on literature data, response rates of brentuximab vedotin or nivolumab as single agent in this setting are considerably lower which demonstrates the contribution of both components.

Brentuximab vedotin was administered 1 week prior to nivolumab in cycle 1 (staggered dosing) and this is described in the SmPC. It was anticipated that tumour associated antigens would be released

and available for presentation to resident cytotoxic T-cells at the same time that these cells become activated through PD-1 blockade.

The treatment schedule was risk-based and response-adapted. Risk stratification was based on stage at initial diagnosis, time to relapse (from end of therapy), B symptoms or extranodal disease at relapse, extensive disease where radiation therapy was contraindicated at relapse, or relapse in a prior radiation field. This is not a commonly used nor validated risk stratification to guide treatment, and not part of the current treatment guidelines. The EuroNet Paediatric Hodgkin Lymphoma Group considers a highly complex risk stratification not justified nor pragmatic and proposes assessment of 3 pre-salvage prognostic factors to allocate patients to a low risk or a standard risk group namely: (i) time to relapse, (ii) prior treatment in first line and (iii) stage at relapse (Daw et al, 2020). The risk stratification is sufficiently described in the SmPC for application in clinical practice.

All patients entered the induction phase and received treatment with 2 – 4 cycles of nivolumab with brentuximab vedotin. Patients who did not achieve CMR after 4 cycles of nivolumab with brentuximab vedotin moved to the intensification phase and received 2 cycles (cohort R1) or 2 – 4 cycles (cohort R2) of brentuximab vedotin with bendamustine to achieve CMR. Bendamustine in patients with cHL is used off-label, however brentuximab vedotin in combination with bendamustine was studied in R/R cHL and is recommended in the NCCN guidelines (Connor et al, 2018; Broccoli et al, 2019; Forlenza et al, 2021; NCCN guideline Pediatric Hodgkin Lymphoma, NCCN guideline Hodgkin Lymphoma). Patients who achieved CMR following 4 cycles of nivolumab in combination with brentuximab vedotin in cohort R1 received 2 additional cycles of nivolumab with brentuximab vedotin prior to the consolidation phase. The rationale for the two additional cycles was (1) as "bridging" to radiotherapy and (2) to maintain PFS rates comparable to the standard of care as the treatment regimen in cohort R1 is a substantial de-escalation compared to conventional chemotherapy followed by HDCT/ASCT. Although this rationale can be followed, the study design does not allow evaluation if any clinical benefit is derived from 2 additional cycles of nivolumab with brentuximab vedotin. In cohort R2 patients with CMR following 4 cycles of nivolumab in combination with brentuximab vedotin proceeded to consolidation. The consolidation phase consisted of radiation therapy (cohort R1) or HDCT/ASCT (cohort R2).

The SmPC describes the complete risk-based, response-adaptive treatment regimen including both induction and response-based intensification in Section 5.1.

Outcomes

The co-primary outcome of cohort R1 was CMR prior to radiotherapy and EFS rate at 3 years. EFS events were disease progression, death, failure to achieve CMR before consolidation, high-dose chemotherapy followed by autologous stem cell transplant and secondary malignancy. EFS is a complex clinical endpoint which has not been used in regulatory precedents in cHL. Various definitions of EFS can be used, and the definition as chosen by the MAH results in an overlap between the co-primary endpoints, as patients who fail to achieve CMR are counted as an EFS event. Including patients who fail to achieve CMR as EFS event may be the main driver of EFS as this study population has a good overall prognosis. Originally, the primary endpoint of cohort R1 was only EFS. EFS is a time-to-event endpoint and therefore not suitable for a single-arm trial to isolate a treatment effect as it cannot be attributed to the treatment (EMA/CHMP/458061/2024). The co-primary endpoint of CMR prior to radiotherapy was added via an amendment. The primary outcome of cohort R2 was CMR prior to HDCT/ASCT.

For both cohorts, the use of response rate as primary outcome in a single-arm trial in this setting is considered acceptable. As CMR was measured prior to consolidation, it includes the treatment effect of

both induction with nivolumab and brentuximab vedotin as well as response-based intensification with brentuximab vendotin and bendamustine. As the treatment goal is to achieve CMR and proceed to consolidation, this is acceptable. However, the response rate after induction more accurately isolates the treatment effect of the requested indication, namely induction with nivolumab/brentuximab vedotin. The response rate after induction was a secondary endpoint. DoR was censored for subsequent therapy. This might be acceptable for maintenance therapy, however it may result in an optimistic duration in cases where subsequent therapy was started because of disease progression or clinical deterioration without documented progression. Start of subsequent therapy had limited effect on the DoR for cohort R1, but did have an effect on the DoR in cohort R2 (NA to 50 months). However, median duration of response was still above 50 months in R2, which is considered clinically meaningful.

Statistical analyses

The sample size was not based on any formal statistical testing or power considerations, but width of the confidence interval was considered. The confidence level of the CI was lower than usual (90% instead of 95%) without justification but 95% CI were also provided. The final SAP was written more than 2 years after start of the study when all patients had been enrolled and 1.5 year after the first treatment of the last subject. The original version of the SAP (21-Sept-2018) was written after 72 patients (i.e. all patients) had begun treatment (26-Mar-2018 at protocol amendment 03). However, given that the endpoints that can isolate treatment effect (CMR, ORR, DoR) have standard analysis methods and are in line with the first protocol, this is not considered of impact.
An interim analysis in cohort R2 was conducted when all the patients in cohort R2 were response-evaluable. Because of this, CMR and ORR did not change anymore, this interim analysis is not considered to impact the results for these endpoints in cohort R2.

Study conduct

The most important protocol amendments were the addition of CMR as co-primary endpoint for cohort R1 and the early closure of cohort R1. CMR was added as co-primary endpoint after 10 patients were enrolled and treated in cohort R1 (36% of 28) and 49 patients (68%) were enrolled overall. Such a late amendment to the primary endpoint is of concern and could have been data-driven in this open-label study. In principle, the upgrading of CMR to primary endpoint in cohort R1 could be based on early positive results. However, given the high number of responses (26 out of 28 in cohort R1), the CMR must have been also high in the patients after this change. Together with the fact that CMR can isolate treatment effect and the MAH's claim that the change was on request of a health authority, possible bias is considered small. Cohort R1 was closed due to slow enrolment after 28 patients were included.

Twelve sites included at least 3 patients (16 sites only 1 patient and 4 sites with 2 patients, 43 sites had no patients). There was no clear relation between efficacy and site size. The selection of sites was mainly based on previous clinical trial/research experience and expected recruitment, and the selection of sites was considered representative.

Supportive study SGN35-025

Since CA209744 only included paediatric and young-adult patients (5-30 years), data from single-arm study SGN35-025 were provided in support of the proposed indication in all adults. Patients received four cycles of nivolumab and brentuximab vedotin. The study was conducted in different parts including staggered-dosing (part 1 and 2) and same-day dosing of nivolumab and brentuximab vedotin (part 3) during the first cycle. Response rate was measured after the induction phase, which is different from study CA209744 which measured the response before consolidation.

Efficacy data and additional analyses

Cohort R1

The CMR prior to consolidation was 92.9% (95% CI (76.5, 99.1) in the total population and 88.9% (95% CI 65.9, 95.80) in patients <18 years old. Most patients (n=19, 68%) achieved CMR after induction while 3 patients (11%) received additional intensification before consolidation. Consolidation with radiotherapy was achieved in 79% of all treated patients and 72% of paediatric patients.

The 3-year EFS rate by BICR was 87.5% (95% CI 65.9, 95.8) in the total population and 79.8% (90% CI 55.6, 91.7) in patients <18 years old. The 3-year EFS was based on 3 EFS events, of which two were patients who failed to achieve CMR and one case of disease progression.

Cohort R2

The CMR prior to consolidation was 88.6% (95% CI: 75.4, 96.2) in the total population and 90.3% (95% CI: 74.2, 98.0) in patients <18 years old. Most patients (n=23, 52%) achieved CMR after induction while 9 patients (20%) received additional intensification before consolidation. Consolidation with ASCT was achieved in 73% of all treated patients and 81% of paediatric patients.

The reported CMR rates were high for both cohorts. High response rates were observed both in the all-treated and the paediatric population. The response rates were in line with other small single-arm trials investigating anti-PD-1-based combination therapies in relapsed/refractory cHL (Mei et al, 2022; Ding et al, 2023; Moskowitz et al, 2021).

The EFS is unreliable due to the single arm trial design and immaturity as there were only three EFS events, of which two were caused by failure to achieve CMR.

Other endpoints were in line with the primary endpoint. The median duration of response was not reached in both cohorts. The 3-year PFS rate was 95.2% (cohort R1) and 91.1% (cohort R2) with four events of progressive disease. Although interpretation is hampered due to the single-arm trial design, the low event rate with a median follow-up over 5 years is noted. The 5-year OS rate was 97.6% with one OS event.

The endpoints per investigator assessment were similar to the assessment by BICR. The ORR following induction, which isolates the treatment effect of nivolumab/brentuximab vedotin, was 96.4% in cohort R1 and 93.2% in cohort R2. The CMR rate after induction was 82.1% in cohort R1 and 75.0% in cohort R2. The CMR rate after induction was high therefore only a small number of patients (24%) proceeded to intensification treatment.

The association between PD-L1 expression and efficacy could not be reliable assessed in both cohorts as only two patients had a low PD-L1 expression. In the approved indication of nivolumab for adult cHL patients there was no clear relationship between PD-L1 expression and efficacy of treatment (EPAR Nivolumab).

Patient-reported outcomes were difficult to assess due to the single-arm trial design, but no detriment was observed during the first four cycles. After four cycles, the questionnaire completion rates were very low.

Most patients in cohort R1 did not receive subsequent therapy. In cohort R2, 50% of patients received subsequent therapy while only 3 patients had disease progression. This was mainly with brentuximab vedotin (30%), although the role of maintenance with brentuximab vedotin has not been well defined in patients who received brentuximab vedotin earlier in the management of their disease (NCCN

guideline Hodgkin Lymphoma). Due to the small sample size and heterogeneity in subsequent treatments, no firm conclusion can be made with regard to maintenance treatment.

Supportive study SGN35-025

In total 93 patients were enrolled and 91 patients were treated. The median age was 34 years. The median number of prior therapies was 1 (range 1 – 3) and most patients were primary refractory (42%) or relapsed ≤12 months (30%). Fifty-two subjects had Stage II (57%) or III (18%) disease at initial diagnosis. The disease characteristics are comparable to the pooled cohorts (R1/R2). No patients were previously treated with anti-PD1, anti-PDL1, anti-PD-L2 and brentuximab vedotin.

The CR rate was 67% with an ORR of 85%. The median duration of response was not reached. In total 74% proceeded to ASCT. Reasons for not proceeding to ASCT were not recorded. No information was provided on subsequent therapy in patients who did not receive ASCT. The 3-year PFS rate was 92%.

The response rates were slightly lower than the response rates after induction observed in study CA209744, however comparing data across trials is methodologically difficult and study SGN35-025 included a more heavily pretreated population as also patients with >1 prior line of treatment were included.

There are several important differences between study CA209744 and study SGN35-025. A risk-based treatment approach with a pre-specified intensification regimen was used in study CA209744 while study SGN35-025 did not apply a risk-based approach and different intensification regimens were used. Study SGN35-025 did not investigate a transplant-free approach for low risk patients, as the goal was ASCT in all patients. Furthermore, while study SGN35-025 was submitted to provide supportive data for patients beyond the age population studied in CA209744 (>30 years), a large number of AYA patients (43%) were included in study SGN35-025 as reflected by the median age of 34 years. These concerns limit the added value of the supportive data from study SGN35-025 for efficacy.

Unbiased estimates are difficult to obtain from single-arm trials (EMA/CHMP/458061/2024). A literature search to support contextualization of the results observed in study CA209744 was provided. Comparing data across trials is methodologically difficult, especially as the data on patient and disease characteristics was very limited. However, response rates observed with conventional chemotherapy regimens were substantially lower than the response rates observed in study CA209744. Several studies investigated a combination of novel agents with conventional chemotherapy and with some combinations the efficacy in terms of response rates was similar to the response rates observed in pivotal trial CA209744. However, due to the differences in safety profile a potential chemotherapy-free regimen with a manageable safety profile and minimal late toxicity is considered an important benefit especially in young patients with cHL.

An indication beyond the pivotal trial population of study CA209744 is not considered justified due to differences in patient and disease characteristics and treatment. The incidence of cHL has a bimodal distribution with a peak in AYA and in patients older than 55 years (Aslani et al, 2024). Older patients have a worse prognosis, which is caused by several factors including biologic differences (higher incidence of EBV-related disease and mixed cellularity), higher incidence of advanced stage disease, more comorbidities, and poorer tolerability of treatment (Rodday et al, 2021; Punnett et al, 2010; Carter et al, 2020). Furthermore, while a transplant-free regimen is recommended in paediatric patients with low risk disease (Schellong et al, 2005; Stoneham et al, 2004; Daw et al, 2020), in adults the standard approach for relapsed/refractory cHL is HDCT/ASCT if patients are transplant-eligible (Eichenauer et al, 2018). Even though the Scientific Advisory Group (SAG-see below) considered that there are no obvious reasons why the reported favourable and unfavourable effects

would differ in patients older than 30 years, the CHMP recommended to restrict the indication to align with the study population, due to the limited data on efficacy and safety in patients aged >30 years. Importantly, no contextualization data were provided by the MAH for adults older than 30 years of age. Therefore, the indication was restricted to children aged 5 years and older, adolescents, and adults ≤30 years of age covering the studied population.

Additional expert consultation

Upon request from the Committee for Human Medicinal Products, a SAG Oncology meeting was convened on the 20th of January 2026 to answer the following questions:

1. **Please discuss the current clinical treatment practice in children and young adults, including the use of risk-based approach and response-adapted treatment.**

   a) **Is it clinical practice to use risk stratification at the point of relapse to decide between consolidation with radiotherapy (low risk) or HDCT/ASCT (high risk)? If so, which factors are used for risk stratification?**

The SAG discussed that there are variable practices but that, in general, risk stratification to choose between radiotherapy and autologous stem cell transplant (ASCT) is not used for most adult patients in Europe for relapsed patients. Exceptions may include, for example, maintenance treatment in elderly patients or late relapses with very limited disease. In general, the opportunity of optimising treatment using risk-stratification was welcomed, also from a patient perspective. Indeed, most fit adult patients don't undergo RT as consolidation, rather adjuvant RT in certain conditions (i.e. extranodal disease, bulky disease, residual PET+ lesions). Also, due to toxicity of ASCT in paediatric populations, a risk-guided approach seems desirable.

   b) **Which treatment regimens are used for induction treatment in children and young adults with R/R cHL?**

      The SAG discussed that there are variable regimens used for induction treatment in R/R cHL, without a single agreed standard. Current treatment guidelines identify multiple treatment regimens as possible options. Treatment choices depend on local practices and guidelines and may be impacted by prior treatments and availability of checkpoint inhibitors.

   c) **Is it clinical practice to proceed to intensification treatment in patients who do not achieve CMR after induction treatment (response-adapted treatment)? If so, which treatment regimens are used as intensification treatment?**

      The SAG discussed that currently, intensification treatments are sometimes employed in patients who do not experience CMR after induction treatment. There are different approaches that can be used, generally including a switch to different subsequent regimens for patients not achieving CMR after initial re-induction.

2. **How do the efficacy and toxicity results of the risk-based, response-adapted treatment with N+Bv in study CA209744 compare to the available clinical treatment options as discussed in question 1?**

   In general, comparisons are difficult on the basis of small populations in the available studies and indirect comparisons. Therefore, it is difficult to draw strong conclusions. However, it is

acknowledged that this is a small population and that that the evidence presented is not unusual in this setting.

Based on the observed antitumour response, lower limits of confidence intervals, and indirect comparisons, the N+Bv compares favourably to what is observed in this setting. Some limitations may be the low recruitment in the low risk population (R1) and the high rate of >50% subsequent therapies in the standard risk group (R2).

The toxicity compares favourably to the chemotherapy regimens used in this setting. The toxicity profile of N+Bv (e.g., lack of permanent infertility) may also be a consideration as it appears potentially better than available therapy in the actual follow-up period.

It is noted that the toxicity data did not raise important concerns compared to what is already extensively known for each agent, individually. However, the long-term toxicity data are limited.

- Long-term data collection may be considered to further rule out important long-term toxicity.

3. Are the perceived positive effects of N+Bv substantial enough to overcome limitations and uncertainties of the phase 2 study CA209744 with 72 patients?

In general, it is difficult to draw formal conclusions due to the aforementioned limitations of the data presented (small study size; lack of randomization). However, this level of uncertainty is acceptable in this rare population with high unmet needs; current treatment choices are based on similar uncertainties from small studies and are considered established. The role of CMR is considered well established as likely predictor of benefit that is the basis for treatment choices and management in clinical practice. N+Bv compared favourably to available standard treatments. Similarly, the toxicity profile seems acceptable and favourable compared to many standard options used in clinical practice. There is extensive experience with the two agents in cHL and other diseases to support the efficacy and safety of the combination. Thus, the effects observed are considered clinically important.

In conclusion, the perceived favourable effects are considered substantial enough to outweigh unfavourable effects and uncertainties based on reasonable assumptions.

- Uncertainties about long-term effects, including impact on subsequent stem cell transplant, can be reduced by submitting further long-term data about favourable and unfavourable effects.

The SAG discussed the difficulty in recruiting despite the favourable results observed and promise of the combination. Competing trials may also have played a role.

Regardless of the reasons for slow enrolment, the suitability for treatment with N+Bv in r/r cHL should be discussed also considering the response to prior treatments, including these two agents (e.g., early relapse/refractory disease). While this type of consideration is generally discussed in clinical practice, information to guide the prescriber may be useful.

- Consideration should be given on whether the favourable and unfavourable effects of N+Bv are established after prior treatment with similar agents.
- Further data may be collected to confirm the favourable and unfavourable effects after prior treatment with similar agents.

4. **Considering the study population aged 5 – 30 years, what would be the preferred clinical upper age limit to target young adult patients with R/R cHL considering treatment of AYA in clinical practice?**

   The threshold at 30 years seems to be mainly reflective of the design of the study CA209744. Although differences in biology/epidemiology are possible, there are no obvious reasons why these would significantly impact the observed favourable and unfavourable effects by age being older than 30 years. Substantial activity was observed in all age subgroups studied, with possibly lower activity in older adults, although no strong conclusions can be drawn. Therefore, a fixed threshold does not seem justified.

   - Further data may be collected to confirm the favourable and unfavourable effect in older adults.

2.4.4. Conclusions on the clinical efficacy

The risk-based, response-adapted treatment regimen with nivolumab and brentuximab vedotin resulted in a high CMR prior to consolidation in the studied population of patients 5-30 years of age. Although the single uncontrolled pivotal trial with a limited sample size introduces inherent uncertainty about the observed effects, the response rates observed with nivolumab and brentuximab vedotin are substantially higher than response rates reported in the literature for conventional chemotherapy regimens.

2.5. Clinical safety

Introduction

Safety analyses were performed in All Treated subjects of study CA209744 (including Treated Paediatric subjects), by cohort, and included incidence of AEs, SAEs, AEs leading to discontinuation of study treatment, select AEs, IMAEs, deaths, and clinical laboratory abnormalities.

Descriptive statistics of safety were presented using NCI CTCAE version 4. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs were tabulated using worst grade per NCI CTCAE 4.0 criteria by system organ class and MedDRA (version 27.0) preferred term.

Patient exposure

The number of All Treated and Treated Paediatric subjects entering/completing induction, intensification, and consolidation phases, and the reasons for not completing these phases are summarized in **Table 20** and **Table 21**, respectively.

The median duration of follow-up (All Treated Subjects) was 64.95 months (min-max: 40.7-79.8 months) for Cohort R1 and 78.03 months (min-max: 72.2-85.6 months) for Cohort R2. The median duration of follow-up (Treated Paediatric) was very similar to that for All Treated subjects: Cohort R1 = 64.95 months (min-max: 42.5-79.8 months); Cohort R2 = 78.95 months (min-max: 72.2-85.1 months). In CA209744, minimum follow-up time for the overall study period, as reported above, was defined as time from last subject's treatment start date to the clinical cutoff date.

Table 20. Subject Status Summary by Study Phase, All Treated Subjects (CA209744)

	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 (6.4)	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)
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 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)

Table 21. Subject Status Summary by Study Phase, Treated Paediatric Subjects (CA209744)

	Cohort R1 N = 18	Cohort R2 N = 31
SUBJECTS ENTERING INDUCTION PHASE (%)	18 (100.0)	31 (100.0)
SUBJECTS CONTINUING IN PERIOD (%)	0	0
SUBJECTS NOT COMPLETING PERIOD (%)	1 (5.6)	0
REASON FOR NOT CONTINUING IN PERIOD (%)		
STUDY DRUG TOXICITY	1 (5.6)	0
SUBJECTS COMPLETED PERIOD (%)	17 (94.4)	31 (100.0)
SUBJECTS CONTINUING IN STUDY AFTER INDUCTION PHASE (%)	17 (94.4)	31 (100.0)
INTENSIFICATION PHASE	6 (33.3)	10 (32.3)
CONSOLIDATION PHASE	10 (55.6)	17 (54.8)
FOLLOW-UP	1 (5.6)	4 (12.9)
SUBJECTS NOT CONTINUING IN STUDY AFTER INDUCTION PHASE (%)	1 (5.6)	0
REASON FOR NOT CONTINUING IN STUDY (%)		
LOST TO FOLLOW-UP	1 (5.6)	0
SUBJECTS ENTERING INTENSIFICATION PHASE (%)	6 (33.3)	10 (32.3)
SUBJECTS CONTINUING IN PERIOD (%)	0	0
SUBJECTS NOT COMPLETING PERIOD (%)	1 (16.7)	0
REASON FOR NOT CONTINUING IN PERIOD (%)		
STUDY DRUG TOXICITY	1 (16.7)	0
SUBJECTS COMPLETED PERIOD (%)	5 (83.3)	10 (100.0)
SUBJECTS CONTINUING IN STUDY AFTER INTENSIFICATION PHASE (%)	6 (100.0)	9 (90.0)
CONSOLIDATION PHASE	3 (50.0)	8 (80.0)
FOLLOW-UP	3 (50.0)	1 (10.0)
SUBJECTS NOT CONTINUING IN STUDY AFTER INTENSIFICATION PHASE (%)	0	1 (10.0)
REASON FOR NOT CONTINUING IN STUDY (%)		
SUBJECT WITHDREW CONSENT	0	1 (10.0)
SUBJECTS ENTERING CONSOLIDATION PHASE (%)	13 (72.2)	25 (80.6)
SUBJECTS CONTINUING IN PERIOD (%)	0	0
SUBJECTS NOT COMPLETING PERIOD (%)	0	0
SUBJECTS COMPLETED PERIOD (%)	13 (100.0)	25 (100.0)
SUBJECTS CONTINUING IN STUDY AFTER CONSOLIDATION PHASE (%)	13 (100.0)	25 (100.0)
FOLLOW-UP	13 (100.0)	25 (100.0)
SUBJECTS NOT CONTINUING IN STUDY AFTER CONSOLIDATION PHASE (%)	0	0
FOLLOW-UP		
SUBJECTS CONTINUING TO BE FOLLOWED IN THE STUDY (%)	17 (94.4)	30 (96.8)
SUBJECTS NOT CONTINUING TO BE FOLLOWED IN THE STUDY (%)	1 (5.6)	1 (3.2)
REASON FOR NOT CONTINUING TO BE FOLLOWED IN THE STUDY (%)		
LOST TO FOLLOW-UP	1 (5.6)	0
SUBJECT WITHDREW CONSENT	0	1 (3.2)

Cumulative dose and relative dose intensity for All treated subjects and all treated paediatric subjects are summarised in **Table 22** and **Table 23**.

Table 22. Cumulative Dose and Relative Dose Intensity Summary, All Treated Subjects (CA209744)

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

Induction Phase	Cohort R1		Cohort R2	
	Nivolumab N = 28	Brentuximab Vedotin N = 28	Nivolumab N = 44	Brentuximab Vedotin N = 44
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

Table 23. Cumulative Dose and Relative Dose Intensity Summary, Treated Paediatric Subjects (CA209744)

Induction Phase	Cohort R1		Cohort R2	
	Nivolumab N = 18	Brentuximab Vedotin N = 18	Nivolumab N = 31	Brentuximab Vedotin N = 31
NUMBER OF DOSES RECEIVED				
MEAN (SD)	5.1 (1.2)	5.1 (1.2)	4.3 (0.6)	4.3 (0.5)
MEDIAN (MIN - MAX)	6.0 (2 - 6)	6.0 (2 - 6)	4.0 (4 - 6)	4.0 (4 - 6)
CUMULATIVE DOSE				
MEAN (SD)	15.27 (3.79)	9.16 (2.27)	12.83 (1.74)	7.55 (0.99)
MEDIAN (MIN - MAX)	17.75 (6.0 - 18.5)	10.59 (3.6 - 11.3)	12.04 (11.7 - 17.8)	7.23 (5.9 - 10.7)
RELATIVE DOSE INTENSITY				
>= 110%	0	0	0	0
>= 90% TO < 110%	17 (94.4)	17 (94.4)	29 (93.5)	27 (87.1)
>= 70% TO < 90%	1 (5.6)	1 (5.6)	2 (6.5)	4 (12.9)
>= 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 = 10	Bendamustine N = 10
NUMBER OF DOSES RECEIVED				
MEAN (SD)	2.0 (0.0)	3.8 (0.4)	2.6 (0.8)	5.2 (1.7)
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)	4.62 (1.59)	467.49 (164.26)
MEDIAN (MIN - MAX)	3.57 (3.5 - 3.6)	344.82 (278.3 - 372.4)	3.53 (3.3 - 7.4)	369.57 (326.2 - 752.2)
RELATIVE DOSE INTENSITY				
>= 110%	0	0	0	0
>= 90% TO < 110%	6 (100.0)	5 (83.3)	8 (80.0)	8 (80.0)
>= 70% TO < 90%	0	1 (16.7)	2 (20.0)	2 (20.0)
>= 50% TO < 70%	0	0	0	0
< 50%	0	0	0	0

Discontinuation of Study Therapy

- Cohort R1: study drug toxicity (1 subject completed 2 cycles of Induction, then discontinued N+Bv due to nivolumab toxicity and proceeded to Consolidation).
- Cohort R2: disease progression (1 subject completed 4 cycles of Induction, then discontinued treatment due to disease progression and withdrew consent) and study drug toxicity (1 subject completed 2 cycles of Induction, then discontinued N+Bv due to Bv toxicity and proceeded to Follow-up).

Interruption of Study Therapy:

- In Cohort R1: 2 (7.1%) subjects had nivolumab dose interruptions while 7 (25.0%) subjects had Bv dose interruptions. No subjects had bendamustine dose interruptions. The reasons for dose interruptions were reported as:
  - Nivolumab: hypersensitivity reaction and infusion administration issues (1 interruption each).
  - Bv: hypersensitivity reaction (8 interruptions), other (2 interruptions), and infusion administration issues (1 interruption).
- In Cohort R2: 1 (2.3%) subject had nivolumab dose interruption while 9 (20.5%) subjects had Bv dose interruptions. No subjects had bendamustine dose interruptions. The reasons for dose interruptions were reported as:
  - Nivolumab: other (1 interruption).
  - Bv: hypersensitivity reaction (17 interruptions).

Adverse events

Table 24. Safety Summary - All Treated and Treated Paediatric Subjects in Cohorts R1 and R2 (CA209744)

	No. of Subjects (%)							
	Cohort R1 - Low Risk Cohort				Cohort R2 - Standard Risk Cohort			
	All Treated Subjects (n = 28)		Treated Paediatric Subjects (n = 18)		All Treated Subjects (n = 44)		Treated Paediatric 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)

	No. of Subjects (%)							
	Cohort R1 - Low Risk Cohort				Cohort R2 - Standard Risk Cohort			
	All Treated Subjects (n = 28)		Treated Paediatric Subjects (n = 18)		All Treated Subjects (n = 44)		Treated Paediatric Subjects (n = 31)	
All-causality AEs leading to DC	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 DC	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 (requirement of IMM treatment)								
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
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
All-causality Endocrine IMAEs within 100 Days of Last Dose, by Category (no requirement of IMM treatment)								
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
Hyperthyroidism	2 (7.1)	0	1 (5.6)	0	0	0	0	0
Hypophysitis	0	0	0	0	0	0	0	0

a) The subject had disease progression at the time of death; the site reported "disease" as the reason for death.

Includes events reported between first dose and 30 days after last dose of study therapy, except for deaths which includes all follow-up time. No other events of special interest (OESIs) were reported between first dose and 100 days after last dose of study therapy.

Cohort R1:

The most frequently (≥ 25% subjects) reported all-causality AEs are summarised in **Table 25**.

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.

Table 25. Adverse Events (Any Grade) Reported in ≥ 10% of All Treated/Treated Paediatric Subjects in Cohort R1 (CA209744)

	Cohort R1	
Preferred Term	**All-Treated Subjects (N=28)**	**Treated Paediatric Subjects (N=18)**
Total Subjects with an Event	26 (92.9)	18 (100.0)
Headache	12 (42.9)	6 (33.3)
Nausea	11 (39.3)	8 (44.4)
Pyrexia	7 (25.0)	6 (33.3)
Alanine aminotransferase increased	7 (25.0)	4 (22.2)
Diarrhoea	6 (21.4)	2 (11.1)
Pain in extremity	6 (21.4)	4 (22.2)
Vomiting	5 (17.9)	3 (16.7)
Aspartate aminotransferase increased	5 (17.9)	2 (11.1)
Infusion related reaction	5 (17.9)	3 (16.7)
Asthenia	4 (14.3)	2 (11.1)
Fatigue	4 (14.3)	3 (16.7)
Constipation	4 (14.3)	3 (16.7)
Oropharyngeal pain	4 (14.3)	3 (16.7)
Alopecia	4 (14.3)	3 (16.7)
Hypersensitivity	4 (14.3)	3 (16.7)
Pruritus	3 (10.7)	2 (11.1)
Rash maculo-papular	3 (10.7)	2 (11.1)
Epistaxis	3 (10.7)	2 (11.1)
Rhinitis	3 (10.7)	3 (16.7)
Urticaria	2 (7.1)	2 (11.1)
Blood bilirubin increased	2 (7.1)	2 (11.1)
Lymphocyte count decreased	2 (7.1)	2 (11.1)
Arthralgia	2 (7.1)	2 (11.1)
Cough	2 (7.1)	2 (11.1)
Abdominal pain upper	2 (7.1)	2 (11.1)
Hyperglycaemia	2 (7.1)	2 (11.1)
Hypoalbuminaemia	2 (7.1)	2 (11.1)
Anaemia	2 (7.1)	2 (11.1)
Dysmenorrhoea	2 (7.1)	2 (11.1)

Includes events reported between first dose and 30 days after last dose of study therapy.

Cohort R2:

The most frequently (≥ 25%) reported all-causality AE are summarised in **Table 26**. Grade 3-4 AEs reported in > 1 subject were neutropenia (3 subjects) and infusion-related reaction (2 subjects) in All Treated subjects, while neutropenia (3 subjects) was reported in Treated Paediatric subjects.

Table 26. Adverse Events (Any Grade) Reported in ≥ 10% of All Treated/Treated Paediatric Subjects in Cohort R2 (CA209744)

	Cohort R2	
Preferred Term	**All-Treated Subjects (N=44)**	**Treated Paediatric Subjects (N=31)**
Total Subjects with an Event	42 (95.5)	29 (93.5)
Nausea	25 (56.8)	20 (64.5)
Diarrhoea	12 (27.3)	8 (25.8)
Pyrexia	11 (25.0)	8 (25.8)
Hypersensitivity	10 (22.7)	7 (22.6)
Abdominal pain upper	9 (20.5)	6 (19.4)
Vomiting	8 (18.2)	7 (22.6)
Infusion related reaction	8 (18.2)	7 (22.6)
Cough	7 (15.9)	3 (9.7)
Rash	6 (13.6)	3 (9.7)
Headache	6 (13.6)	5 (16.1)
Fatigue	5 (11.4)	4 (12.9)
Arthralgia	5 (11.4)	4 (12.9)
Decreased appetite	5 (11.4)	5 (16.1)
Rash maculo-papular	5 (11.4)	3 (9.7)
Abdominal upper pain	4 (9.1)	4 (12.9)

Drug-related AEs

Cohort R1

The most frequently reported drug-related AEs in the all-treated subjects and the all-treated paediatric subjects are summarised in .

The only Grade 3-4 related AE that was reported in > 1 subject in the all-treated subjects was AST increased (2 subjects). None of the Grade 3-4 related AEs were reported in > 1 subject in the treated paediatric population.

Table 27. Drug-Related AEs (Any Grade) Reported in ≥ 10% of All Treated/Treated Paediatric Subjects in Cohort R1 (CA209744)

	Cohort R1	
Preferred Term	**All-Treated Subjects (N=28)**	**Treated Paediatric Subjects (N=18)**
Total Subjects with an Event	22 (78.6)	14 (77.8)
Alanine aminotransferase increased	6 (21.4)	4 (22.2)
Nausea	5 (17.9)	4 (22.2)
Headache	5 (17.9)	3 (16.7)
Infusion related reaction	5 (17.9)	3 (16.7)
Alopecia	4 (14.3)	3 (16.7)
Aspartate aminotransferase increased	4 (14.3)	2 (11.1)
Diarrhoea	4 (14.3)	2 (11.1)
Hypersensitivity	4 (14.3)	3 (16.7)
Pain in extremity	4 (14.3)	2 (11.1)
Rash maculo-papular	3 (10.7)	2 (11.1)
Asthenia	3 (10.7)	1 (5.6)
Fatigue	3 (10.7)	2 (11.1)
Pyrexia	3 (10.7)	3 (16.7)
Constipation	3 (10.7)	2 (11.1)
Pruritus	2 (7.1)	2 (11.1)
Blood bilirubin increased	2 (7.1)	2 (11.1)
Lymphocyte count decreased	2 (7.1)	2 (11.1)
Anaemia	2 (7.1)	2 (11.1)

Includes events reported between first dose and 30 days after last dose of study therapy

Cohort R2

The most frequently (≥ 10% subjects) reported drug-related AEs are presented in ***Table 28*** . The only Grade 3-4 drug related AE that was reported in > 1 subject in the all-treated and treated paediatric subjects was neutropenia (2 subjects).

Table 29. Drug-Related AEs (Any Grade) Reported in ≥ 10% of All Treated/Treated Paediatric Subjects in Cohort R2 (CA209744)

	Cohort R2	
Preferred Term	**All-Treated Subjects (N=44)**	**Treated Paediatric Subjects (N=31)**
Total Subjects with an Event	32 (72.7)	24 (77.4)
Nausea	12 (27.3)	11 (35.5)
Diarrhoea	7 (15.9)	6 (19.4)
Vomiting	7 (15.9)	6 (19.4)

Table 29. Drug-Related AEs (Any Grade) Reported in ≥ 10% of All Treated/Treated Paediatric Subjects in Cohort R2 (CA209744)

	Cohort R2	
Preferred Term	**All-Treated Subjects (N=44)**	**Treated Paediatric Subjects (N=31)**
Hypersensitivity	8 (18.2)	6 (19.4)
Infusion related reaction	6 (13.6)	5 (16.1)
Pyrexia	5 (11.4%)	4 (12.9%)

Serious adverse event/deaths/other significant events

Serious Adverse Events

Cohort R1

The overall frequencies of SAEs were similar between all-treated subjects and treated paediatric subjects (**Table 29**). 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.

Table 30. Serious Adverse Events (Any Grade), All Treated and Treated Paediatric Subjects, Cohort R1 (CA209744)

	Cohort R1	
Preferred Term	**All-Treated Subjects (N=28)**	**Treated Paediatric Subjects (N=18)**
Total Subjects with an Event	8 (28.6)	5 (27.8)
Pyrexia	5 (17.9)	4 (22.2)
Rash	1 (3.6)	1 (5.6)
Urticaria	1 (3.6)	1 (5.6)
Febrile neutropenia	1 (3.6)	0
Hypersensitivity	1 (3.6)	0
Otitis media	1 (3.6)	1 (5.6)
Infusion related reaction	1 (3.6)	1 (5.6)
Pain in extremity	1 (3.6)	1 (5.6)
Acute kidney injury	1 (3.6)	1 (5.6)

Cohort R2

The overall frequencies of SAEs (all causality and drug related) 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 (**Table 30**).

None of the Grade 3-4 SAEs were reported in > 1 subject in the all-treated and treated paediatric subjects.

Table 31. Serious Adverse Events (any grade), All-Treated and Treated Paediatric Subjects, Cohort R2

	Cohort R2	
Preferred Term	**All-Treated Subjects (N=44)**	**Treated Paediatric Subjects (N=31)**
Total Subjects with an Event	9 (20.5)	5 (16.1)
Pyrexia	2 (4.5)	0
Hypersensitivity	2 (4.5)	2 (6.5)
Infusion related reaction	1 (2.3)	0
Anaphylactic reaction	1 (2.3)	0
Vascular access complication	1 (2.3)	1 (3.2)
Activated partial thromboplastin time prolonged	1 (2.3)	1 (3.2)
Blood phosphorus increased	1 (2.3)	1 (3.2)
Dyspnoea	1 (2.3)	0
Orthopnoea	1 (2.3)	1 (3.2)
Pericardial effusion	1 (2.3)	0

Drug-related SAEs

The overall frequencies of drug-related SAEs were similar between all treated subjects and treated paediatric subjects. Pyrexia was the only drug-related SAE that was reported in > 1 subject in the all-treated and treated paediatric subjects (**Table 31**).

Table 32. Drug-Related Serious Adverse Events (any grade), All Treated and Treated Paediatric Subjects, Cohort R1

	Cohort R1	
Preferred Term	**All-Treated Subjects (N=28)**	**Treated Paediatric Subjects (N=18)**
Total Subjects with an Event	6 (21.4)	4 (22.2)
Pyrexia	2 (7.1)	2 (11.1)
Rash	1 (3.6)	1 (5.6)
Urticaria	1 (3.6)	1 (5.6)
Febrile neutropenia	1 (3.6)	0
Hypersensitivity	1 (3.6)	0
Infusion related reaction	1 (3.6)	1 (5.6)
Pain in extremity	1 (3.6)	1 (5.6)
Acute kidney injury	1 (3.6)	1 (5.6)

Cohort R2

The overall frequencies of drug-related SAEs were similar between all treated subjects and treated paediatric subjects. Hypersensitivity was the only drug-related SAE that was reported in > 1 subject in the all-treated and treated paediatric subjects (**Table 33**).

Table 33. Drug-Related Serious Adverse Events (any grade), All Treated and Treated Paediatric Subjects, Cohort R2

	Cohort R2	
Preferred Term	**All-Treated Subjects (N=44)**	**Treated Paediatric Subjects (N=31)**
Total Subjects with an Event	5 (11.4)	3 (9.7)
Hypersensitivity	2 (4.5)	2 (6.5)
Infusion related reaction	1 (2.3)	0
Anaphylactic reaction	1 (2.3)	0
Activated partial thromboplastin time prolonged	1 (2.3)	1 (3.2)

Deaths

Cohort R1

No deaths were reported in Cohort R1.

Cohort R2

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; however, the site reported “disease” as the reason for death.

Select Adverse Events

Drug-related select AEs were reported more frequently in the hepatic, pulmonary, skin, and hypersensitivity/infusion reaction categories than in other select AE categories, in both cohorts and across All Treated and Treated paediatric populations. All events in both cohorts were reported as resolved prior to the clinical cutoff date (28-May-2024).

Cohort R1: Details of the drug-related select AEs are provided in **Table 33** (All Treated subjects) and **Table 34** (Treated Paediatric subjects). For All Treated Subjects, the majority of drug-related select AEs across categories were Grade 1-2. Two events led to discontinuation. Relatively few events required IMM treatment and only 2 events (1 skin, 1 hypersensitivity) required treatment with high-dose corticosteroids.

Table *34*. Onset and Management of Drug-Related Select AEs in the Overall Treatment Period (CA209744) - All Treated Subjects in Cohort R1 (N = 28)

Category	N (%) Treated Subj. with Any Grade Drug-related Select AE	N (%) Treated Subj. with Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), weeks	N (%) Treated Subj. with Drug-related Select AE Leading to DC	N (%) Subj. with Drug-Related Select AE Treated with IMM[a]	N (%) Subj. with Drug-Related Select AE Treated with High-dose Corticosteroids[a]
Endocrine	1 (2.3%)	0	8.50 (3.1 - 13.9)	0	0	0
Gastrointestinal	5 (17.9)	1 (3.6)	12.57 (0.6 - 26.3)	0	0	0
Hepatic	8 (28.6)	2 (7.1)	3.64 (1.1 - 15.4)	0	0	0
Pulmonary	0	0	N.A. (N.A. - N.A.)	0	0	0
Renal	1 (3.6)	0	17.00 (17.0 - 17.0)	1 (3.6)	1 (100.0)	0
Skin	8 (28.6)	3 (10.7)	1.57 (1.1 - 15.3)	1 (3.6)	3 (37.5)	1 (12.5)
Hypersensitivity/ Infusion Reaction	8 (28.6)	0	3.14 (0.1 - 13.1)	0	4 (50.0)	1 (12.5)

[a] Denominator is based on the number of subjects who experienced the event. Includes events reported between first treatment and 30 days after last treatment of study therapy.

Table *35*. Onset and Management of Drug-Related Select AEs in the Overall Treatment Period (CA209744) - Treated Paediatric Subjects in Cohort R1 (N = 18*)*

Category	N (%) Treated Subj. with Any Grade Drug-related Select AE	N (%) Treated Subj. with Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), weeks	N (%) Treated Subj. with Drug-related Select AE Leading to DC	N (%) Subj. with Drug-Related Select AE Treated with IMM[a]	N (%) Subj. with Drug-Related Select AE Treated with High-dose Corticosteroids[a]
Endocrine	0	0	13.86 (13.9 - 13.9)	0	0	0
Gastrointestinal	3 (16.7)	1 (5.6)	12.57 (0.6 - 26.3)	0	0	0
Hepatic	6 (33.3)	0	3.64 (1.1 - 15.4)	0	0	0
Pulmonary	0	0	N.A. (N.A. - N.A.)	0	0	0
Renal	1 (5.6)	0	17.00 (17.0 - 17.0)	1 (5.6)	1 (100.0)	0
Skin	6 (33.3)	3 (16.7)	1.50 (1.1 - 15.3)	1 (5.6)	2 (33.3)	1 (16.7)
Hypersensitivity/ Infusion Reaction	5 (27.8)	0	3.14 (1.1 - 3.1)	0	3 (60.0)	0

[a] Denominator is based on the number of subjects who experienced the event. Includes events reported between first treatment and 30 days after last treatment of study therapy. **Error! Bookmark not defined.**

Cohort R2: Details of the drug-related select AEs are provided in **Table 35** (All Treated subjects) and (Treated Paediatric subjects). For All Treated Subjects, the majority of drug-related select AEs across categories were Grade 1-2. One event led to discontinuation. Relatively few events required IMM treatment, and 7 events (mostly hypersensitivity/IRR) required treatment with high-dose corticosteroids.

Table 36. Onset and Management of Drug-Related Select AEs in the Overall Treatment Period (CA209744) - All Treated Subjects in Cohort R2 (N = 44)

Category	N (%) Treated Subj. with Any Grade Drug-related Select AE	N (%) Treated Subj. with Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), weeks	N (%) Treated Subj. with Drug-related Select AE Leading to DC	N (%) Subj. with Drug-Related Select AE Treated with IMM[a]	N (%) Subj. with Drug-Related Select AE Treated with High-dose Corticosteroids[a]
Endocrine	1 (2.3)	0	7.71 (7.7 - 7.7)	0	0	0
Gastrointestinal	7 (15.9)	0	1.14 (0.4 - 12.9)	0	0	0
Hepatic	4 (9.1)	1 (2.3)	4.14 (1.7 - 15.1)	0	0	0
Pulmonary	1 (2.3)	0	11.29 (11.3 - 11.3)	0	1 (100.0)	1 (100.0)
Renal	0	0	N.A. (N.A. - N.A.)	0	0	0
Skin	12 (27.3)	0	1.79 (1.0 - 11.3)	0	5 (41.7)	0
Hypersensitivity/ Infusion Reaction	13 (29.5)	2 (4.5)	3.14 (1.1 - 16.9)	1 (2.3)	7 (53.8)	6 (46.2)

[a] Denominator is based on the number of subjects who experienced the event. Includes events reported between first treatment and 30 days after last treatment of study therapy.

Table 37. Onset and Management of Drug-Related Select AEs in the Overall Treatment Period (CA209744) - Treated Paediatric Subjects in Cohort R2 (N = 31)

Category	N (%) Treated Subj. with Any Grade Drug-related Select AE	N (%) Treated Subj. with Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), weeks	N (%) Treated Subj. with Drug-related Select AE Leading to DC	N (%) Subj. with Drug-Related Select AE Treated with IMM[a]	N (%) Subj. with Drug-Related Select AE Treated with High-dose Corticosteroids[a]
Endocrine	1 (3.2)	0	7.71 (7.7 - 7.7)	0	0	0
Gastrointestinal	6 (19.4)	0	1.14 (0.4 - 12.9)	0	0	0
Hepatic	2 (6.5)	1 (3.2)	3.93 (1.7 - 6.1)	0	0	0

Category	N (%) Treated Subj. with Any Grade Drug-related Select AE	N (%) Treated Subj. with Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), weeks	N (%) Treated Subj. with Drug-related Select AE Leading to DC	N (%) Subj. with Drug-Related Select AE Treated with IMM[a]	N (%) Subj. with Drug-Related Select AE Treated with High-dose Corticosteroids[a]
Pulmonary	0	0	N.A. (N.A. - N.A.)	0	0	0
Renal	0	0	N.A. (N.A. - N.A.)	0	0	0
Skin	8 (25.8)	0	1.71 (1.0 - 11.3)	0	2 (25.0)	0
Hypersensitivity/ Infusion Reaction	9 (29.0)	0	3.14 (1.1 - 16.9)	0	6 (66.7)	5 (55.6)

[a] Denominator is based on the number of subjects who experienced the event. Includes events reported between first treatment and 30 days after last treatment of study therapy.

Immune-mediated adverse events within 100 days of Last Dose in the Overall Treatment Period in cohorts RI and R2 in the all treated subjects and all treated paediatric subjects are summarised in **Table 37.**

Table 38. All-Causality IMAEs within 100 days of Last Dose in the Overall Treatment Period - All Treated Subjects in Cohort R1 (N = 28)

IMAE Category	N (%) Subj. with Any Grade IMAEs	N (%) Subj. with Grade 3-4 IMAEs	% Subj. with IMAE leading to DC	% Subj. with IMAEs Receiving IMM[a]	% Subj. with IMAEs Receiving High-dose Corticosteroids[a]
Pneumonitis	0	0	0	0	0
Diarrhoea/Colitis	0	0	0	0	0
Hepatitis	0	0	0	0	0
Nephritis/Renal Dysfunction	1 (3.6)	0	1 (3.6)	1 (100.0)	0
Rash	3 (10.7)	1 (3.6)	1 (3.6)	3 (100.0)	1 (33.3)
Hypersensitivity	2 (7.1)	0	0	2 (100.0)	0
Adrenal Insufficiency	0	0	0	0	0
Hypothyroidism/Thyroiditis	1 (3.6)	0	0	0	0
Diabetes Mellitus	0	0	0	0	0
Hyperthyroidism	2 (7.1)	0	0	0	0
Hypophysitis	0	0	0	0	0

[a] Denominator is based on the number of subjects who experienced the event.

Table 39. All-Causality IMAEs within 100 days of Last Dose in the Overall Treatment Period - Treated Paediatric Subjects in Cohort R1 (N = 18)

IMAE Category	N (%) Subj. with Any Grade IMAEs	N (%) Subj. with Grade 3-4 IMAEs	% Subj. with IMAE leading to DC	% Subj. with IMAEs Receiving IMM[a]	% Subj. with IMAEs Receiving High-dose Corticosteroids[a]
Pneumonitis	0	0	0	0	0
Diarrhoea/Colitis	0	0	0	0	0
Hepatitis	0	0	0	0	0
Nephritis/Renal Dysfunction	1 (5.6)	0	1 (5.6)	1 (100.0)	0
Rash	2 (11.1)	1 (5.6)	1 (5.6)	2 (100.0)	1 (50.0)
Hypersensitivity	2 (11.1)	0	0	2 (100.0)	0
Adrenal Insufficiency	0	0	0	0	0
Hypothyroidism/Thyroiditis	0	0	0	0	0
Diabetes Mellitus	0	0	0	0	0
Hyperthyroidism	1 (5.6)	0	0	0	0
Hypophysitis	0	0	0	0	0

[a]Denominator is based on the number of subjects who experienced the event.

Table 40. All-Causality IMAEs within 100 days of Last Dose in the Overall Treatment Period - All Treated Subjects in Cohort R2 (N = 44)

IMAE Category	N (%) Subj. with Any Grade IMAEs	N (%) Subj. with Grade 3-4 IMAEs	% Subj. with IMAE leading to DC	% Subj. with IMAEs Receiving IMM[a]	% Subj. with IMAEs Receiving High-dose Corticosteroids[a]
Pneumonitis	1 (2.3)	0	0	1 (100.0)	1 (100.0)
Diarrhoea/Colitis	0	0	0	0	0
Hepatitis	0	0	0	0	0
Nephritis/Renal Dysfunction	0	0	0	0	0
Rash	6 (13.6)	0	0	6 (100.0)	1 (16.7)
Hypersensitivity	4 (9.1)	1 (2.3)	0	4 (100.0)	4 (100.0)
Adrenal Insufficiency	0	0	0	0	0
Hypothyroidism/ Thyroiditis	1 (2.3)	0	0	0	0

IMAE Category	N (%) Subj. with Any Grade IMAEs	N (%) Subj. with Grade 3-4 IMAEs	% Subj. with IMAE leading to DC	% Subj. with IMAEs Receiving IMM[a]	% Subj. with IMAEs Receiving High-dose Corticosteroids[a]
Diabetes Mellitus	0	0	0	0	0
Hyperthyroidism	0	0	0	0	0
Hypophysitis	0	0	0	0	0

[a]Denominator is based on the number of subjects who experienced the event.

Table 41. All-Causality IMAEs within 100 days of Last Dose in the Overall Treatment Period - Treated Paediatric Subjects in Cohort R2 (N = 31)

IMAE Category	N (%) Subj. with Any Grade IMAEs	N (%) Subj. with Grade 3-4 IMAEs	% Subj. with IMAE leading to DC	% Subj. with IMAEs Receiving IMM[a]	% Subj. with IMAEs Receiving High-dose Corticosteroids[a]
Pneumonitis	0	0	0	0	0
Diarrhoea/Colitis	0	0	0	0	0
Hepatitis	0	0	0	0	0
Nephritis/Renal Dysfunction	0	0	0	0	0
Rash	3 (9.7)	0	0	3 (100.0)	1 (33.3)
Hypersensitivity	3 (9.7)	0	0	3 (100.0)	3 (100.0)
Adrenal Insufficiency	0	0	0	0	0
Hypothyroidism/Thyroiditis	1 (3.2)	0	0	0	0
Diabetes Mellitus	0	0	0	0	0
Hyperthyroidism	0	0	0	0	0
Hypophysitis	0	0	0	0	0

[a]Denominator is based on the number of subjects who experienced the event.

Laboratory findings

Haematology

Abnormalities in haematology tests (SI units) performed during treatment or within 30 days of last dose of study treatment were mostly Grade 1 or 2 in severity in both R1 and R2 cohorts.

Cohort R1:

Grade 3 or 4 hematologic abnormalities reported included:

- All Treated subjects: haemoglobin (n=1), lymphocytes (n=2), absolute neutrophil count (n=3).
- Treated Paediatric subjects: haemoglobin (n=1), lymphocytes (n=1).

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

- All Treated subjects: haemoglobin (n=1), absolute neutrophil count (n=3), lymphocytes (n=2).
- Treated Paediatric subjects: haemoglobin (n=1) and lymphocytes (n=1).

Cohort R2

Grade 3 or 4 hematologic abnormalities reported included:

- All Treated subjects: platelet count (n=1), leukocytes (n=3), lymphocytes (n=8), and absolute neutrophil count (n=5).
- Treated Paediatric subjects: platelet count (n=1), leukocytes (n=3), lymphocytes (n=7), and absolute neutrophil count (n=5).

A shift from Grade 0/1/2 at baseline to Grade 3/4 post-baseline was reported for

- platelet count (n=1), leukocytes (n=3), lymphocytes (n=4), absolute neutrophil count (n=5) in All Treated subjects and Treated Paediatric subjects.

Clinical Chemistry

Liver Function Tests

Abnormalities in hepatic parameters (SI units) during treatment or within 30 days of last dose of study treatment were primarily Grade 1 or 2 in severity in both cohorts.

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 Paediatric subjects were reported with Grade 3 or 4 hepatic abnormalities.

8 (28.6%) of All Treated subjects and 3 (16.7%) of Treated Paediatric subjects were reported with ALT or AST increased > 3× ULN; 3 (10.7%) of All Treated subjects were reported with ALT or AST increased > 5× ULN; and none of these subjects were reported with 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 Paediatric subjects.

5 (11.4%) of All Treated subjects and 4 (12.9%) of Treated Paediatric subjects were reported with ALT or AST increased > 3× ULN; 1 (2.3%) among All Treated subjects were reported with ALT or AST

increased > 5× ULN; and none of these subjects were reported with concurrent elevation in bilirubin > 2× ULN.

Kidney Function Tests

Most subjects in both cohorts with at least 1 on-treatment measurement had normal creatinine values (SI units).

Cohort R1

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 Paediatric subjects.

Cohort 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 Paediatric subjects.

Discontinuation due to adverse events

Cohort R1

The overall frequencies of AEs leading to discontinuation of study treatment were similar between all treated and treated paediatric subjects in Cohort R1. None of the AEs leading to discontinuation of study treatment was reported in more than 1 subject in the all-treated and treated paediatric subjects **Table 41**). All the AEs that led to discontinuation of study treatment were considered as related to the study drug in the all-treated and treated paediatric subjects.

Table 42. Adverse Events Leading to Discontinuation of Study Treatment, All Treated and Treated Paediatric Subjects, Cohort R1

	Cohort R1	
Preferred Term	**All-Treated Subjects (N=28)**	**Treated Paediatric Subjects (N=18)**
Total Subjects with an Event	2 (7.1)	2 (11.1)
Pyrexia	1 (3.6)	1 (5.6)
Acute kidney injury	1 (3.6)	1 (5.6)
Rash	1 (3.6)	1 (5.6)

Cohort R2

One subject among the all-treated subjects was reported with an AE of anaphylactic reaction that led to discontinuation of the study treatment in Cohort R2. The AE was considered as related to the study drug. None of the treated paediatric subjects were reported with AEs that led to discontinuation of the study treatment.

Safety data in Adults Treated with N+Bv for R/R cHL after failure of Front-line Therapy (SGN035-025)

In SGN35-025, AEs, regardless of relationship to study drug, were recorded from study Day 1 through 100 days after the last dose of nivolumab and included the ASCT period unless otherwise noted. Safety

was monitored by a safety monitoring committee. AEs were classified using MedDRA, version 23.0, with a standard MedDRA query performed to identify events of peripheral neuropathy (PN). AE grade of severity was determined per NCI CTCAE, version 4.03.

Of the 105 subjects screened, 93 patients with R/R cHL were enrolled at 11 sites. 2 enrolled subjects did not receive treatment due to consent withdrawal or reason stated as 'other'. 91 subjects received study treatment of which 86 subjects completed all 4 cycles of N+Bv. Early treatment discontinuations were reported as due to AEs (n=2), patient decision (n=2), progressive disease (n=1), or investigator decision (n=1). Median follow-up as of the data cutoff date was 34.3 months (range: 1.8 - 49.9 months). 90 patients entered LTFU to monitor for disease progression or death. As of the data cutoff, 77 patients were still in LTFU, 6 had died, 5 were lost to follow-up, and 2 had withdrawn consent.

Safety Results:

All Causality Adverse Events: Across study Parts 1, 2, and 3, a total of 90 subjects (99%) were reported with any-grade AEs prior to per-protocol ASCT. The most frequently reported AEs were nausea in 47 subjects (52%), infusion-related reactions (IRRs) in 39 subjects (43%), and fatigue in 36 subjects (40%); all were Grades 1-2, except 1 incidence of Grade 3 fatigue.

Peripheral sensory neuropathy (a known AE associated with Bv) was reported in 16 subjects (18%), all were Grade 1 except for 1 Grade 3 (not specified) PN that led to treatment discontinuation.

Other Grade 3 or 4 AEs in 2 or more subjects (prior to ASCT and salvage therapy) were reported for a total of 30 subjects (33%) across study Parts 1, 2, and 3. No Grade 5 AEs occurred.

IRRs (any grade) were reported in 28 subjects (46%) in total in Parts 1 and 2 and in 11 subjects (37%) in Part 3, mostly at Cycle 2 (34% and 23%, respectively).

Deaths: Overall, there were 7 deaths among all treated subjects in SGN35-025, none of which were reported during the safety reporting period. No deaths were considered related to study treatment.

AEs Leading to Discontinuation: Two subjects (2%) were reported to discontinue treatment due to AEs (1 with PN and 1 with increased gamma-glutamyl transferase).

AEs leading to dose delay of Bv or nivolumab were reported in 10 subjects (11%) and 11 subjects (12%), respectively. AEs leading to Bv dose delay in > 1 subject were neutropenia and hyperlipasemia (n=2 each). Events leading to nivolumab dose delay in > 1 subject were neutropenia (n=2). All subjects who had dose delay were able to receive another dose of the delayed drug, and all but 1 subject reported with a dose delay received 4 cycles of treatment.

Potential Immune-related Adverse Events: Across Parts 1, 2, and 3, immunosuppressive treatment (systemic corticosteroids) was administered to 16 subjects (18%) for potential IrAEs (any grade), excluding IRRs. No subject was reported to discontinue study treatment due to an IrAE.

Grade 3 or higher IrAEs included pneumonitis (n=3 [Gr. 4]), maculopapular rash (n=1 [Gr. 3]), increased AST (n=1 [Gr. 3]), diarrhoea (n=1 [Gr. 3]), and Guillain-Barre syndrome (n=1 [Gr. 3]). Other IrAEs reported (Grade 1-2) consisted of PTs related to rash/skin condition (n=10), and pneumonitis (n=1).

All 3 subjects with Grade 4 pneumonitis events were treated successfully with systemic corticosteroids. All of these pneumonitis events were reported 2 to 4 months after the last dose of study therapy.

2.5.1. Discussion on clinical safety

The safety of the combination of nivolumab with brentuximab vedotin for the treatment of paediatrics and adults with R/R HL after failure of first line treatment is presented with data from the phase 2 study CA209744 in patients aged 5-30 years. The MAH has presented safety data per cohort (R1 and R2) and for all treated patients and paediatrics separately. To supplement the data in adults the MAH presented data from a phase 1/2 study SGN35-025 conducted in adults with R/R HL after failure of prior treatment. The presented data from SGN-035 are consistent regarding frequency and types of AE with that of study CA209744. However, due to differences in patient and disease characteristics between studies CA209744 and SGN35-025, study SGN35-025 is only considered to be supportive.

The pivotal safety data consists of 72 subjects (CA209744) of which 49 paediatric subjects across 2 cohorts (at low risk of relapse (Cohort R1) and at standard risk of relapse (Cohort R2). The median duration of follow-up (All Treated Subjects) was 64.95 months (min-max: 40.7-79.8 months) for Cohort R1 and 78.03 months (min-max: 72.2-85.6 months) for Cohort R2. The median duration of follow-up and exposure for the paediatric patients was in general similar as for the all-treated subjects. The median follow-up is sufficient to allow safety assessment, however the sample size with an uncontrolled study design is considered limited in a heterogenous population with respect to age (paediatric and adults) as well as disease characteristics (low and standard risk of relapse).

Per study design, the patients in cohort R1 could receive up to 6 doses of N+Bv and in cohort R2 4 cycles, this is reflected in the exposure (the mean number of doses and cumulative dose). The majority of patients (>90%) received the intended dose. The safety assessment entailed AEs occurring within 30 days after last dose of study therapy unless otherwise specified (i.e., IMAEs, deaths), as such the unexpected late AEs (e.g. secondary malignancies) are not collected. Due to this 30-day window the safety of RT (R1 cohort) and ASCT (R2 cohort) is likely not taken into account, which is accepted.

The number of discontinuations of study therapy was low (3 subjects of which 2 discontinued due to study drug toxicity). None of the AEs leading to discontinuation of study treatment was reported in more than 1 subject, reported were pyrexia, rash, acute kidney injury in cohort R1 and anaphylactic reaction in cohort R2. There was no clear difference in paediatric, or all treated patients observed (with the caveat that this was based on a low sample size). Dose interruptions with nivolumab occurred in a limited number of cases (3 in total) whereas 16 subjects had a dose interruption of BV (25% in R1 and 20.5% in R2) mainly due to hypersensitivity.

Adverse events

Almost all patients reported an any grade all-causality AE during the study treatment period (>90%), drug related AEs occurred in >70% with app 25% grade 3-4. Results were similar between cohort R1, R2 and all treated and paediatric subjects. Regarding the type of AEs occurring most frequently, results were mainly of low grade and overlapping in both cohorts. In cohort R1 the most frequently (≥ 15% subjects) reported drug-related AEs were ALT increased, nausea, headache, and infusion related reaction in All-Treated subjects while ALT increased, nausea, alopecia, pyrexia, headache, hypersensitivity, and infusion related reaction were the most frequently reported AEs in Treated Paediatric subjects. In cohort R2 the most frequently (≥ 15% subjects) reported drug-related AEs were nausea, diarrhoea, vomiting and hypersensitivity in All-Treated subjects as well as the paediatric population (with the addition of infusion related reaction for paediatric patients).

In cohort R1, the only Grade 3-4 related AE reported in > 1 subject in All-Treated subjects was AST increased (2 subjects) while no Grade 3-4 related AEs were reported in > 1 subject in the Treated Paediatric population. In cohort R2 the only Grade 3-4 drug related AE that was reported in > 1 subject in All-Treated and Treated Paediatric subjects was neutropenia (2 subjects). The presented

safety profile is consistent with that previously reported for nivolumab or BV as well was between R1 and R2 cohorts and all-treated and paediatric patients.

There were no cases of drug-related AE leading to death in either cohort. One death (disease progression) was reported in the Treated Paediatric population in Cohort R2. No deaths were related to study drug toxicity.

The overall frequencies of drug-related SAEs were similar between all treated subjects (cohort R1 21.4%; R2 11.4%) and treated paediatric subjects (cohort R1 22.2%, R2 9.7%). In cohort R1, pyrexia was the only drug-related SAE that was reported in > 1 subject in the all-treated (7.1%) and treated paediatric subjects (11.1%). In cohort R2 this was hypersensitivity (4.5%) in all-treated subjects and in paediatric patients (6.5%).

Drug-related select AEs were reported more frequently in the hepatic, pulmonary, skin, and hypersensitivity/infusion reaction categories than in other select AE categories, in both cohorts and across All-Treated and Treated paediatric populations. The majority of drug-related select AEs across categories were Grade 1-2, few events required treatment of which 2 events (1 skin, 1 hypersensitivity) in R1 cohort and 7 events (mostly hypersensitivity/IRR) in R2 cohort required treatment with high-dose corticosteroids. All events in both cohorts were reported as resolved prior to the clinical cutoff date (28-May-2024).

Immune mediated adverse events reported were rash, hypersensitivity, hyperthyroidism, nephritis, pneumonitis and hypothyroidism all reported in <15% of subjects of low grade of which only rash required high dose corticosteroid treatment. No clear difference is observed between cohort R1 and R2 or age.

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 populations.

All-causality AEs known to be of special interest for Bv (i.e., peripheral neuropathy [PN], infection) were generally of low grade. In both cohorts, low frequencies of PN (< 6%) were reported; all PN cases were reported as not related to study drug, Grade 1-2, and non-serious. The frequencies of infection reported (events in the SOC 'Infections and infestations') were < 40% in both cohorts; few events were serious most were Grade 1-2 and not related to study drug.

Available safety data in adults older than 30 years from study SGN35-025 are very limited as median age in this study was 34.0 years (range: 18 to 69). Due to the bimodal distribution of HL and the worse prognosis in older patients caused by biologic differences (higher incidence of EBV-related disease and mixed cellularity), higher incidence of advanced stage disease, more comorbidities, and poorer tolerability of (Rodday et al, 2021; Punnett et al, 2010; Carter et al, 2010), this lack of data is important. Therefore, the safety of the proposed combination treatment in adults over 30 years of age is not well characterised.

The SAG also considered the long-term toxicity data limited and that collection of such data should be considered to further rule out important long-term toxicity. Such data can be provided by an ongoing observational post-authorisation safety study retrospective cohort study based on secondary use of data from a registry in pediatric patients (12 to < 18 and < 12 years of age) with advanced (unresectable or metastatic) melanoma and with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Data from this study are expected to become available in Q4 2026 (interim analysis) and in 2033 (final analysis).

Additional expert consultations

See discussion on clinical efficacy section.

2.5.2. Conclusions on clinical safety

The overall safety profile of the treatment regimens in Cohort R1 and Cohort R2 (All-Treated subjects and Treated Paediatric subjects) was manageable and consistent with the known safety profile of the therapeutic agents. No new safety signals or toxicities were identified. The presented dataset focusses on patients 5-30 years (e.g. children, adolescents and young adults) as reflected in the indication. The toxicity of the combination of N+BV is considered a tolerable treatment option for paediatric patients and young adults without the toxicity commonly seen with chemotherapy otherwise administered within this setting.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the Risk Management Plan version 44.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 44.1 with the following content:

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 with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Long-term safety in adolescent patients ≥ 12 years of age (IV only)[a]

a This safety concern is relevant to paediatric indications approved for nivolumab 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				
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 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

Safety Concern	Risk Minimisation Measures
	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
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 with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4 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)[a]	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, 5.1 and 5.2 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

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.

3.1.2. Available therapies and unmet medical need

Patients with R/R cHL after failure of front-line therapy typically receive re-induction (2L salvage) therapy with chemotherapy or other novel agents that may be followed by RT alone as consolidation (in lower-risk paediatric patients) or may be subsequently followed by HDCT/ASCT (in higher-risk patients). There is currently no consensus on best reinduction regimen.

3.1.3. Main clinical studies

The pivotal study is a risk-based, response-adapted phase 2 open-label single-arm trial to evaluate the efficacy and safety of nivolumab in combination with brentuximab vedotin in children, adolescents and young adults with relapsed/refractory cHL after failure of first-line therapy (CA209744). Patients aged 5 to 30 years, with pathologically confirmed cHL after failure or non-response to first-line therapy were eligible for inclusion. Depending on risk factors patients were included in a low-risk cohort R1 or a standard risk cohort R2.

The treatment was response adapted. Induction consisted of 4 cycles of nivolumab with brentuximab vedotin for both cohort 1 and 2 and two additional cycles in cohort R1 in case of CMR. Intensification in case of failure to achieve CMR consisted of 2 cycles (cohort R1) or 2 – 4 cycles (cohort R2) of brentuximab vedotin with bendamustine. Patients who achieved CMR moved to the consolidation phase where they received radiation therapy (cohort R1) or HDCT/ASCT (cohort R2).

The co-primary endpoint of cohort R1 was CMR prior to radiotherapy and EFS rate at 3 years. The primary endpoint of cohort R2 was CMR before ASCT.

Cohort R1 included 28 patients in total including 18 paediatric patients. Cohort R2 included 44 patients including 31 paediatric patients.

3.2. Favourable effects

In cohort R1, 26/28 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 92.9% (95% CI: 76.5, 99.1). In the paediatric population, 16/18 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 88.9% (90% CI: 65.3, 98.6). Consolidation with radiotherapy was achieved in 79% of all treated patients and 72% of paediatric patients. The median DOR was not reached at a median follow-up of 64 months. The ORR per BICR after 4 cycles of nivolumab and

brentuximab vedotin was 96.4% (95% CI: 81.7, 99.9) in all treated subjects and 94.4% (95% CI: 72.7, 99.9) in the paediatric population.

In cohort R2 39/44 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 88.6% (95% CI: 75.4, 96.2). In the paediatric population, 28/31 had a CMR by BICR prior to consolidation therapy, resulting in a CMR of 90.3% (95% CI: 74.2, 98.0). Consolidation with ASCT was achieved in 73% of all treated patients and 81% of paediatric patients. The median DOR was not reached at a median follow-up of 78 months. The ORR per BICR after 4 cycles of nivolumab and brentuximab vedotin was 93.2% (95% CI: 81.3, 98.6) in all treated subjects and 93.5% (95% CI: 78.6, 99.2) in the paediatric population.

3.3. Uncertainties and limitations about favourable effects

Efficacy is based on a single uncontrolled pivotal trial with a limited sample size with no formal power calculation and is considered exploratory in nature. However, indirect comparisons with literature studies, support a clinical benefit for the proposed combination of nivolumab and brentuximab vedotin, despite the methodological limitations of such comparisons.

The pivotal study only included patients aged 5 – 30 years. Supportive data from study SGN35-025 were provided, however due to several important differences between study CA209744 and study SGN35-025, the added value of study SGN35-025 is limited. Therefore, the indication was restricted to patients aged 5 – 30 years.

In cohort R1 patients who achieved CMR received 2 additional cycles of nivolumab with brentuximab vedotin. The clinical benefit of 2 additional cycles after CMR is achieved is uncertain.

The role of maintenance treatment after ASCT in patients without disease progression is unknown.

The efficacy in patients that were previously treated with anti-PD-1, anti-PD-L1, anti-PD-L2, or brentuximab vedotin is unknown.

3.4. Unfavourable effects

The safety population in the pivotal study comprised 72 patients (28 in Cohort R1; 44 in Cohort R2) of which 49 paediatric subjects in the intended R/R cHL population. The median duration of follow-up (All Treated Subjects) was 64.95 months (min max: 40.7-79.8 months) for Cohort R1 and 78.03 months (min-max: 72.2-85.6 months) for Cohort R2.

Almost all patients reported an any grade all-causality AE during the study treatment period (>90%), drug related AEs occurred in >70% with app 25% grade 3-4. Results were similar between cohort R1, R2 and all treated and paediatric subjects.

The overall frequencies of drug-related SAEs were similar between all treated subjects (cohort R1 21.4%; R2 11.4%) and treated paediatric subjects (cohort R1 22.2%, R2 9.7%). In cohort R1, pyrexia was the only drug-related SAE that was reported in > 1 subject in the all-treated (7.1%) and treated paediatric subjects (11.1%). In cohort R2 this was hypersensitivity (4.5%) in all treated subjects and in paediatric patients (6.5%).

There were no cases of drug-related AE leading to death in either cohort. One death (disease progression) was reported in the Treated paediatric population in Cohort R2.

Immune-mediated adverse events reported were rash, hypersensitivity, hyperthyroidism, nephritis, pneumonitis and hypothyroidism all reported in <15% of subjects and were of low grade. No clear difference was observed between cohort R1 and R2 or age.

3.5. Uncertainties and limitations about unfavourable effects

The median follow-up is sufficient to allow safety assessment however the sample size with an uncontrolled study design is considered limited in a heterogenous paediatric and adult population.

3.6. Effects Table

Table 43. Effects Table for nivolumab in combination with brentuximab vedotin for the treatment of children 5 years of age and older, adolescents and adults up to 30 years of age with relapsed or refractory classical Hodgkin lymphoma after one prior line of therapy (data cut-off: 28-May-2024)

Effect	Short description	Unit	Cohort R1 (N=28)	Cohort R2 (N=44)	Uncertainties / Strength of evidence	References
Favourable Effects						
CMR	proportion of all response-evaluable participants who, assessed by the BICR, achieve best response of CMR using Lugano 2014 criteria any time prior to consolidation	% (95% CI)	92.9 (76.5, 99.1)	88.6 (75.4, 986.2)	Small uncontrolled study with mainly paediatric patients (n=49) Different treatment pathways due to risk-based, response-adapted approach which fragments the results	CA209744
ORR	Proportion of all response-evaluable participants who assessed by the BICR, achieve a best response of CMR or PMR using Lugano 2014 criteria after 4 cycles of N + Bv	% (95% CI)	96.4 (81.7, 99.9)	93.2 (81.3, 98.6)	Limited sample size in an uncontrolled study. Mostly grade 1-2 events. Results were similar between all treated and paediatric subjects.	

Effect	Short description	Unit	Cohort R1 (N=28)	Cohort R2 (N=44)	Uncertainties / Strength of evidence	References
					Underrepresentation of adult HL patients	
Unfavourable Effects						
IMAEs within 100 days	Pneumonitis	%	0	2.3	Limited sample size in an uncontrolled study.	CA209744
	Nephritis/renal dysfunction	%	3.6	0		
	Rash	%	10.7	13.6	Mostly grade 1-2 events.	
	Hypersensitivity	%	7.1	9.1	Results were similar between all treated and paediatric subjects. Underrepresentation of adult HL patients	

Abbreviations: AE adverse event; BICR blinded independent central review; Bv brentuximab vedotin; CI confidence interval; CMR complete metabolic response; DOR duration of response; HL Hodgkin Lymphoma; IMAE Immune-mediated adverse events; N nivolumab; NA not applicable; ORR objective response rate

Notes: Cohort R1 is low risk and cohort R2 is standard risk.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An extension of indication is requested based on a single-arm trial for children, adolescents and young adults with relapsed/refractory cHL after failure of first-line therapy. There are various second-line reinduction regimens, but there is no consensus on the optimal regimen. Lack of comparative data hampers causality assessment in single-arm trials.

Patients aged 5 to 30 years were included in the pivotal trial, in line with the peak incidence of cHL in children, adolescents and young adults (AYA). AYA patients are treated according to either adult or paediatric protocols pending on local and individual preferences (Flerlage et al, 2018; Townsend et al, 2019; Belsky et al, 2023). Therefore, the indication was restricted to children aged 5 years and older, adolescents and adults ≤30 years of age in line with the studied population and considering the clinical practice.

Despite the important uncertainties related to the single-arm study design, complex risk-based response adapted treatment schedule, small study size and the heterogeneous study population, the observed response rates in study CA209744 exceed the response rates reported for chemotherapy-based salvage regimens. The presented safety profile was consistent with that previously reported for

nivolumab and brentuximab vedotin in both cohorts (R1 and R2) in the all-treated and paediatric population. Importantly, the combination of nivolumab and brentuximab vedotin has a well-known safety profile and provides a tolerable treatment option for R/R cHL patients after failure of prior treatment without the toxicity commonly seen with chemotherapy (otherwise administered within this setting). Since treatment with a chemotherapy regimen is associated with premature ovarian failure, occurrence of second primary malignancies, and coronary diseases (Greve et al, 2023) a chemo-free regimen is an important benefit especially in young patients with cHL.

3.7.2. Balance of benefits and risks

The benefit-risk balance of the combination nivolumab with brentuximab vedotin for the treatment of paediatrics and adults aged 5-30 years old with R/R cHL after failure of first line treatment is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Opdivo in combination with brentuximab vedotin for the treatment of children 5 years of age and older, adolescents and adults up to 30 years of age with relapsed or refractory classical Hodgkin lymphoma after one prior line of therapy 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 for OPDIVO to include treatment of children 5 years of age and older, adolescents and adults up to 30 years of age with relapsed or refractory classical Hodgkin lymphoma after one prior line of therapy, based on results from study CA209744; a phase 2, open-label study of nivolumab + brentuximab vedotin for children, adolescents, and young adults with R/R CD30+ classical Hodgkin lymphoma after failure of first-line therapy, followed by brentuximab vedotin + bendamustine for participants with a suboptimal response. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 44.1 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.

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 PIP P/0138/204 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.