13 October 2016
EMA/CHMP/741329/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0012

Note

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

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List of abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
ADA	anti-drug antibody
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
BOR	Best overall response
Cavgss	Average steady state concentration
cHL	Classical Hodgkin lymphoma
CL	Clearance
CI	Confidence interval
CR	Complete remission
CT	computer tomography
DBL	Database lock
DOR	Duration of response
EORTC	European Organisation for Research and Treatment of Cancer
ECOG	European Cooperative Oncology Group
E-R	Exposure-response
FDG-PET	Fluorodeoxyglucose–positron emission tomography
FISH	Fluorescence in situ hybridization
HL	Hodgkin lymphoma
HRQoL	Health-related quality of life
ICE	Ifosfamide, carboplatin, and etoposide
IHC	Immunohistochemistry
IRRC	Independent Radiology Review Committee
IV	Intravenous
IVRS	interactive voice response system
IWG	Revised International Working Group criteria for Malignant Lymphoma
LPFT	Last patient first treatment
MRI	magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Not available
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PR	Partial remission
Q2W	Every 2 weeks
QLQ-C30	Quality of Life Questionnaire - 30 items
RCC	Renal cell carcinoma
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease, standard deviation
TILs	Tumour infiltrating lymphocytes
TRM	Transplant related mortality
TTR	Time to response
WT	weight

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 9 March 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL):

- after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or
- after at least two prior therapies in patients who are not candidates for ASCT,

for OPDIVO as monotherapy; as a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL, and update the safety and pharmacodynamic information. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.0. Moreover, the updated RMP version 5.0 has been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0040/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0040/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aranzazu Sancho-Lopez Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	9 March 2016
Start of procedure:	26 March 2016
CHMP Rapporteur Assessment Report	2 June 2016
CHMP Co-Rapporteur Assessment Report	20 May 2016
PRAC Rapporteur Assessment Report	25 May 2016
PRAC members comments	1 June 2016
Updated PRAC Rapporteur Assessment Report	2 June 2016
PRAC Outcome	9 June 2016
CHMP members comments	13 June 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 June 2016
Request for supplementary information (RSI)	23 June 2016
CHMP Rapporteur Assessment Report	18 August 2016
PRAC Rapporteur Assessment Report	19 August 2016
PRAC members comments	24 August 2016
Updated PRAC Rapporteur Assessment Report	25 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	5 September 2016
Updated CHMP Rapporteur Assessment Report	9 September 2016
2nd Request for supplementary information (RSI)	15 September 2016
CHMP Rapporteur Assessment Report	4 October 2016
PRAC Rapporteur Assessment Report	4 October 2016
CHMP members comments	4 October 2016
PRAC members comments	6 October 2016
Updated PRAC Rapporteur Assessment Report	7 October 2016
Updated CHMP Rapporteur Assessment Report	7 October 2016
Opinion	13 October 2016

2. Scientific discussion

2.1. Introduction

Hodgkin lymphoma (HL) is a lymphoid malignancy characterised by the presence of multinucleated Reed-Sternberg cells, which usually account for only 1% to 10% of the cells in the tumour tissue. Classical HL is characterized by small numbers of Reed-Sternberg cells within an extensive but ineffective inflammatory and immune-cell infiltrate. PD-L1 and PD-L2 is over expressed on Reed-Sternberg (R-S) cells.

The majority of cells in HL tumour tissue are a mixed infiltrate of various lymphoid cells, including effector and regulatory T-cells and macrophage. The updated 2008 WHO classification recognizes 2 histologic groups: nodular lymphocyte predominant, which accounts for about 5% of all HL cases and classical HL (cHL) which accounts for the remaining 95%.

There are marked geographic epidemiologic differences in HL with highly variable incidence rates due to age, ethnicity, region, prior infections and other factors. The median age HL is diagnosed in the US is 38 years, where the incidence is highest between 15 and 34 years, declines between ages 35 and 54, and increases again after 55 years. In 2015, the National Cancer Institute estimated that 9,050 men and women would be diagnosed with HL in the US and 1,150 would die of HL. The incidence in Europe is approximately 2.4 cases per 100,000 persons.

Hodgkin Lymphoma is a potentially curable disease in first line patients, with a cure rate of approximately 80% with the use of current therapies. For patients who relapse, treatment of choice consists of a chemotherapy regimen (different than that used in the first line) followed by high dose chemotherapy and autologous stem cell rescue with or without radiation therapy. After the initial multi-drug treatment regimen, approximately 5% to 10% of patients with HL suffer from primary refractory disease, defined as no response or progression within 90 days of treatment, and an additional 10 to 30% will relapse. In this population, an additional 10% to 30% will relapse. Once a subject undergoes ASCT and subsequently relapses, the outcomes are generally poor and efficacious therapeutic options are limited. The median OS of patients who relapse after ASCT was initially reported to be < 1 year; more recent data suggests that the median OS is evolving and may be closer to 2 years because of the availability of newer therapies like brentuximab vedotin (see Table 1).

Nivolumab is a programmed death receptor 1 (PD-1) blocking antibody that is currently approved as OPDIVO in the US, EU, Japan and other countries. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor on T cells and blocks its interaction with PD-L1 and PD-L2, releasing the T cells from PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. The genes encoding the PD-1 ligands, PD-L1 and PD-L2, are located on chromosome 9p24.1. Recurrent genetic alterations in 9p24.1 in R-S cell in cHL (including amplification, copy gain, and polysomy) and associated overexpression of PD-L1 and PD-L2 in R-S cells may have prognostic significance and may also be predictive of response to nivolumab.

The applicant applied for the following indication:

Classical Hodgkin lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL):

- after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin, or
- after at least two prior therapies in patients who are not candidates for ASCT.

The final agreed indication is as follows:

Classical Hodgkin lymphoma (cHL)

OPDIVO is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

.

Section 4.2

Posology

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

OPDIVO as monotherapy

The recommended dose of OPDIVO is 3 mg/kg nivolumab administered intravenously over 60 minutes every 2 weeks.

Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Table 1: Treatment of Relapsed or Refractory Hodgkin Lymphoma, after ASCT - Prospective Studies within the Past 15 Years

Agent(s)	Pub Date	Target Population	No. Treated	Prior ASCT	ORR (%)	CR (%)	PFS	DOR	Overall Survival
Brentuximab vedotin[1]	2012	Relapsed Refractory after ASCT	102	102	75%	34%	6 Month PFS: ~45% 1 Year PFS: ~35%	6.7 months	6 Month OS: ~95% 1 Year OS:89%
Panobinostat[2]	2012	Relapsed Refractory after ASCT	129	129	27%	4%	6 Month PFS: ~ 60% 1 Year PFS: ~ 40%	6.7 months (median)	6 Month OS: ~90% 1 Year OS: 78%
Everolimus[3]	2010	Relapsed Refractory HL	19	16	47%	5%	6 Month PFS: ~ 50% 1 Year PFS: ~ 26%	7.1 months (median)	6 Month OS: ~85% 1 Year OS: ~75%
Bortezomib[4]	2006	Relapsed Refractory HL with 2 prior regimens including stem cell transplant	14	13	7%	0	NS	NS	NS
Gemcitabine[5]	2004	Relapsed of chemo-refractory HL; received ≥ 2 prior different chemo regimens	27	16	22%	0	1 Year PFS: 24%	NS	1 Year OS: 64% 2 Year OS: 55%
Rituximab[6]	2003	Recurrent cHL with minimum 2 prior treatment regimens	22	18	22%	5%	NS	7.8 months (median)	NS

Abbreviations: ASCT = autologous stem cell transplant; cHL = classical Hodgkin lymphoma; CR = complete response; DOR = duration of response; HL = Hodgkin lymphoma; NS = not stated; ORR = objective response rate; OS = overall survival; PFS = progression free survival.

Note: Approximate (~) indicates estimation from Kaplan-Meier curve.

2.2. Non-clinical aspects

No new non-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, which is expected to biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), nivolumab is unlikely to result in a significant risk to the environment and as such a justification is provided for not submitting an Environmental Risk Assessment.

2.2.2. Discussion on non-clinical aspects

The applicant did not submit studies for the ERA. The justification was acceptable as nivolumab contains proteins as active pharmaceutical ingredient(s) and no risk to the environment is expected.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical data was submitted in this application. It is not anticipated to lead to a significant increase in environmental exposure to the use of nivolumab. Therefore, nivolumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2: Study Design / Key Study Characteristics - CA209205 and CA209039

Study No (Phase) / Subject Population / Study Design	Number of Treated Subjects	Nivo Dose / Regimen	Study Objectives
CA209205 (Phase 2) Subjects with cHL who received prior high-dose conditioning chemotherapy and failed ASCT and: (**Cohort A**) are brentuximab vedotin-naive (**Cohort B**) received brentuximab vedotin treatment as salvage after	Treated with Nivo monotherapy: N = 240 n = 63 Cohort A n = 80 Cohort B n = 97 in Cohort C Median extent of follow-up (months) as of DBL (05-Oct-2015): • Cohort A: 5.09 • Cohort B: 8.92 • Cohort C: 2.83 Median duration of study therapy was not reached in any cohort.	Nivo 3 mg/kg IV Q2W	Primary: To assess the clinical benefit of Nivo (ORR per IRRC), and defined as proportion of subjects achieving either a PR or CR according to the revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria). Secondary: To assess the: DOR per IRRC; CR and PR rate and duration of CR and PR per IRRC; ORR and DOR based on investigator assessment. Exploratory: To assess PFS per IRRC; OS; overall safety and tolerability of Nivo; investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy measures; characterize PK and

Study No (Phase) / Subject Population / Study Design	Number of Treated Subjects	Nivo Dose / Regimen	Study Objectives
failure of ASCT (**Cohort C**) received prior treatment with brentuximab vedotin at any time Open-label, non-comparative, multi-cohort, single-arm, study of Nivo in cHL. Subjects in Cohort C who achieved and maintained CR for 1 year could discontinue Nivo and restart Nivo upon progression.			immunogenicity; evaluate health related QoL and cancer specific QoL.
CA209039 (Phase 1) Relapsed/refractory hematologic malignancies (dose escalation phase with Nivo 1 and 3 mg/kg) followed by 4 expansion cohorts (multiple myeloma, B-cell, T-cell, and HL [any type]). All HL subjects had cHL. Open-label, multicenter, study of Nivo with a dose escalation phase followed by 4 expansion cohorts studying different types of hematologic malignancy. This study also included expansion cohorts of subjects with relapsed/refractory hematologic malignancies treated with Nivo + ipilimumab or lirilumab.	Expansion cohort treated with Nivo 3 mg/kg monotherapy in HL: N = 23 (all cHL) • n = 15 received prior brentuximab vedotin after failure of ASCT • n = 8 with alternative history of prior treatment Median extent of follow-up for all cHL subjects as of 11-Aug-2015 DBL was 23.3 months. Median duration of study therapy was 8.18 months.	Nivo 1-3 mg/kg IV Q2W (dose escalation) Nivo 3 mg/kg (mono-therapy expansion cohorts)	Primary: To establish the dose limiting toxicities, MTD, and recommended Phase 2 dose for Nivo up to a maximum dose of 3 mg/kg administered Q2W to subjects with relapsed/refractory hematologic malignancy Secondary (monotherapy cohorts): To characterize/assess the: PK of Nivo, preliminary antitumor activity of various dose levels of Nivo; immunogenicity of Nivo; potential association between PD-L1 expression on tumor cells as measured by immunohistochemistry and clinical efficacy measures Exploratory (monotherapy cohorts): To investigate/assess the: PD effects of Nivo on selected markers of immune modulation in peripheral blood and tumor samples; potential association between selected biomarker measures and clinical efficacy measures; OS up to 5 years.

CA209205: Interim CSR available based on a 05-Oct-2015 database lock.
CA209039: Interim CSR available based on an 11-Aug-2015 database lock.

2.3.2. Pharmacokinetics

The nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics, drug-drug interaction potential, and dose selection for phase 2/3 studies was well characterized and described in the marketing authorization procedure (see EPAR Opdivo).

Pharmacokinetics and pharmacodynamics of nivolumab in patients with relapsed or refractory classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) have been characterized with data from phase 2 Study CA209205 and Phase 1 Study CA209039.

These studies have been used to update the population pharmacokinetics model and to perform the exposure-response (E-R) (efficacy and safety) models (pharmacodynamic section).

Additionally, an immunogenicity analysis across studies CA209205 and CA209039 and an integrated immunogenicity analysis across tumour types were performed to assess the incidence and potential effect of immunogenicity on nivolumab treatment.

The recommended dose and schedule of nivolumab monotherapy for cHL is the same as that approved for melanoma, squamous non-small cell lung cancer (SQ NSCLC) and renal cell carcinoma (RCC) monotherapy: 3 mg/kg IV infusion over 60 minutes Q2W.

Special populations

Population Pharmacokinetic (PPK) Model

The PPK analysis was performed using data from 4 Phase 1 studies (MDX1106-01, MDX1106-03, ONO-4538-01 [CA209005], and CA209039), 4 Phase 2 studies (CA209010, ONO-4538-02, CA209063, and CA209205) and 3 Phase 3 studies (CA209017, CA209057, and CA209025), with a total of 1677 patients included. Data from Study CA209037 was not included as baseline serum albumin levels were not available in this study. Inclusion of data from studies CA209039 (cHL cohort treated with nivolumab monotherapy)* and CA209205 (all subjects treated with nivolumab monotherapy, cohort A+B+C)** allowed for the assessment of nivolumab PK in subjects with relapsed or refractory cHL. Bioanalytical methods used for quantifying nivolumab serum concentrations across the development program were cross-validated, thereby allowed merging of the exposure data for PPK analysis.

*CA209039: PPK (cHL: all cohorts; N = 23 patients); E-R efficacy (cHL: ASCT – brentuximab failure cohort; N = 15 patients); E-R safety (cHL: all cohorts; N = 23 patients). Nominal PK Sampling Schedule: W1D1: 0, 1, 3, 24-72, 168, 336, 504 h; W6D1: 0 h; W12D1: 0, 1 h; W20D1: 0 h; Q16W: 0 h (1st year); Q32W: 0 h (2nd year); FU visit 1 and 2.

**CA209205: PPK (cHL: all cohort; N=170 patients [239 subject treated; 206 subjects in PK database and 36 subjects excluded since only pre-treated sample were available for them]); E-R efficacy (cHL: failure of brentuximab following ASCT cohort; N=77 patients); E-R safety (cHL: all cohort; N=170 patients). Nominal PK Sampling Schedule: C1D1: predose: C3D1: predose: C7D1: predose; C13D1: predose; Q12C: predose; FU visit 1 and 2.

The PPK model was developed using a previously developed final model and included the effect of tumour type (cHL, RCC, NSCLC, or other), immunogenicity, and albumin on CL. The final model was a 2-compartment model with zero-order IV infusion input and first-order elimination with a proportional residual error model. The final PPK model included effects of baseline WT, eGFR, PS, ALB, tumour type, and anti-drug antibody (ADA) status on CL and baseline WT, sex, and NSCLC histology (using the combined SQ and NSQ groups) on VC.

Estimates of Individual Exposure

A summary of the individual PK parameter estimates obtained from the final PPK model for patients with solid tumours and cHL is provided in Table 3 and Table 4, respectively. A separate table summarising the individual measures of exposure for only the subjects enrolled in studies CA209205 and CA209039 (who received nivolumab 3 mg/kg Q2W) is provided in Table 5.

Table 3: Summary statistics of individual PK parameters for subjects with solid tumours (final model, n=1484)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Clearance [L/h]	0.01 (0.00454)	0.00923 (45.2)	0.00912 (0.00138, 0.0436)
Volume of the Central Cmt [L]	4.15 (1.28)	3.94 (30.8)	4.01 (0.141, 9.87)
Volume of the Peripheral Cmt [L]	3.89 (1.64)	3.64 (42.2)	3.65 (0.808, 22.1)
Volume of Distribution [L][a]	8.04 (2.32)	7.74 (28.8)	7.74 (2.5, 27.1)
Alpha half-life [h]	41.1 (10.7)	39.7 (26.1)	40.2 (2.56, 102)
Beta half-life [d]	28.6 (20.4)	26.2 (71.2)	26.1 (5.78, 554)

Source: M:\bms\nivolumab\010017\d1pk\tables\rtf\sumstat-exp-solid.rtf

[a] Volume of Distribution (L) at steady-state = Volume of the Central Compartment (L) + Volume of the Peripheral Compartment (L)

Table 4: Summary statistics of individual PK parameters for subjects with cHL (n=193)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Clearance [L/h]	0.00622 (0.00264)	0.00583 (42.4)	0.0057 (0.00292, 0.024)
Volume of the Central Cmt [L]	4.13 (0.992)	4.02 (24)	4.03 (2.56, 8.92)
Volume of the Peripheral Cmt [L]	3.65 (0.918)	3.55 (25.1)	3.47 (2.06, 8.35)
Volume of Distribution [L][a]	7.78 (1.63)	7.63 (20.9)	7.6 (4.72, 17.2)
Alpha half-life [h]	42.1 (8.05)	41.4 (19.1)	40.9 (26.3, 86.4)
Beta half-life [d]	40.6 (8.57)	39.6 (21.1)	40.6 (11.5, 64.4)

Source: M:\bms\nivolumab\010017\d1pk\tables\rtf\sumstat-exp-chl.rtf

[a] Volume of Distribution (L) at steady-state = Volume of the Central Compartment (L) + Volume of the Peripheral Compartment (L)

SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; Cmt: compartment

Table 5: Summary statistics of individual measures of nivolumab exposure for subjects enrolled in studies CA209039 and CA209205 (3mg/kg Q2W; n=193)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
C_{min1} (mcg/mL)	20.8 (4.86)	20.2 (23.3)	20.9 (4.73, 34.8)
C_{max1} (mcg/mL)	54.4 (8.48)	53.7 (15.6)	53.2 (15.7, 79.1)
C_{avg1} (mcg/mL)	27.9 (5.94)	27.2 (21.3)	28.2 (4.9,45.2)
C_{minss} (mcg/mL)	97.3 (27.7)	92.8 (28.5)	98.8 (25, 186)
C_{maxss} (mcg/mL)	152 (33.2)	148 (21.9)	152 (40.7, 246)
C_{avgss} (mcg/mL)	115 (29.7)	111 (25.8)	116 (29.6, 206)

Source: M:\bms\nivolumab\010017\d1pk\tables\rtf\s39_205-sumstat-exp-q2wk.rtf

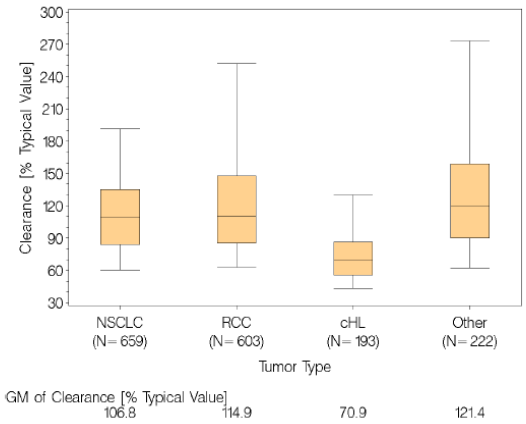
SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; Cmt: compartment; Cmin1: minimum concentration after first dose; Cmax1: maximum concentration after first dose; Cavg1: time-averaged concentration after first dose; Cminss: minimum concentration at steady state; Cmaxss: maximum concentration at steady state; Cavgss: time-averaged concentration at steady state

Evaluation of the Effect of Tumor Type on Nivolumab CL and Exposure

Nivolumab CL and exposure (measured as dose-normalized Cavgss, other exposure measurements are highly correlated with Cavgss) appear to be similar across NSCLC, RCC, and other tumour types as shown in Figure 1and Figure 2, suggesting that nivolumab PK is independent of tumour type for the types tested. cHL tumour type was associated with a 32% lower nivolumab CL relative to the reference value as

determined in NSCLC. The decrease in CL resulted in a 43% increase in nivolumab exposure (Cavgss) in cHL subjects.

Figure 1: Distribution of nivolumab clearance estimates by tumour type

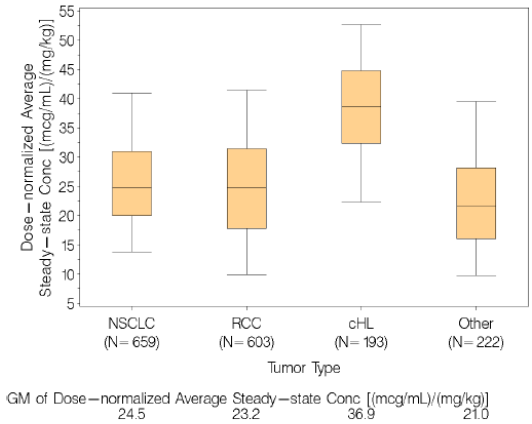


Source: M:\bms\nivolumab\010017\d1pk\graphs\pnghi\rpt-b-cl-typen3.png

Note: The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend from the 5th to 95th percentiles. The predicted GM is shown at the bottom of each boxplot for the various tumor type groups.

GM: geometric mean; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; cHL: classical Hodgkin Lymphoma

Figure 2: Distribution of nivolumab exposure (dose-normalised Cavgss) by tumour type following 3 mg/kg Q2W administration



Source: M:\bms\nivolumab\010017\d1pk\graphs\pnghi\rpt-b-dncavss-typen3.png

Note: The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend from the 5th to 95th percentiles. The predicted GM is shown at the bottom of each boxplot for the various tumor type groups.

GM: geometric mean; MEL: melanoma; NSCLC: non-small cell lung cancer; RCC, renal cell carcinoma; cHL: classical Hodgkin Lymphoma

Evaluation of the Effect of Immunogenicity on Nivolumab CL

The effects of immunogenicity on nivolumab PK in cHL subjects were consistent with previous analyses. Nivolumab clearance was approximately 13% greater in the presence of nivolumab ADA.

Evaluation of the Effect of Age on Nivolumab CL

Given the relatively younger age in the cHL population (median age of 35 years versus 61 years in the overall analysis population), the effect of age on nivolumab CL was also evaluated. The effects of age on nivolumab PK in cHL subjects were consistent with the previous analyses. Age did not affect nivolumab CL. There was no change in nivolumab CL with either an increase in age from the median value of 61 years

to the 95th percentile value of 77 years (increase of 0.5%), or with a decrease in age from the median value to the 5th percentile value of 31 years (decrease of 1.5%).

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

The recommended dose for nivolumab monotherapy is 3 mg/kg Q2W which has been investigated across melanoma, NSCLC, RCC, and cHL indications. Combined results from both CA209205 and CA209039 showed that patients with cHL after failure of ASCT and brentuximab treated with nivolumab 3 mg/kg Q2W had an ORR of 65.3% by IRRC assessment and 74.7% by investigator assessment. These results are further supported by E-R analyses, which examined the relationship between exposure and IRRC and investigator-assessed OR and the relationship between nivolumab exposure and probability of Grade 3+ drug-related adverse events. The E-R efficacy analysis showed a relationship between exposure and IRRC-assessed OR; however, the proportion of OR plateaued at greater exposures. Further, E-R analysis on investigator-assessed OR indicated that there was a flat relationship between nivolumab exposure and OR. No trend was observed between nivolumab exposure and the risk of G3+ DR-AEs, as nivolumab Cavgss was not a significant predictor of G3+ DR-AEs.

Immunogenicity Results from Study CA209205 and CA209039

A summary of the ADA assessments for nivolumab subjects on Study CA209205 and CA209039 who had evaluable ADA data at baseline and on treatment is presented in Table 6.

Table 6: Summary of anti-drug antibody assessment in study CA209205 and CA209039, based on 16-week definition for persistent positive - all nivolumab treated subjects with baseline and at least one post-baseline assessment

	Number of Subjects (%)		
	CA209205 Cohort A+B+C (N=159)	CA209039 cHL: all (N=19)	Total (N=178)
Baseline ADA Positive	7 (4.4)	3 (15.8)	10 (5.6)
ADA Positive	1 (0.6)	1 (5.3)	2 (1.1)
Persistent Positive	0	0	0
Only Last Sample Positive[a]	1 (0.6)	1 (5.3)	2 (1.1)
Other Positive	0	0	0
Neutralizing ADA Positive	0	0	0
ADA Negative	158 (99.4)	18 (94.7)	176 (98.9)

[a] See the narratives for Subject CA209205-8-103 and CA209039-2-96 in Appendix 7.4A of the CA209205 and CA205039 Interim CSR

There were 2 (1.1%) subjects who were ADA positive (last sample positive). No subject was considered persistent positive and no subjects were neutralizing ADA positive. The greatest titer value was 32.

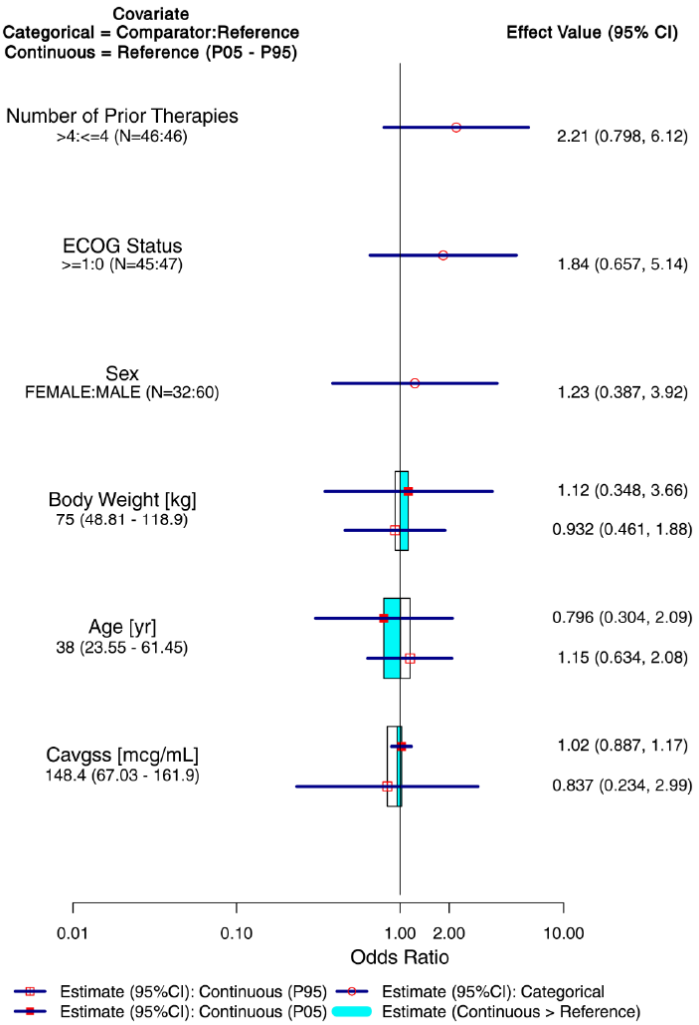
Among those two subjects who were ADA positive, one subject developed ADA after 2 doses (Day 29) of nivolumab, went on to experience a partial response, and continued treatment to Day 169. The other subject had stable disease while on study and ADA was developed after 18 doses of nivolumab (Day 249).

2.3.4. PK/PD modelling

The exposure-response relationship was characterized for nivolumab exposure (Cavgss) and OR using data from 92 previously treated subjects with cHL after failure of both ASCT and brentuximab vedotin treatment from studies CA209205 (cohort B) and CA209039 (ASCT-Bren failure cHL cohort), who had

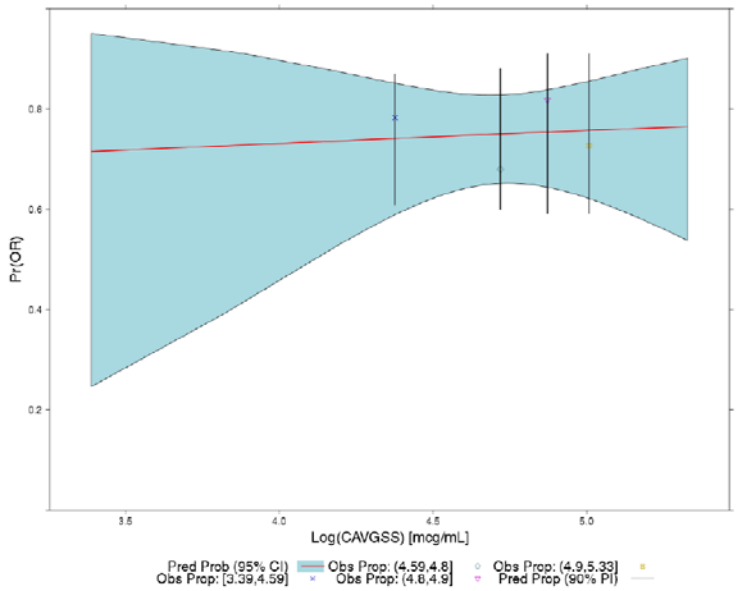
exposure data available. The relationship between the nivolumab exposure and OR was characterized using a logistic regression model that incorporated the effects of covariates that may modulate the E-R relationship. The covariate variables investigated in the E-R analysis of OR included age, baseline body weight, sex, PD-L1 status, chromosome 9p24.1, ECOG, number of prior therapies, and nivolumab Cavgss.

Figure 3: Effect of predictors on investigator-assessed OR (full model) for cHL (Studies CA209205 and CA209039)



A visual predictive check of the ER analysis on investigator-assessed OR (Figure 4) showed that the observed proportion of investigator-assessed OR at each quartile of log(Cavgss) lies well within the corresponding 90% PI (Pred proportion), obtained by simulation from the final model, indicating that the model is consistent with the observed data.

Figure 4: Visual predictive check of probability of investigator-assessed OR versus Cavgss in cHL (studies CA209205 and CA209039)



Program Source: M:\bms\nivolumab\010017\d1pkpd-eff\R\R-inv\cog-inv-plot-vpc.r

Source: M:\bms\nivolumab\010017\d1pkpd-eff\R\R-inv\plots\inv-vpc-response-cavgss.png

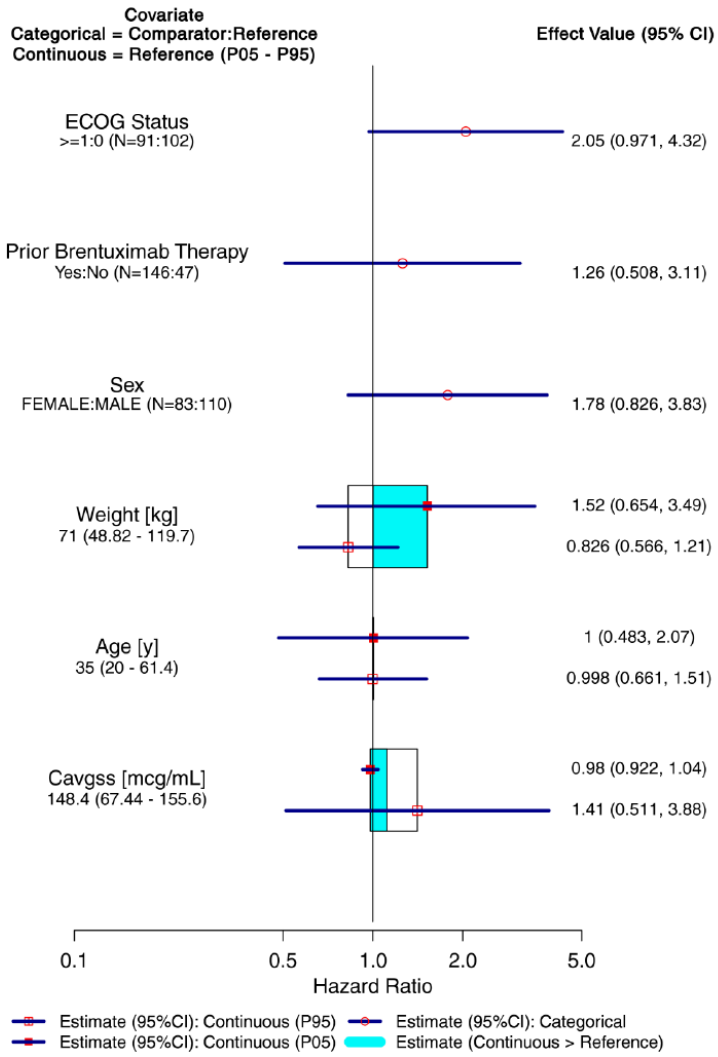
Note: Pred Prob (95% CI): lowess smooth line of the predicted probability and 95% CI; Obs: open symbols representing the observed proportion of OR responders for each log(Cavgss) quartile, plotted at the median of the quartile; Pred Proportion (90% PI): vertical bars represent the 90% PI corresponding to the observed proportion of OR.

Exposure-Response Analysis for Safety in cHL: G3+ DR-AEs

The E-R relationship for safety was characterized for nivolumab exposure (Cavgss) and G3+ DR-AEs in 193 previously treated subjects with cHL who failed ASCT with or without brentuximab vedotin in studies CA209205 (cohort A+B+C) and CA209039 (all cHL cohort), and who had exposure data available. The relationship between nivolumab exposure (Cavgss) and time to G3+ DR-AEs was described by a semi-parametric CPH model, and included assessments of the modulatory effect of covariates on the E-R relationship. Figure 5 presents the estimated effects of all of the predictor variables on the hazard of G3+ DR-AEs in the Full Model.

The covariate ECOG status was a significant predictor of experiencing a Grade 3+ DR-AE in the final model. A patient with ECOG score ≥ 1 is 2.14 times more likely to experience a Grade 3+ DR-AE compared to a subject with ECOG status of 0. Baseline weight, age, sex, and prior brentuximab therapy were not significant predictors of the risk of Grade 3+ DR-AEs in patients with cHL.

Figure 5: Estimated covariate effects of E-R (AE-DC/D) full model for cHL



2.3.5. Discussion on clinical pharmacology

Studies CA209205 and CA209039, conducted with cHL patients, have been used to update the population pharmacokinetics model and to performed the exposure-response (efficacy and safety) models. The ORR observed in this population and the flat E-R safety relationship support the recommended dose and schedule of nivolumab 3 mg/kg Q2W in the treatment of cHL after failure of ASCT and brentuximab.

In the population PK model, differences in clearance (cHL tumour type was associated with a 32% lower nivolumab CL relative to the reference value as determined in NSCLC) and beta half-life parameters have been observed between patients with solid tumours and patients with cHL. These differences could be attributed to the limited and sparse sampling in cHL. However, main reasons for these differences should be other factors in relations with performance status due to previous treatments or in relation with course of disease. It should be noted that the distribution of subjects with better PS (PS =0) was slightly different in subjects with cHL (52.8%) versus subjects with solid tumours (41.5%). Although nivolumab clearance was approximately 13% greater in the patients with worse PS (PS=1), the effect was not considered clinically meaningful because the magnitude was modest. Thus, while having a slightly different distribution of PS may contribute to the cHL tumour type effect, it may not fully explain the difference due to the relatively small effect. Age could be also a potential factor with impact on these results. It should

be noted that a relevant proportion of younger population in the population PK model has been included due to cHL population. However, age has been analysed as covariate and it is not expected to have a relevant impact on nivolumab PK. While a conclusive reason for lower CL (i.e., longer beta half-life in cHL) is unknown, it may be associated with the lower expression of PD-1 in cHL versus solid tumours. It has been reported that tumour-infiltrating T cells from cHL biopsy samples express lower levels of PD-1 compared to corresponding T cells from solid tumours. Because the target of nivolumab is PD-1 on T cells, these differences in PD-1 expression between tumour types may have an effect on the PK of nivolumab. Additionally, differences in CL among different diseases due to altered target cell binding have been observed for another monoclonal antibody.

The results of the E-R analysis indicated that the risk of AEs did not increase with increasing nivolumab exposure (represented by Cavgss). The findings are consistent with the overall safety profile of nivolumab, which has been shown to be well tolerated over a wide dose range (0.1 mg/kg to 10 mg/kg Q2W).

With current available safety data (266 treated cHL patients), this increase exposure does not seem to be clinically meaningful, although data cannot be considered fully conclusive. The safety profile following administration of nivolumab to subjects with cHL can be considered more or less similar to that observed in other tumour types, with the exception of the higher frequency of infusion-related reactions (acute infusion related and delayed hypersensitivity reactions) and pyrexia in cHL patients. A total of 30 (26 from CA209205 and 4 from CA209039) nivolumab treated subjects experienced hypersensitivity/infusion reactions and all were ADA negative. Thus, the presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions (see also clinical safety).

Hence, considering the currently available data, no specific recommendations about dose adjustments or specific precaution are required in cHL patients. However, the information included in the SmPC section 5.2 has been updated and highlights that the decrease in CL observed in cHL patients is not clinically meaningful.

Immunogenicity

Additionally, an immunogenicity analysis across studies CA209205 and CA209039 and an integrated immunogenicity analysis across tumour types were performed to assess the incidence and potential effect of immunogenicity on nivolumab treatment. Results in cHL population can be considered in line with the results observed previously in other type of tumour. Nivolumab has low immunogenic potential. There was no evidence of loss of efficacy in subjects with neutralizing antibodies.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology in cHL patients is considered to be adequately characterised.

2.4. Clinical efficacy

2.4.1. Dose response study

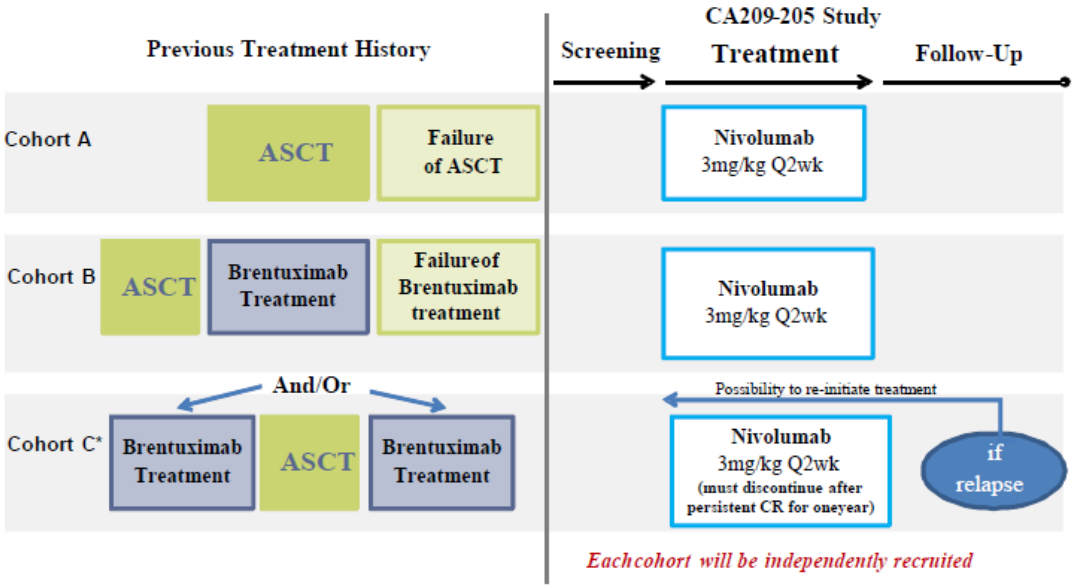
The dose of nivolumab 3 mg/kg Q2W was selected to be studied in heavily pretreated subjects with cHL. Combined results from both CA209205 and CA209039 showed that subjects with cHL after failure of ASCT and brentuximab treated with nivolumab 3 mg/kg Q2W had an ORR of 65.3% per IRRC and 74.7% per investigator. These results are further supported by ER analyses, which examined the relationship between exposure and IRRC and investigator-assessed OR and the relationship between nivolumab exposure and probability of ≥Grade 3 dose-related adverse events (AEs) (see PD section).

2.4.2. Main study(ies)

Study CA209205: Non-Comparative, Multi-Cohort, Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Classical Hodgkin Lymphoma (cHL) Subjects After Failure of Autologous Stem Cell Transplant (ASCT)

Methods

Figure 6: Study design schematic for CA209205



*Cohort C: Subjects who failed autologous stem cell transplant (ASCT) and who have received prior treatment with brentuximab vedotin at any timepoint. Patients may have brentuximab vedotin treatment only before ASCT and failure of ASCT. Patients may have failure of ASCT, and failure of post-ASCT brentuximab vedotin treatment. Or, patients may have brentuximab vedotin treatment before and after ASCT, and failure of brentuximab vedotin at enrollment.

Study participants

Key Inclusion Criteria

- Must have had a confirmed documentation of cHL after failure of ASCT or after failure of ASCT and brentuximab vedotin.
- Must have had at least 1 lesion that was >15 mm (1.5 cm) in the longest diameter on cross-sectional imaging and measureable in 2 perpendicular dimensions on CT (or MRI) and FDG avid by positron emission tomography (PET)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Must have received prior high-dose conditioning chemotherapy followed by ASCT as a part of salvage therapy for cHL.
- Cohort A: Subjects who were naïve to brentuximab vedotin treatment and who met 1 of the following criteria according to the 2007 IWG criteria:
    - Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT; or,
    - Documented relapsed disease (after CR) or disease progression (after PR or SD).

- Cohort B: Subjects who failed treatment with brentuximab vedotin which was administered following failure of ASCT, and who met one of the following criteria according to the 2007 IWG criteria:
    - Documented failure to achieve at least PR after the most recent treatment; or,
    - Documented relapse disease (after CR) or disease progression (after PR or SD).
- Cohort C: Subjects who failed ASCT and who received prior treatment (this included brentuximab vedotin treatment as an initial therapy or salvage therapy before ASCT, and/or brentuximab vedotin treatment after ASCT (eg, salvage and maintenance therapy after ASCT) with brentuximab vedotin at any time point, and who met one of the following criteria according to the 2007 IWG criteria:
    - Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT; or,
    - Documented failure to achieve at least PR after the most recent chemotherapy or radiation therapy; or,
    - Documented relapse disease (after CR) or disease progression (after PR or SD).
- A prior history of chemotherapy-induced or radiation-induced pulmonary toxicity required confirmation of diffusing capacity of the lung for carbon monoxide (DLCO) over 60% (adjusted for haemoglobin) by a pulmonary function test prior to study enrolment.

Submission of tumour tissue (formalin-fixed, paraffin-embedded [FFPE] tumour tissue block or 10 unstained slides) from a biopsy performed during screening or archival tumour tissue from a biopsy performed previously was mandatory.

Key exclusion criteria

- Known central nervous system lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma (HL).
- Active, known or suspected autoimmune disease.
- A condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease.
- Subjects with the following prior treatment history were excluded:
    - Prior treatment history with brentuximab vedotin administered before first ASCT, for Cohorts A and B.
    - ASCT ≤90 days prior to first dose of study drug.
    - Prior chemotherapy within 4 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin immunoconjugates (excluding brentuximab vedotin) within 10 weeks and brentuximab vedotin within 4 weeks or major surgery within 2 weeks prior to first dose of study drug.
    - Carmustine (BCNU) ≥600 mg/m^2 received as part of the pre-transplant conditioning regimen.
    - Prior radiation therapy within 3 weeks, or chest radiation ≤24 weeks prior to first dose of the study drug.

- Prior treatment with an anti-programmed death-1 (PD-1), anti-PD-L1, anti-programmed death ligand 2 (PD-L2), anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Prior allo-SCT

Treatments

Nivolumab at 3 mg/kg, on Day 1 of each 2-week cycle, was administered as an IV infusion over 60 minutes. Subjects were to be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. Dosing calculations were based on the subject's body weight.

Doses reductions and escalations of nivolumab were not permitted. Dose delays were permitted. Subjects were permitted to continue treatment beyond progression.

Subjects were permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids were permitted, even if >10 mg/day prednisone equivalents were administered. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) was permitted.

The following medications were prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids >10 mg daily prednisone equivalent
- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer)

Objectives

The primary objective was to assess the clinical benefit of nivolumab, as measured by ORR based on IRRC assessment, and defined as proportion of subjects achieving either a PR or CR according to the 2007 IWG criteria.

The secondary objectives of this study were to assess the duration of objective response (DOR) based on IRRC assessments; the CR rate and the duration of CR based on IRRC assessment; the PR rate and the duration of PR based on IRRC assessment; and the ORR and DOR based on investigator assessments.

Outcomes / endpoints

Objective	Endpoint	Endpoint Definition
Primary		
To assess the clinical benefit of nivolumab, as measured by ORR based on IRRC assessment, and defined as proportion of subjects achieving either a PR or CR according to the 2007 IWG criteria	ORR based on IRRC assessments	The ORR was defined as the number of subjects with a BOR of CR or PR, according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent therapy, whichever occurred first. allo-SCT and ASCT were considered as subsequent anticancer therapy. For subjects without documented progression or subsequent anticancer therapy, all available response designations contributed to the BOR determination. For subjects who continued treatment beyond progression, the BOR was determined based on response designations recorded up to the time of the initial 2007 IWG defined progression. The objective response was further characterized by TTR. TTR was defined as the time from first dosing date to the date of the first response, based on IRRC assessment.
Secondary		
To assess DOR based on IRRC assessments	DOR based on IRRC assessments	DOR was defined as the time from first response (CR or PR) to the date of the first documented tumor progression as determined by the investigator using the 2007 IWG criteria or death due to any cause, whichever occurred first For subjects who neither progressed nor died, the DOR was to be censored on the date of their last evaluable tumor assessment. Subjects who started subsequent therapy without a prior reported progression was to be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. This endpoint was only to be evaluated in subjects with a BOR of CR or PR.
To assess the CR rate and the duration of CR based on IRRC assessment	CR rate and duration of CR based on IRRC assessments	The CR rate was defined as the number of subjects with a BOR of CR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of CR was only evaluated in subjects with BOR of CR and was defined as the time from first documentation of CR (the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow (if required), whichever occurred later) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurred first. Censoring was applied as per DOR definition.
To assess the PR rate and the duration of PR based on IRRC assessment	PR rate and duration of PR based on IRRC assessments	The PR rate was defined as the number of subjects with a BOR of PR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of PR was only evaluated in subjects with BOR of PR and was defined as the time from first documentation of PR to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurred first. Censoring was applied as per DOR definition.
To assess the ORR and DOR, based on investigator assessments	ORR and DOR based on Investigator assessments	Investigator-assessed ORR and DOR were defined similarly as described for ORR and DOR per IRRC assessment above, but were assessed per investigator using the 2007 IWG criteria. It was further characterized by TTR, time to CR and duration of CR.
Exploratory[a]		
To assess the PFS based on IRRC assessment	PFS based on IRRC assessments	PFS was defined as the time from the first dosing date to the date of the first documented tumor progression as determined by the investigator (per 2007 IWG criteria) or death due to any cause whichever occurred first. Subjects who died without a reported prior progression were to be

		considered to have progressed on the date of their death. Subjects who did not progress or die were to be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die were to be censored on the date they were randomized. Subjects who received any subsequent anti-cancer therapy without a prior reported progression were to be censored at the last evaluable tumor assessment prior to or on the date of the initiation of the subsequent anti-cancer therapy.
To assess the OS	OS	OS was defined as the time from first dosing date to the date of death. For subjects without documentation of death, OS was censored on the last date the subject was known to have been alive.

Subjects were assessed for response by imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) at screening and on-treatment. Subjects received first dose of nivolumab on Day 1 of Week 1. On-treatment assessment began at Week 9 (± 7 days) after the start of nivolumab therapy and continued at Weeks 17, 25, 37, and 49 during the first year of treatment, then every 16 weeks (± 14 days) up to Week 97, continuing every 26 weeks (± 21 days) beyond Week 97, until disease progression was documented. [18F]Fluorodeoxyglucose positron emission tomography (FDG-PET) scan was required at screening, Weeks 17 and 25 in all subjects, and at Week 49 for subjects who did not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49, and to confirm CR.

The method used to assess PD-L1 expression was an exploratory assay employing the Dako 28-8 antibody, similar to the verified or validated versions used in other nivolumab solid tumor studies, but notably, differed in estimating the percentage of PD-L1 expression based on the number of any detected R-S cells rather than on a minimum of 100 malignant cells.

Sample size

The planned sample size for this study was to be approximately 320 treated subjects, placed into three cohorts of subjects: brentuximab vedotin-naïve (n=60; Cohort A), treatment with brentuximab vedotin after failure of ASCT (n=60; Cohort B) and treatment with brentuximab vedotin before or after ASCT (n=200; Cohort C).

The sample size for Cohorts A and B was determined based on 2 considerations: the ability to produce a confidence interval (CI), which would exclude an ORR of 20% that is not considered clinically relevant and providing sufficient information for a reliable understanding of the safety profile. The sample size for Cohort C was empirically determined to support expanded assessment of the benefit-risk profile of nivolumab in cHL through observation of less common safety events.

Randomisation

The investigator (or designee) enrolled subjects into the study via an IVRS. Since this was a single-arm study, all enrolled subjects who met eligibility criteria were treated with nivolumab at 3 mg/kg IV Q2W.

Blinding (masking)

This was an open-label study.

Statistical methods

Continuous variables were summarized using descriptive statistics, ie, median, minimum, maximum, and mean with standard deviations (SDs). Categorical variables were summarized by frequencies and percentages. Percentages were rounded and may not always add up to 100. Times to event distributions (ie, DOR, time to response [TTR], PFS, and OS) were estimated using Kaplan-Meier (K-M) methodology. When appropriate, the median along with 95% CI was provided using Brookmeyer and Crowley methodology. Rate at fixed time point (e.g., PFS at 6 months) was derived from the K-M estimate and

corresponding CI was derived based on Greenwood formula. CIs for binomial proportions were derived using the Clopper-Pearson method.

Analyses of efficacy endpoints were to be performed separately for each cohort. Efficacy data for Cohorts A was immature for efficacy analyses. Statistical methods used to analyse these endpoints were the same for both IRRC assessments and investigator assessments.

As sensitivity analyses for ORR, IRRC-assessed ORR and investigator-assessed ORR in response evaluable subjects instead of all treated subjects was summarized. Response evaluable subjects were subjects with i) a BOR of CR, PR, SD, or progressive disease (PD), ii) target lesion(s) assessed at baseline, and iii) at least 1 on-study time point with all baseline target lesion(s) assessed.

Sensitivity analyses were also performed for DOR based on both IRRC assessment and investigator assessment. Subjects who remained alive and had not progressed were censored on the last visit date prior to initiation of subsequent cancer therapy. The last visit date was the last date of dosing, evaluable tumour assessment or laboratory assessment, whichever occurred last.

To assess the association between baseline PD-L1 expression and response to nivolumab, the following analyses were performed for PD-L1 expression subgroups using a 1% cutoff and for the subgroup of subjects without quantifiable PD-L1 in all treated subjects:

- Frequency and percentage of BOR per IRRC.
- ORR per IRRC along with its 95% CI using the Clopper-Pearson method.

Subjects with an available tumour biopsy specimen tested for 9p24.1 status were classified into the following subgroups: polysomy positive, polysomy negative, copy gain positive, copy gain positive, amplification positive, amplification negative, and not evaluable for 9p24.1. To assess the association between baseline 9p24.1 alteration and response to nivolumab, the following analyses were performed for each of the subgroups based on 9p24.1 status:

- Frequency and percentage of BOR per IRRC.
- ORR per IRRC along with its 95% CI using the Clopper-Pearson method.

Results

Participant flow

Table 7: Subject status summary - All enrolled and treated subjects

	Cohort A	Cohort B	Cohort C	Cohort A+B+C
SUBJECTS ENROLLED				276
SUBJECTS NOT ENTERING THE TREATMENT PERIOD (%)				36 (13.0)
SUBJECTS ENTERING THE TREATMENT PERIOD	63	80	97	240
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	54 (85.7)	51 (63.8)	90 (92.8)	195 (81.3)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	9 (14.3)	29 (36.3)	7 (7.2)	45 (18.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)				
DISEASE PROGRESSION	4 (6.3)	13 (16.3)	3 (3.1)	20 (8.3)
STUDY DRUG TOXICITY	3 (4.8)	4 (5.0)	3 (3.1)	10 (4.2)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	2 (2.5)	1 (1.0)	3 (1.3)
LOST TO FOLLOW-UP	0	1 (1.3)	0	1 (0.4)
OTHER	2 (3.2)	8 (10.0)	0	10 (4.2)
NOT REPORTED	0	1 (1.3)	0	1 (0.4)
SUBJECTS CONTINUING IN THE STUDY (%) (A) (B)	61 (96.8)	74 (92.5)	94 (96.9)	229 (95.4)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (B)	2 (3.2)	5 (6.3)	3 (3.1)	10 (4.2)
NOT REPORTED (%)	0	1 (1.3)	0	1 (0.4)
REASON FOR NOT CONTINUING IN THE STUDY (%)				
DEATH	1 (1.6)	1 (1.3)	3 (3.1)	5 (2.1)
SUBJECT WITHDREW CONSENT	1 (1.6)	2 (2.5)	0	3 (1.3)
LOST TO FOLLOW-UP	0	2 (2.5)	0	2 (0.8)
PERSISTENT CR SUBJECTS (%) (C)	N.A.	N.A.	0	0

Percentages based on subjects entering period or continuing study
(A) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period.
(B) Subject status at end of treatment.
(C) Treated subjects in Cohort C who discontinued treatment following a CR of 1 year duration.

Recruitment

This study was conducted at 34 sites in 10 countries (Austria, Belgium, Canada, Czech Republic, Germany, Italy, Netherlands, Spain, United Kingdom, and US). The first patient's first treatment (FPFT) date was 26-Aug-2014 for Cohort B, 19-Sep-2014 for Cohort A, and 13-Feb-2015 for Cohort C, the LPFT date was 20-Feb-2015 for Cohort B, 06-Aug-2015 for Cohort A, and 03-Sep-2015 for Cohort C, and the LPLV date was 20-Aug-2015 for all 3 cohorts. Thus, the minimum follow-up relative to LPFT was 6 months, 2 weeks, and 0 day for Cohorts B, A, and C, respectively. The clinical DBL occurred on 05-Oct-2015 and the IRRC DBL occurred on 20-Oct-2015 for all 3 cohorts.

Conduct of the study

The original protocol for this study was dated 25-Apr-2014. The revised protocol incorporated 3 country-specific amendments, 3 global amendments, and 1 administrative letter. The major amendments were related to the how patients were managed for safety and assessed for disease progression during the trial. A change in the first assessment for early disease progression would occur at week 9, the first PET scan would occur at week 17 instead of week13, permitted subjects to continue treatment beyond investigator-assessed disease progression. At the request of a health authority, an IDMC was established for amendment 04. The administrative letter announced the change of duration of follow-up for the primary endpoint.

Baseline data

Table 8: Baseline demographic characteristics - All treated subjects

	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
AGE				
N	63	80	97	240
MEAN	36.3	38.7	36.2	37.1
MEDIAN	33.0	37.0	32.0	34.0
MIN , MAX	18 , 65	18 , 72	19 , 69	18 , 72
STANDARD DEVIATION	12.54	13.00	12.47	12.67
AGE CATEGORIZATION (%)				
< 65	62 (98.4)	77 (96.3)	94 (96.9)	233 (97.1)
>= 65 AND < 75	1 (1.6)	3 (3.8)	3 (3.1)	7 (2.9)
>= 75 AND < 85	0	0	0	0
>= 85	0	0	0	0
>= 75	0	0	0	0
>= 65	1 (1.6)	3 (3.8)	3 (3.1)	7 (2.9)
< 30	25 (39.7)	27 (33.8)	36 (37.1)	88 (36.7)
>= 30 AND < 45	21 (33.3)	28 (35.0)	33 (34.0)	82 (34.2)
>= 45 AND < 60	12 (19.0)	18 (22.5)	25 (25.8)	55 (22.9)
>= 60	5 (7.9)	7 (8.8)	3 (3.1)	15 (6.3)
GENDER (%)				
MALE	34 (54.0)	51 (63.8)	56 (57.7)	141 (58.8)
FEMALE	29 (46.0)	29 (36.3)	41 (42.3)	99 (41.3)
RACE (%)				
WHITE	54 (85.7)	71 (88.8)	83 (85.6)	208 (86.7)
BLACK OR AFRICAN AMERICAN	2 (3.2)	4 (5.0)	6 (6.2)	12 (5.0)
ASIAN	3 (4.8)	1 (1.3)	5 (5.2)	9 (3.8)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	2 (2.1)	2 (0.8)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0
OTHER	4 (6.3)	4 (5.0)	1 (1.0)	9 (3.8)
ETHNICITY (%)				
HISPANIC OR LATINO	3 (4.8)	1 (1.3)	1 (1.0)	5 (2.1)
NOT HISPANIC OR LATINO	30 (47.6)	63 (78.8)	54 (55.7)	147 (61.3)
NOT REPORTED	30 (47.6)	16 (20.0)	42 (43.3)	88 (36.7)

Table 9: Baseline disease characteristics - All treated subjects

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
PERFORMANCE STATUS (ECOG) [%]				
0	40 (63.5)	42 (52.5)	49 (50.5)	131 (54.6)
1	23 (36.5)	38 (47.5)	48 (49.5)	109 (45.4)
SMOKING STATUS				
CURRENT/FORMER	22 (34.9)	32 (40.0)	34 (35.1)	88 (36.7)
NEVER SMOKED	38 (60.3)	45 (56.3)	60 (61.9)	143 (59.6)
UNKNOWN	3 (4.8)	3 (3.8)	3 (3.1)	9 (3.8)
REGION				
US/CANADA	26 (41.3)	47 (58.8)	41 (42.3)	114 (47.5)
EUROPE	37 (58.7)	33 (41.3)	56 (57.7)	126 (52.5)
REST OF THE WORLD	0	0	0	0
DISEASE STAGE AT INITIAL DIAGNOSIS				
STAGE I	2 (3.2)	2 (2.5)	3 (3.1)	7 (2.9)
STAGE II	28 (44.4)	32 (40.0)	39 (40.2)	99 (41.3)
STAGE III	22 (34.9)	23 (28.8)	22 (22.7)	67 (27.9)
STAGE IV	10 (15.9)	22 (27.5)	31 (32.0)	63 (26.3)
NOT REPORTED	1 (1.6)	1 (1.3)	2 (2.1)	4 (1.7)
IPS AT INITIAL DIAGNOSIS				
0-2	19 (30.2)	18 (22.5)	13 (13.4)	50 (20.8)
>= 3	8 (12.7)	19 (23.8)	15 (15.5)	42 (17.5)
NOT REPORTED	36 (57.1)	43 (53.8)	69 (71.1)	148 (61.7)
DISEASE STAGE AT STUDY ENTRY				
STAGE I	1 (1.6)	1 (1.3)	2 (2.1)	4 (1.7)
STAGE II	20 (31.7)	11 (13.8)	20 (20.6)	51 (21.3)
STAGE III	17 (27.0)	14 (17.5)	17 (17.5)	48 (20.0)
STAGE IV	24 (38.1)	54 (67.5)	58 (59.8)	136 (56.7)
NOT REPORTED	1 (1.6)	0	0	1 (0.4)
B-SYMPTOMS AT INITIAL DIAGNOSIS				
PRESENT	34 (54.0)	46 (57.5)	49 (50.5)	129 (53.8)
ABSENT	28 (44.4)	34 (42.5)	42 (43.3)	104 (43.3)
NOT REPORTED	1 (1.6)	0	6 (6.2)	7 (2.9)
BULKY DISEASE AT BASELINE				
YES	10 (15.9)	17 (21.3)	21 (21.6)	48 (20.0)
NO	53 (84.1)	63 (78.8)	76 (78.4)	192 (80.0)

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
EXTRA LYMPHATIC INVOLVEMENT AT BASELINE				
YES	24 (38.1)	36 (45.0)	39 (40.2)	99 (41.3)
NO	39 (61.9)	44 (55.0)	58 (59.8)	141 (58.8)
BONE MARROW INVOLVEMENT AT BASELINE				
YES	3 (4.8)	8 (10.0)	7 (7.2)	18 (7.5)
NO	60 (95.2)	72 (90.0)	90 (92.8)	222 (92.5)
TIME FROM INITIAL DIAGNOSIS TO FIRST TRANSPLANT (YEARS)				
N	62	80	97	239
MEDIAN (MIN - MAX)	1.62 (0.6 - 24.5)	1.34 (0.1 - 15.7)	1.63 (0.5 - 14.5)	1.50 (0.1 - 24.5)
TIME FROM MOST RECENT TRANSPLANT TO FIRST DOSE OF STUDY THERAPY (YEARS)				
N	63	80	97	240
MEDIAN (MIN - MAX)	1.03 (0.3 - 18.2)	3.37 (0.2 - 19.0)	1.70 (0.2 - 17.0)	2.02 (0.2 - 19.0)
TIME FROM MOST RECENT TRANSPLANT TO FIRST SUBSEQUENT THERAPY (MONTHS)				
N	63	80	97	240
MEDIAN (MIN - MAX)	8.54 (0.0 - 136.9)	12.85 (0.0 - 159.0)	8.15 (0.0 - 200.9)	9.33 (0.0 - 200.9)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE OF STUDY THERAPY (YEARS)				
N	62	80	97	239
MEDIAN (MIN - MAX)	3.02 (1.0 - 30.8)	6.15 (1.3 - 25.1)	3.41 (1.0 - 24.9)	4.43 (1.0 - 30.8)

Abbreviation: IPS = International Prognostic Score.

Table 10: Prior cancer therapy - All treated subjects

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED (A)				
1	2 (3.2)	0	0	2 (0.8)
2	29 (46.0)	0	6 (6.2)	35 (14.6)
3	19 (30.2)	19 (23.8)	28 (28.9)	66 (27.5)
4	10 (15.9)	22 (27.5)	33 (34.0)	65 (27.1)
>= 5	3 (4.8)	39 (48.8)	30 (30.9)	72 (30.0)
MEDIAN (MIN, MAX)	3 (1, 5)	4 (3, 15)	4 (2, 9)	4 (1, 15)
FIRST LINE REGIMEN				
ABVD	45 (71.4)	68 (85.0)	83 (85.6)	196 (81.7)
ESCALATED BEACOPP	1 (1.6)	0	2 (2.1)	3 (1.3)
OTHER	17 (27.0)	12 (15.0)	12 (12.4)	41 (17.1)
SECOND LINE REGIMEN				
ABVD	4 (6.3)	2 (2.5)	4 (4.1)	10 (4.2)
ESCALATED BEACOPP	2 (3.2)	2 (2.5)	2 (2.1)	6 (2.5)
DHAP	11 (17.5)	9 (11.3)	7 (7.2)	27 (11.3)
ESHAP	5 (7.9)	6 (7.5)	5 (5.2)	16 (6.7)
ICE	13 (20.6)	28 (35.0)	23 (23.7)	64 (26.7)
GVD	0	1 (1.3)	2 (2.1)	3 (1.3)
IGEV	2 (3.2)	8 (10.0)	18 (18.6)	28 (11.7)
OTHER	23 (36.5)	24 (30.0)	34 (35.1)	81 (33.8)
NUMBER OF PRIOR ASCT				
1	62 (98.4)	74 (92.5)	97 (100.0)	233 (97.1)
>= 2	1 (1.6)	6 (7.5)	0	7 (2.9)
TYPE OF ASCT PREPARATIVE REGIMEN RECEIVED FOR MOST RECENT PRIOR TRANSPLANT				
ANY PREPARATIVE REGIMEN	35 (55.6)	51 (63.8)	47 (48.5)	133 (55.4)
BEAM	15 (23.8)	22 (27.5)	15 (15.5)	52 (21.7)
CBV	3 (4.8)	5 (6.3)	4 (4.1)	12 (5.0)
SUBJECTS WITH OTHER PREPARATIVE REGIMEN	17 (27.0)	24 (30.0)	28 (28.9)	69 (28.8)

BEST RESPONSE TO REGIMEN PRIOR TO MOST RECENT ASCT				
CR OR PR	52 (82.5)	71 (88.8)	79 (81.4)	202 (84.2)
SD	5 (7.9)	3 (3.8)	8 (8.2)	16 (6.7)
RELAPSE/PD	5 (7.9)	4 (5.0)	8 (8.2)	17 (7.1)
UNABLE TO DETERMINE/NOT REPORTED	1 (1.6)	2 (2.5)	2 (2.1)	5 (2.1)
RESPONSE AT MOST RECENT ASCT				
CR OR PR	35 (55.6)	50 (62.5)	60 (61.9)	145 (60.4)
SD	5 (7.9)	6 (7.5)	8 (8.2)	19 (7.9)
RELAPSE/PD	7 (11.1)	4 (5.0)	16 (16.5)	27 (11.3)
UNABLE TO DETERMINE/NOT REPORTED	16 (25.4)	20 (25.0)	13 (13.4)	49 (20.4)
BEST REPOSNSE TO MOST RECENT ASCT				
CR OR PR	36 (57.1)	29 (36.3)	42 (43.3)	107 (44.6)
SD	2 (3.2)	6 (7.5)	3 (3.1)	11 (4.6)
RELAPSE/PD	20 (31.7)	37 (46.3)	43 (44.3)	100 (41.7)
UNABLE TO DETERMINE/NOT REPORTED	5 (7.9)	8 (10.0)	9 (9.3)	22 (9.2)
BEST RESPONSE TO REGIMEN POST MOST RECENT ASCT				
CR OR PR	6 (9.5)	37 (46.3)	31 (32.0)	74 (30.8)
SD	1 (1.6)	10 (12.5)	11 (11.3)	22 (9.2)
RELAPSE/PD	2 (3.2)	25 (31.3)	28 (28.9)	55 (22.9)
UNABLE TO DETERMINE/NOT REPORTED	54 (85.7)	8 (10.0)	27 (27.8)	89 (37.1)
TIME FROM COMPLETION OF MOST RECENT PRIOR REGIMEN TO TREATMENT				
< 3 MONTHS	7 (11.1)	44 (55.0)	46 (47.4)	97 (40.4)
3-6 MONTHS	7 (11.1)	18 (22.5)	16 (16.5)	41 (17.1)
> 6 MONTHS	49 (77.8)	18 (22.5)	35 (36.1)	102 (42.5)
PRIOR SURGERY RELATED TO CANCER				
YES	34 (54.0)	46 (57.5)	41 (42.3)	121 (50.4)
NO	29 (46.0)	34 (42.5)	56 (57.7)	119 (49.6)
PRIOR RADIOTHERAPY				
YES	36 (57.1)	59 (73.8)	66 (68.0)	161 (67.1)
NO	27 (42.9)	21 (26.3)	31 (32.0)	79 (32.9)

	Number of Subjects (%)			
	Cohort A N = 63	Cohort B N = 80	Cohort C N = 97	Cohort A+B+C N = 240
IMMUNOTHERAPY BY MONOCLONAL ANTIBODIES	8 (12.7)	80 (100.0)	97 (100.0)	185 (77.1)
BEVACIZUMAB	1 (1.6)	0	0	1 (0.4)
BRENTUXIMAB VEDOTIN	0	80 (100.0)	97 (100.0)	177 (73.8)
INVESTIGATIONAL ANTINEOPLASTIC	1 (1.6)	4 (5.0)	0	5 (2.1)
RITUXIMAB	6 (9.5)	14 (17.5)	9 (9.3)	29 (12.1)
STEROID	40 (63.5)	45 (56.3)	60 (61.9)	145 (60.4)
DEXAMETHASONE	28 (44.4)	31 (38.8)	30 (30.9)	89 (37.1)
METHYLPREDNISOLONE	6 (9.5)	8 (10.0)	12 (12.4)	26 (10.8)
PREDNISOLONE	8 (12.7)	11 (13.8)	8 (8.2)	27 (11.3)
PREDNISONE	12 (19.0)	18 (22.5)	31 (32.0)	61 (25.4)
CHEMOTHERAPY - OTHER THAN ANTHRACYCLINES	63 (100.0)	80 (100.0)	97 (100.0)	240 (100.0)
BENDAMUSTINE	4 (6.3)	26 (32.5)	21 (21.6)	51 (21.3)
BLEOMYCIN	63 (100.0)	77 (96.3)	95 (97.9)	235 (97.9)
BUSULFAN	2 (3.2)	1 (1.3)	0	3 (1.3)
CARBOPLATIN	20 (31.7)	37 (46.3)	32 (33.0)	89 (37.1)
CARMUSTINE	14 (22.2)	5 (6.3)	16 (16.5)	35 (14.6)
CHLORAMBUCIL	2 (3.2)	4 (5.0)	5 (5.2)	11 (4.6)
CISPLATIN	35 (55.6)	40 (50.0)	42 (43.3)	117 (48.8)
CYCLOPHOSPHAMIDE	21 (33.3)	22 (27.5)	26 (26.8)	69 (28.8)
CYTARABINE	33 (52.4)	28 (35.0)	35 (36.1)	96 (40.0)
DACARBAZINE	51 (81.0)	72 (90.0)	88 (90.7)	211 (87.9)
ETOPOSIDE	47 (74.6)	65 (81.3)	72 (74.2)	184 (76.7)
FLUDARABINE	0	1 (1.3)	0	1 (0.4)
FOTEMUSTINE	1 (1.6)	0	0	1 (0.4)
GEMCITABINE	20 (31.7)	54 (67.5)	55 (56.7)	129 (53.8)
IFOSFAMIDE	35 (55.6)	59 (73.8)	73 (75.3)	167 (69.6)
IRINOTECAN	0	1 (1.3)	0	1 (0.4)
LOMUSTINE	1 (1.6)	1 (1.3)	3 (3.1)	5 (2.1)
MELPHALAN	15 (23.8)	10 (12.5)	17 (17.5)	42 (17.5)
METHOTREXATE	1 (1.6)	2 (2.5)	6 (6.2)	9 (3.8)
NITROGEN MUSTARD	0	5 (6.3)	1 (1.0)	6 (2.5)
OXALIPLATIN	1 (1.6)	3 (3.8)	2 (2.1)	6 (2.5)
PACLITAXEL	0	1 (1.3)	0	1 (0.4)
PROCARBAZINE	21 (33.3)	23 (28.8)	23 (23.7)	67 (27.9)
THIOTEPA	0	2 (2.5)	1 (1.0)	3 (1.3)
TROFOSFAMIDE	0	1 (1.3)	1 (1.0)	2 (0.8)
VINBLASTINE	56 (88.9)	72 (90.0)	91 (93.8)	219 (91.3)

VINCRISTINE	21 (33.3)	24 (30.0)	27 (27.8)	72 (30.0)
VINORELBINE	10 (15.9)	39 (48.8)	42 (43.3)	91 (37.9)
CHEMOTHERAPY - ANTHRACYCLINES	63 (100.0)	80 (100.0)	97 (100.0)	240 (100.0)
DOXORUBICIN	63 (100.0)	79 (98.8)	97 (100.0)	239 (99.6)
DOXORUBICIN LIPOSOMAL	0	12 (15.0)	3 (3.1)	15 (6.3)
EPIRUBICIN	2 (3.2)	4 (5.0)	6 (6.2)	12 (5.0)
MITOXANTRONE	0	1 (1.3)	4 (4.1)	5 (2.1)
KINASE INHIBITORS	0	5 (6.3)	0	5 (2.1)
IDELALISIB	0	1 (1.3)	0	1 (0.4)
INVESTIGATIONAL ANTINEOPLASTIC	0	2 (2.5)	0	2 (0.8)
SORAFENIB	0	2 (2.5)	0	2 (0.8)
IMMUNOMODULARY DERIVATIVES	1 (1.6)	10 (12.5)	3 (3.1)	14 (5.8)
ARSENIC TRIOXIDE	0	1 (1.3)	0	1 (0.4)
LENALIDOMIDE	1 (1.6)	7 (8.8)	3 (3.1)	11 (4.6)
THALIDOMIDE	0	2 (2.5)	0	2 (0.8)
RADIOIMMUNOTHERAPY	0	1 (1.3)	0	1 (0.4)
INVESTIGATIONAL ANTINEOPLASTIC	0	1 (1.3)	0	1 (0.4)
OTHER	3 (4.8)	21 (26.3)	4 (4.1)	28 (11.7)
BORTEZOMIB	0	1 (1.3)	0	1 (0.4)
EVEROLIMUS	2 (3.2)	15 (18.8)	2 (2.1)	19 (7.9)
INVESTIGATIONAL ANTINEOPLASTIC	2 (3.2)	8 (10.0)	2 (2.1)	12 (5.0)
INVESTIGATIONAL IMMUNOMODULATING AGENT	0	1 (1.3)	0	1 (0.4)
INVESTIGATIONAL IMMUNOTHERAPY	0	1 (1.3)	0	1 (0.4)
MESNA	1 (1.6)	1 (1.3)	1 (1.0)	3 (1.3)
SIROLIMUS	0	1 (1.3)	0	1 (0.4)
T CELL INFUSION	0	1 (1.3)	0	1 (0.4)
VORINOSTAT	0	2 (2.5)	1 (1.0)	3 (1.3)

All subjects in Cohort B received at least 3 prior systemic regimens. All subjects received at least 1 prior systemic regimen before ASCT and all but 1 subject received at least 1 prior systemic regimen after brentuximab vedotin. Only one-third of the subjects had at least 1 systemic regimen between ASCT and brentuximab vedotin.

Table 11: Timing of prior systemic regimen relative of ASCT and brentuximab vedotin - Cohort B - All treated subjects

	Therapy Timing Relative to ASCT and Brentuximab			
	BEFORE ASCT N = 80	BETWEEN ASCT AND BREN N = 80	AFTER BREN N = 80	TOTAL N = 80
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED				
0	0	50 (62.5)	1 (1.3)	0
1	4 (5.0)	14 (17.5)	36 (45.0)	0
2	49 (61.3)	8 (10.0)	22 (27.5)	0
3	15 (18.8)	2 (2.5)	9 (11.3)	19 (23.8)
4	8 (10.0)	0	6 (7.5)	22 (27.5)
>= 5	4 (5.0)	6 (7.5)	6 (7.5)	39 (48.8)

Timing Relative to most recent ASCT - Brentuximab sequence

Numbers analysed

Within each cohort the following key populations were defined.

- Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- Treated subjects: All subjects who received at least one dose of nivolumab. This is the primary population for efficacy and safety.
- Response evaluable subjects: All treated subjects who have baseline and at least one on-study evaluable tumour measurement. Response evaluable subjects were those subjects with (i) a BOR of CR, PR, SD or PD, (ii) target lesion(s) assessed at baseline, and (iii) at least 1 on-study timepoint with all baseline target lesion(s) assessed.

Efficacy analyses were performed for treated subjects in Cohort B (Table 12).

Table 12: Analysis populations

Population	Cohort A	Cohort B	Cohort C	Cohort A+B+C
Enrolled subjects: All subjects who signed an ICF and were registered into the IVRS.	NA	NA	NA	276
Treated population: All subjects who received at least 1 dose of nivolumab. This is the primary population for efficacy and safety.	63	80	97	240
Response-evaluable subjects per IRRC: Subjects with (i) a BOR of CR, PR, SD, or PD, (ii) target lesion(s) assessed at baseline, and (iii) at least 1 on-study timepoint with all baseline target lesion(s) assessed.	NA	74	NA	NA
All responders per IRRC: All subjects with a BOR of CR or PR	NA	53	NA	NA
All responders per investigator: All subjects with a BOR of CR or PR	NA	58	NA	NA
PD-L1 tested subjects: All subjects who had a tumor tissue sample available for assessment of PD-L1 expression.	51	76	55	182
PD-L1 quantifiable subjects: All treated subjects with quantifiable PD-L1 expression at baseline	36	63	31	130
Outcomes research subjects: All treated subjects who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment				
EORTC QLQ-C30 subjects	49	64	52	165
EQ-5D subjects	49	62	51	162
Immunogenicity subjects: All nivolumab-treated subjects with baseline and at least 1 post baseline assessment for ADA	42	73	44	159

Abbreviations: ADA = antidrug antibody; BOR = best overall response; CR = complete remission; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life; Questionnaire-C30; EQ-5D = a standardized instrument for use as a measure of health outcome; ICF = informed; consent form; IVRS = interactive voice response system; NA = not applicable; PD-L1 = programmed death ligand-1.

Outcomes and estimation

Primary endpoint: ORR

Treatment with nivolumab resulted in a rate of IRRC-assessed ORR= 66.3% in Cohort B and 72.5% in Investigator-assessed ORR. Concordance rate between IRRC and investigators for objective response was 76.3%. The CR rate was 8.8% (7/80) per IRRC and 27.5% (22/80) per investigators.

Table 13: Summary of best overall response per IRRC and investigator - Cohort B - All treated subjects

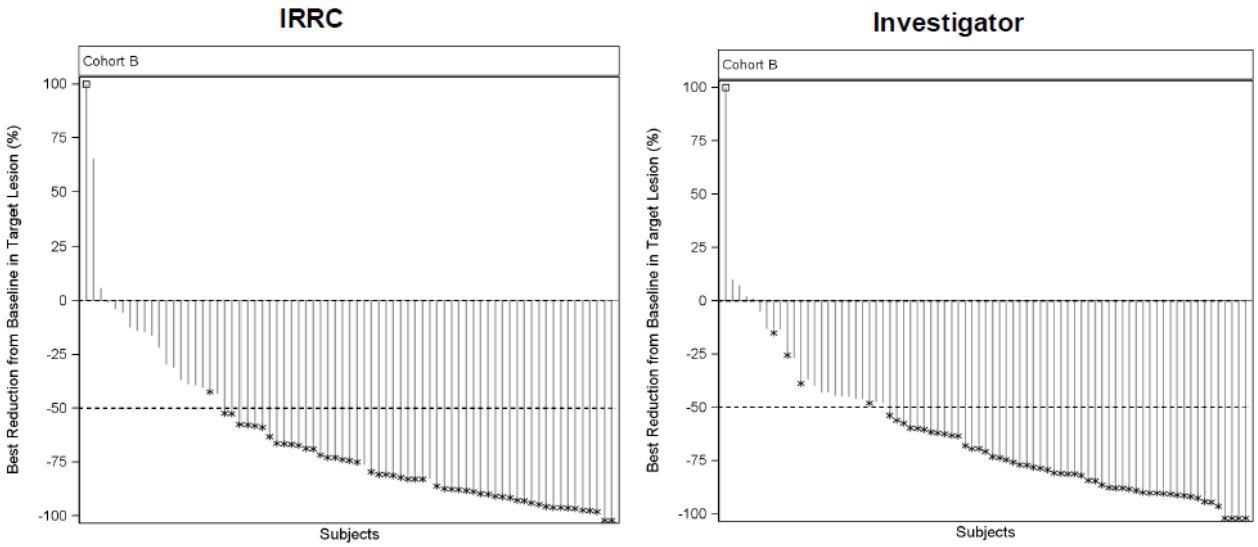
	Cohort B, N=80	
	IRRC	Investigator
Best Overall Response[a] (BOR), n (%)		
Complete Remission (CR)	7 (8.8)	22 (27.5)
(95% CI)	(3.6, 17.2)	(18.1, 38.6)
Partial Remission (PR)	46 (57.5)	36 (45.0)
(95% CI)	(45.9, 68.5)	(33.8, 56.5)
Stable Disease (SD)	18 (22.5)	18 (22.5)
Relapsed or Progressive Disease (PD)	6 (7.5)	3 (3.8)
Unable to Determine (UTD)	3 (3.8)	1 (1.3)
Objective Response Rate (ORR)[b], n (%)	**53 (66.3)**	**58 (72.5)**
(95% CI)	(54.8, 76.4)	(61.4, 81.9)

[a] Per Revised International Working Group Criteria for Malignant Lymphoma (2007)

[b] CR+PR, confidence interval based on the Clopper and Pearson method

In a sensitivity analysis, the IRRC-assessed ORR in response evaluable subjects in Cohort B (n=74) was 71.6% (95% CI: 59.9, 81.5).

Figure 7: Waterfall plot of best changes in target lesion per IRRC - Cohort B - All response evaluable subjects



Response Evaluable: Subjects with i) a BOR of CR, PR, SD or PD, ii) target lesion(s) assessed at baseline, and iii) at least one on-study timepoint with all baseline target lesion(s) assessed.
Negative/positive value means maximum tumor reduction /minimum tumor increase
Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy
Horizontal reference line indicates the 50% reduction consistent with a response per revised 2007 IWG criteria
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%

Response Evaluable: Subjects with i) a BOR of CR, PR, SD or PD, ii) target lesion(s) assessed at baseline, and iii) at least one on-study timepoint with all baseline target lesion(s) assessed.
Negative/positive value means maximum tumor reduction /minimum tumor increase
Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy
Horizontal reference line indicates the 50% reduction consistent with a response per revised 2007 IWG criteria
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%

Duration of response (DOR)

Objective responses achieved with nivolumab in Cohort B were durable; 62.3% (33/53) of IRRC-assessed responders and 67.2% (39/58) of investigator-assessed responders had their response ongoing at the

data cut-off date. Of the 20 responders not considered to have ongoing response (IRRC-assessed), 11 had events of progression (n=10) or death (n=1), 5 had subsequent anti-cancer therapy (4 underwent SCT), 3 were excluded due to censoring prior to 14 weeks of the clinical data cut-off date (2 still on treatment), and 1 decided to discontinue the study.

In order to account for non-uniform and infrequent tumor assessment schedules, a sensitivity analysis was performed on DOR by censoring subjects who remained alive and did not progress on the last visit date prior to initiation of subsequent cancer therapy. In this analysis, the median DOR per IRRC was not reached.

Table 14: Duration of response per IRRC and per investigator - Cohort B - All responders

	Cohort B Responders	
	IRRC N=53	Investigator N=58
DOR (Months)		
Min, Max[a]	0.0+, 9.5+	0.0+, 9.5+
Median (95% CI)[b]	7.79 (6.64, N.A.)	9.10 (6.74, N.A.)
N Event/N Response (%)	11/53 (20.8)	9/58 (15.5)
Duration of CR (Months)[c]		
Min, Max[a]	0.7+, 4.6	0.0+, 8.7
Median (95% CI)[b]	4.63 (N.A., N.A.)	8.74 (N.A., N.A.)
N Event/N Response (%)	1/7 (14.3)	1/22 (4.5)
Duration of PR (Months)[d]		
Min, Max[a]	0.0+, 9.5+	0.0+, 7.8
Median (95% CI)[b]	7.79 (6.64, N.A.)	7.79 (6.74, 7.79)
N Event/N Response (%)	10/46 (21.7)	8/36 (22.2)
Number of Subjects with DOR of at least (%)		
3 Months	38 (71.7)	37 (63.8)
6 Months	14 (26.4)	13 (22.4)
Subjects with Ongoing Response[e]	33/53 (62.3)	39/58 (67.2)
Subjects with Ongoing Response of Duration of ≥4 Months[e]	20/53 (37.7)	21/58 (36.2)
Subjects with Ongoing Response of Duration of ≥6 Months[e]	9/53 (17.0)	10/58 (17.2)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete remission; DOR = duration of response; IRRC = Independent Radiologic Review Committee; N.A. = not available, minimum follow-up not reached; PR = partial response.

[a] Symbol + indicates a censored value

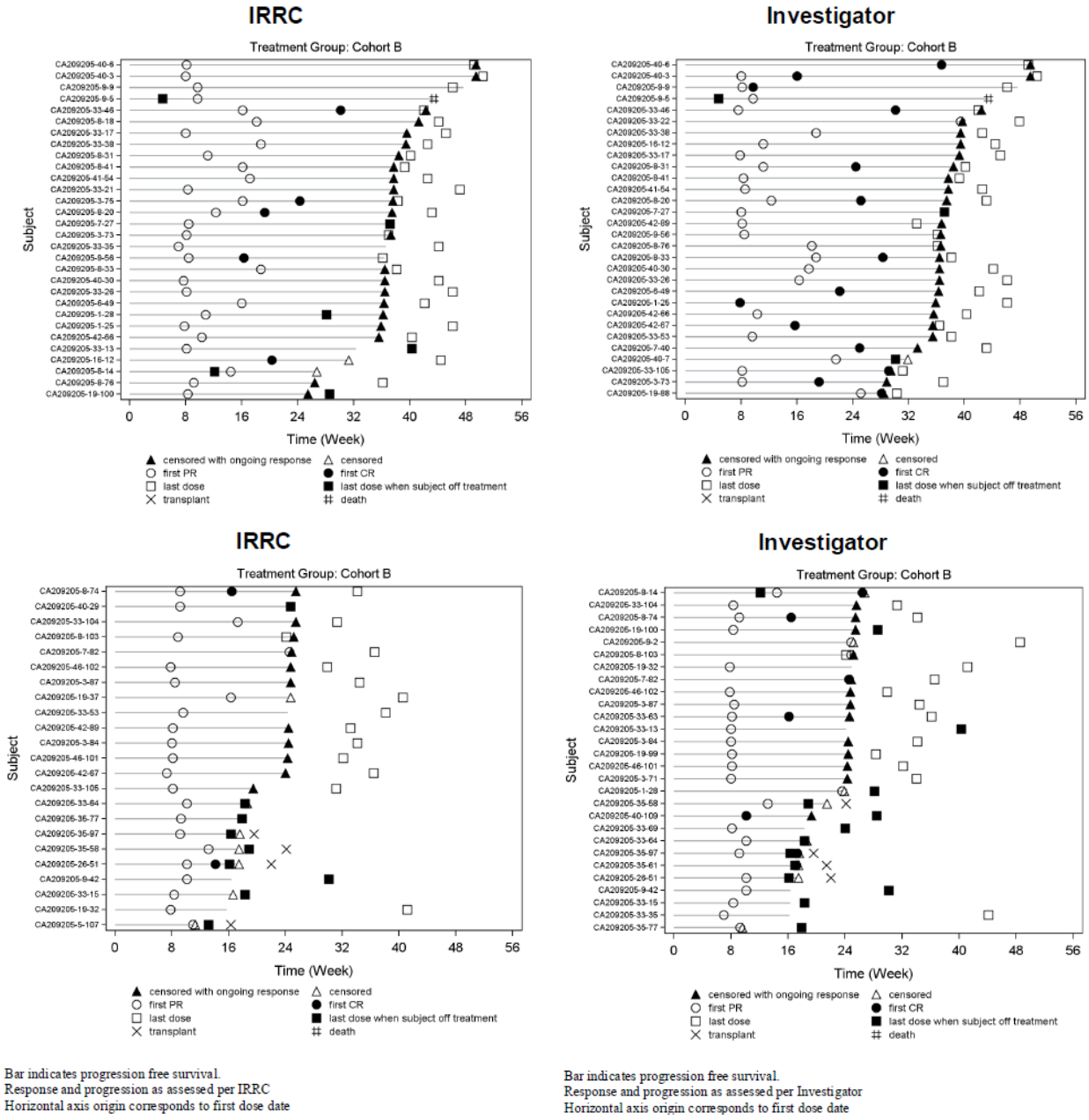
[b] Median computed using Kaplan-Meier method

[c] Subjects with BOR of CR

[d] Subjects with BOR of PR

[e] Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 14 weeks of the clinical data cutoff date.

Figure 8: Event chart for time to response and duration of response - Cohort B - All responders as assessed by IRRC and by investigators



Bar indicates progression free survival.
Response and progression as assessed per IRRC
Horizontal axis origin corresponds to first dose date

Bar indicates progression free survival.
Response and progression as assessed per Investigator
Horizontal axis origin corresponds to first dose date

Time to Response (TTR)

Objective responses achieved with nivolumab in Cohort B subjects occurred early during treatment. The median TTR was 2.10 months with a range of 1.6 months to 5.7 months. 31 of the 53 (58.5%) responders achieved their response by the time of first scan (9 weeks), and all of the responses were achieved within 6 months of treatment initiation. The median time to CR was 4.44 months with a range of 3.3 months to 6.9 months. The median time to PR was 2.10 months with a range of 1.6 months to 5.7 months.

IRRC-assessed PFS

With 24 events (23 progressions and 1 death), the median PFS per IRRC was 9.99 months (95% CI: 8.41, NA). The 6-month PFS rate was 76.9% (95% CI: 64.9, 85.3).

Of the 56 subjects censored for PFS, 53 were censored on-study on last tumour assessment date and the remaining 3 subjects on date of first dose. Among the 53 subjects censored on-study on last tumour

assessment date, the reasons for censoring included receiving subsequent anti-cancer therapy (n=9), still on-treatment (n=39), progression-free in follow-up (n=4), and off-study due to consent withdrawal (n=1). Among the 3 subjects censored on date of first dose, the reasons for censoring were no-baseline tumour assessment/no death (n=1) and no on-study tumour assessment/no death (n=2).

Overall Survival (OS)

With a median follow-up time for OS of 8.9 months and 3 death events in Cohort B, the median OS was not reached. The OS rate at 6 months was 98.7%.

Survival follow-up was current with 52.5% of subjects in Cohort B having either died or having a last known alive date on or after the data cut-off date of 20-Aug-2015.

Of the 77 subjects who were censored for OS, 51 (63.8%) were still on treatment, 21 (26.3%) were in follow-up, and 5 (6.3%) were off study

Updated efficacy

The Applicant provided updated efficacy results (DOR, PFS, OS) from the pivotal Study CA209205 Cohort B (n=80) with a 12-month minimum follow-up (per the 19-Apr-2016 database lock; 14-Jun-2016 for IRRC database lock). Study CA209039 data (n=15) were not updated since mature efficacy data with a median follow-up of 23.26 months were presented previously. The efficacy results on the Integrated Population (Study CA209205 Cohort B + Study CA209039, n=95) are also provided. Median follow-up in the Integrated Population was 15.77 months and CA209205 Cohort B was 15.44 months.

Among the responders in the Integrated Population, the median DOR using Kaplan-Meier methodology increased from 8.74 to 13.14 months per IRRC. The PR rate in the Integrated Population per IRRC with longer follow-up appeared durable (57.9% with 6-month follow-up vs 60.0% with 12-month follow-up). By extending the follow-up duration in CA209205, the median PFS per IRRC in the Integrated Population was updated from 12.55 to 14.78 months and from 9.99 to 14.78 months in CA209205 Cohort B. In addition, OS was 97.9% with 6-month follow-up vs 94.5% with 12-month follow-up in the Integrated Population.

Table 15: Updated overall summary of efficacy in cHL subjects after failure of ASCT and brentuximab

Results and Analysis - Efficacy Summary per IRRC Assessment				
	20-Oct-2015 Database Lock		19-Apr-2016 Database Lock	
Treatment Group	Integrated Population	CA209205 Cohort B	Integrated Population	CA209205 Cohort B
Analysis population	N=95	N=80	N=95	N=80
Efficacy				
ORR[a], n (%)	62 (65.3)	53 (66.3)	63 (66.3)	54 (67.5)
95% CI	(54.8, 74.7)	(54.8, 76.4)	(55.9, 75.7)	(56.1, 77.6)
CR Rate, n (%)	7 (7.4)	7 (8.8)	6 (6.3)	6 (7.5)
95% CI	(3.0, 14.6)	(3.6, 17.2)	(2.4, 13.2)	(2.8, 15.6)
PR Rate, n (%)	55 (57.9)	46 (57.5)	57 (60.0)	48 (60.0)
95% CI	(47.3, 68.0)	(45.9, 68.5)	(49.4, 69.9)	(48.4, 70.8)
SD Rate, n (%)	23 (24.2)	18 (22.5)	22 (23.2)	17 (21.3)
DOR[b] (months)				
Events/Responders	15/62	11/53	22/63	18/54
Median[c] (95% CI)	8.74 (6.83, NA)	7.79 (6.64, NA)	13.14 (9.46, NA)	13.14 (8.74, NA)
Min, Max[d]	0.0+, 23.1+[e]	0.0+, 9.5+	0.0+, 23.1+[e]	0.0+, 14.2+

Results and Analysis - Efficacy Summary per IRRC Assessment				
	Oct-2015 Database Lock		19-Apr-2016 Database Lock	
Treatment Group	**Integrated Population**	**CA209205 Cohort B**	**Integrated Population**	**CA209205 Cohort B**
Analysis population	**N=95**	**N=80**	**N=95**	**N=80**
Duration of CR[f] (months)				
Events/Responders	1/7	1/7	1/6	1/6
Median[c] (95% CI)	4.63 (NA, NA)	4.63 (NA, NA)	NA (4.63, NA)	NA (4.63, NA)
Min, Max[d]	0.7+, 4.6	0.7+, 4.6	0.7+, 10.4+	0.7+, 10.4+
Duration of PR[g] (months)				
Events/Responders	14/55	10/46	21/57	17/48
Median[c] (95% CI)	8.74 (6.83, NA)	7.79 (6.64, NA)	13.14 (8.74, NA)	13.14 (7.79, NA)
Min, Max[d]	0.0+, 23.1+	0.0+, 9.5+	0.0+, 23.1+	0.0+, 13.4+
Median TTR[b] (months)	2.07	2.10	2.04	2.10
Min, Max	0.7, 5.7	1.6, 5.7	0.7, 11.1	1.6, 11.1
Median Time to CR[f] (months)	4.44	4.44	4.11	4.11
Min, Max	3.3, 6.9	3.3, 6.9	3.3, 6.9	3.3, 6.9
Median Time to PR[g] (months)	1.94	2.10	1.97	2.10
Min, Max	0.7, 5.7	1.6, 5.7	0.7, 11.1	1.6, 11.1
Subjects with Ongoing Response[h], n/Responders (%)	36/62 (58.1)	33/53 (62.3)	13/63 (20.6)	10/54 (18.5)
PFS[i]				
Median (95% CI) months	12.55 (8.54, NA)	9.99 (8.41, NA)	14.78 (11.33, NA)	14.78 (11.33, NA)

	Oct-2015 Database Lock		19-Apr-2016 Database Lock	
Treatment Group	**Integrated Population**	**CA209205 Cohort B**	**Integrated Population**	**CA209205 Cohort B**
Analysis population	**N=95**	**N=80**	**N=95**	**N=80**
PFS Rate (95% CI), %				
At 6 months	76.8 (65.8, 84.7)	76.9 (64.9, 85.3)	79.5 (69.4, 86.6)	79.8 (68.6, 87.3)
At 12 months	NA	NA	57.1 (44.7, 67.7)	54.6 (40.9, 66.4)
At 18 months	NA	NA	NA	NA
OS[i]				
Median (95% CI) months	NA (21.13, NA)	NA	NA	NA
OS Rate (95% CI), %				
At 6 months	98.9 (92.5, 99.8)	98.7 (91.0, 99.8)	97.9 (91.7, 99.5)	97.5 (90.2, 99.4)
At 12 months	NA	NA	94.5 (87.3, 97.7)	94.9 (86.9, 98.0)
At 18 months	NA	NA	NA	NA
Median Follow-up (months)	9.46	8.92	15.77	15.44
Min, Max	1.9, 27.6	1.9, 11.7	1.9, 27.6	1.9, 18.5

Abbreviations: ASCT = autologous stem cell transplant; cHL = classical Hodgkin Lymphoma; CI = confidence interval; CR = complete remission; CSR = clinical study report; DOR = duration of objective response; INV = investigator; IRRC = Independent Radiologic Review Committee; IWG = Revised International Working Group Criteria for Malignant Lymphoma; Max = maximum; Min = minimum; NA = not available, minimum follow-up not reached; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial remission; SD = stable disease; TTR = time to response.
Note: IRRC-assessed BOR (CR, PR, SD, PD) was based on the 2007 IWG criteria in both CA209205 and CA209039.
Note: Summary of Clinical Efficacy database lock for Study CA209205: 05-Oct-2015 (clinical database) and 20-Oct-2015 (IRRC); for Study CA209039: 19-Jun-2015 (Oracle database) and 11-Aug-2015 (IRRC).
Note: Updated data per database lock for Study CA209205: 19-Apr-2016 (clinical database) and 14-Jun-2016 (IRRC). Study CA209039 was not updated in the 12-month follow-up analysis.
a CR + PR, CI based on the Clopper and Pearson method.
b Determined for CR + PR.
c Median computed using Kaplan-Meier method
d The symbol + indicates a censored value.
e Maximum value from Subject CA209039-2-63; Study CA209039 data were not updated in the 12-month follow-up analysis.
f Subjects with BOR of CR.
g Subjects with BOR of PR.
h Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 14 weeks or 26 weeks of the clinical data cutoff date for CA209205 and CA209039, respectively.

i Median and rates computed using Kaplan-Meier method

Cohort C

Cohort C subjects (n=100) from the CA209205, provided additional data in the intended target population of adult patients with cHL who have received autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. The primary analysis was recently conducted using the data from the April 2016 DBL. The clinical outcomes are summarized below.

The number of the subjects from each subgroup, per the April 2016 DBL, are shown below:

- ASCT and post-transplant treatment with brentuximab vedotin: n=57 (equivalent to Cohort B in CA209205)
- Brentuximab vedotin treatment only prior to ASCT: n=33
- Brentuximab vedotin treatment before and after ASCT: n=8
- Others: n=2 (subjects whose sequence of prior brentuximab vedotin and ASCT was unable to be determined)

The median age of Cohort C was 32.0 years, which is similar to that of Cohort A+B+C. There were 3 subjects (3.0%) aged 65 years or older from Cohort C. The remaining characteristics (eg, gender, race) from Cohort C were similar to Cohort A+B+C. The median number of prior systemic regimen received was 4 for both cohorts. In Cohort C, 29.0% of subjects received 5 or more previous systemic regimen, which is lower than 48.8% in Cohort B.

The median extent of follow-up, 8.84 months, in Cohort C was comparable with median follow-up, 8.92 months, in Cohort B as of the 06-Oct-2016 DBL (October 2015 DBL) when the primary analysis was conducted for Cohort B.

At the time of the April 2016 DBL, 70.0% of Cohort C subjects were still continuing in the treatment period; the most common reason for treatment discontinuation reported was disease progression (9.0%), followed by others (8.0%) and study drug toxicity (5.0%). 94.0% of Cohort C subjects were continuing in the study (ie, either still on-treatment or off-treatment but in survival follow-up). 9 subjects underwent stem cell transplant after discontinuation of nivolumab; all subjects received allogeneic SCT. Efficacy endpoints related to tumor response were assessed by IRRC and investigators according to the 2007 IWG criteria.

Table 16: Overall summary of efficacy in study CA209205 - Cohort C (DB lock: 19 April 2016)

	N=100	
	IRRC	Investigator
ORR[a], n (%)	73 (73.0)	66 (66.0)
95% CI	(63.2, 81.4)	(55.8, 75.2)
CR Rate, n (%)	17 (17.0)	26 (26.0)
95% CI	(10.2, 25.8)	(17.7, 35.7)
PR Rate, n (%)	56 (56.0)	40 (40.0)
95% CI	(45.7, 65.9)	(30.3, 50.3)
SD Rate, n (%)	17 (17.0)	24 (24.0)
DOR[b] (months)		
Events/Responders	14/73	9/66
Median[c] (95% CI)	7.00 (6.74, NA)	9.76 (6.97, NA)
Min, Max[d]	0.0+, 9.3+	0.0+, 9.9+
Duration of CR[e] (months)		
Events/Responders	1/17	0/26
Median[c] (95% CI)	NA (4.17, NA)	NA (NA, NA)
Min, Max[d]	0.0+, 9.3+	0.0+, 7.4+
Duration of PR[f] (months)		
Events/Responders	13/56	9/40
Median[c] (95% CI)	7.00 (5.36, NA)	9.76 (6.93, NA)
Min, Max[d]	0.0+, 9.0+	0.0+, 9.9+
Median TTR[b] (months)	2.10	2.14
Min, Max	0.8, 6.5	1.4, 8.8
Median Time to CR[e] (months)	3.84	3.75
Min, Max	1.9, 8.3	1.4, 11.5
Median Time to PR[f] (months)	2.10	2.17
Min, Max	0.8, 5.8	1.6, 8.8
Subjects with Ongoing Response[g], n/Responders (%)	29/73 (39.7)	35/66 (53.0)
PFS[h]		
Median (95% CI) months	11.17 (8.51, N.A)	11.40 (11.17, NA)

	N=100	
	IRRC	Investigator
PFS Rate (95% CI), %		
At 6 months	76.6 (66.3, 84.2)	79.4 (69.2, 86.6)
At 12 months	NA	NA
At 18 months	NA	NA
OS[h]		
Median (95% CI), months	NA	
OS Rate (95% CI) at 6 months, %	93.9 (86.9, 97.2)	

Abbreviations: ASCT = autologous stem cell transplant; cHL = classical Hodgkin Lymphoma; CI = confidence interval; CR = complete remission; DOR = duration of objective response; INV = investigator; IRRC = Independent Radiologic Review Committee; IWG = Revised International Working Group Criteria for Malignant Lymphoma; Max = maximum; Min = minimum; NA = not available, minimum follow-up not reached; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial remission; SD = stable disease; TTR = time to response.
Note: IRRC-assessed BOR (CR, PR, SD, PD) was based on the 2007 IWG criteria in both CA209205 and CA209039.
Investigator-assessed BOR (CR, PR, SD, PD) was based on the 2007 IWG criteria in CA209205 and the International Workshop to Standardize Response Criteria for Lymphomas in CA209039.
Note: Database lock for Study CA209205: 19-Apr-2016 (clinical database) and 14-Jun-2016 (IRRC).

a CR + PR, CI based on the Clopper and Pearson method.
b Determined for CR + PR.
c Median computed using Kaplan-Meier method.
d The symbol + indicates a censored value.
e Subjects with BOR of CR.
f Subjects with BOR of PR
g Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 14 weeks of the clinical data cutoff date for CA209205.
h Median and rates computed using Kaplan-Meier method.

Efficacy was described by subgroup in Cohort C according to the sequence of prior brentuximab vedotin treatment relative to prior ASCT.

Table 17: Summary of response rates and best overall response by IRRC in CA209205 Cohort B and CA209205 Cohort C subgroups

	20-Oct 2015 DBL	14-Jun-2016 (IRRC) DBL		
		Cohort C (n=100)		
	Cohort B (n=80)	ASCT and Post-Transplant Treatment With Brentuximab Vedotin (n=57)	Brentuximab Vedotin Treatment Only Prior to ASCT (N=33)	Brentuximab Vedotin Treatment Before and After ASCT (n=8)
ORR[a], n (%)	53 (66.3)	41 (71.9)	23 (69.7)	7 (87.5)
95% CI	(54.8, 76.4)	(58.5, 83.0)	(51.3, 84.4)	(47.3, 99.7)
CR[b], n (%)	7 (8.8)	7 (12.3)	6 (18.2)	3 (37.5)
95% CI	(3.6, 17.2)	(5.1, 23.7)	(7.0, 35.5)	(8.5, 75.5)
PR[b], n (%)	46 (57.5)	34 (59.6)	17 (51.5)	4 (50.0)
95% CI	(45.9, 68.5)	(45.8, 72.4)	(33.5, 69.2)	(15.7, 84.3)

Abbreviations: ASCT = autologous stem cell transplant; BOR = best overall response; CI = confidence interval; CR = complete remission; DBL = database lock; FDG = fluorodeoxyglucose; IRRC = Independent Radiologic Review Committee; IWG = Revised International Working Group Criteria for Malignant Lymphoma; ORR = objective response rate; PET = positron emission tomography; PR = partial remission.

Note: The sequence of prior brentuximab vedotin and ASCT was unable to be determined in 2 subjects whose BOR by IRRC were CR and PR, respectively.

[a] CR + PR, CI based on the Clopper and Pearson method.

[b] Per Revised International Working Group Criteria for Malignant Lymphoma (2007) FDG-PET at baseline used in lieu of a bone marrow biopsy/aspirate. No evidence of FDG-avid disease in bone marrow required for CR regardless of FDG-PET baseline.

Ancillary analyses

- Subgroup analyses were conducted to assess the impact of age, gender, race, region, smoking status, B-symptoms at initial diagnosis, baseline ECOG performance status, time from initial diagnosis to first transplant, time from recent transplant to first subsequent therapy, and number of prior lines of cancer therapy excluding preparative regimens on ORR as assessed by IRRC.
- In addition, best overall response to nivolumab treatment by prior response to brentuximab as documented in subject's medical record was examined on a post-hoc basis. This analysis was performed in CA209205 Cohort B only.

Table 18: Best overall response with nivolumab by best response to most recent prior brentuximab therapy - Cohort B - All treated subjects

	Number of Subjects (%) Best Response to Most Recent Brentuximab (A)				
	CR N = 6	PR N = 17	SD N = 9	RELAPSE/PD N = 34	UTD/NA N = 14
BOR PER INVESTIGATOR (B)					
CR	0	4 (23.5)	4 (44.4)	12 (35.3)	2 (14.3)
PR	2 (33.3)	7 (41.2)	2 (22.2)	17 (50.0)	8 (57.1)
SD	4 (66.7)	6 (35.3)	3 (33.3)	3 (8.8)	2 (14.3)
PD	0	0	0	2 (5.9)	1 (7.1)
UTD	0	0	0	0	1 (7.1)
BOR PER IRRC (B)					
CR	0	1 (5.9)	2 (22.2)	3 (8.8)	1 (7.1)
PR	4 (66.7)	8 (47.1)	4 (44.4)	22 (64.7)	8 (57.1)
SD	2 (33.3)	7 (41.2)	1 (11.1)	5 (14.7)	3 (21.4)
PD	0	1 (5.9)	1 (11.1)	3 (8.8)	1 (7.1)
UTD	0	0	1 (11.1)	1 (2.9)	1 (7.1)

UTD: Unable to Determine. NA: Not Applicable.
(A) As documented in subject's medical record. Relapse is not an option as best response to most recent brentuximab.
(B) Per Revised International Working Group Criteria for Malignant Lymphoma (2007).

Table 19: Subgroup analysis of objective response rate per IRRC - Cohort B - All treated subjects

		Objective Response Rate (%) (A) 95% CI
		Cohort B N = 80
AGE CATEGORIZATION		
	< 65	51/77 (66.2%) (54.6, 76.6)
	>= 65 AND < 75	2/3 (66.7%) (9.4, 99.2)
	>= 65	2/3 (66.7%) (9.4, 99.2)
	< 30	18/27 (66.7%) (46.0, 83.5)
	>= 30 AND < 45	18/28 (64.3%) (44.1, 81.4)
	>= 45 AND < 60	13/18 (72.2%) (46.5, 90.3)
	>= 60	4/7 (57.1%) (18.4, 90.1)
REGION		
	US/CANADA	33/47 (70.2%) (55.1, 82.7)
	EUROPE	20/33 (60.6%) (42.1, 77.1)
GENDER		
	MALE	33/51 (64.7%) (50.1, 77.6)
	FEMALE	20/29 (69.0%) (49.2, 84.7)
RACE		
	WHITE	47/71 (66.2%) (54.0, 77.0)
	BLACK OR AFRICAN AMERICAN	2/4 (50.0%) (6.8, 93.2)
	ASIAN	0/1 (0.0, 97.5)
	OTHER	4/4 (100.0%) (39.8, 100.0)
SMOKING STATUS		
	CURRENT/FORMER	22/32 (68.8%) (50.0, 83.9)
	NEVER SMOKED	29/45 (64.4%) (48.8, 78.1)
	UNKNOWN	2/3 (66.7%) (9.4, 99.2)

PERFORMANCE STATUS (ECOG)		
	0	26/42 (61.9%) (45.6, 76.4)
	1	27/38 (71.1%) (54.1, 84.6)
B-SYMPTOMS AT INITIAL DIAGNOSIS		
	PRESENT	31/46 (67.4%) (52.0, 80.5)
	ABSENT	22/34 (64.7%) (46.5, 80.3)
TIME FROM INITIAL DIAGNOSIS TO FIRST TRANSPLANT (YEARS)		
	< 1 YEAR	15/21 (71.4%) (47.8, 88.7)
	1- < 2 YEARS	25/37 (67.6%) (50.2, 82.0)
	>= 2 YEARS	13/22 (59.1%) (36.4, 79.3)
NUMBER OF PRIOR LINE OF THERAPY RECEIVED EXCLUDING PREPARATIVE REGIMEN		
	<= 3	12/19 (63.2%) (38.4, 83.7)
	4- 6	26/38 (68.4%) (51.3, 82.5)
	>= 7	15/23 (65.2%) (42.7, 83.6)
TIME FROM MOST RECENT TRANSPLANT TO FIRST SUBSEQUENT THERAPY (MONTHS)		
	< 6 MONTHS	15/22 (68.2%) (45.1, 86.1)
	6- < 12 MONTHS	10/16 (62.5%) (35.4, 84.8)
	>= 12 MONTHS	28/42 (66.7%) (50.5, 80.4)

- Subjects Treated Beyond Investigator-assessed Progression

9 Cohort B subjects who had progressed according to the 2007 IWG criteria as assessed by the investigators were subsequently considered eligible per protocol to receive continued nivolumab therapy. Among these 9 subjects, the investigator-assessed BOR was PR in 6 subjects, SD in 2 subjects, and PD in 1 subject before treatment beyond progression was initiated. The number of doses received beyond progression ranged from 1 to 14 and the duration of treatment beyond progression ranged from 0.5 to 6.4+ months.

- PD-L1 status

Of the 80 Cohort B subjects, 63 had quantifiable PD-L1 expression in R-S cells. Reasons for PD-L1 expression not being quantifiable include the following: (1) sample not collected (n=3); (2) sample collected on study only (n=1), (3) not evaluable for R-S cells (n=10), and (4) R-S status not reported (n=3). Among 63 subjects with a quantifiable PD-L1 expression result, 57 (90.5%) had PD-L1 ≥1% expression using a 1% PD-L1 expression cutoff.

Table 20: Best overall response and objective response per IRRC for each PD-L1 expression status at baseline - Cohort B - All treated subjects

Baseline PD-L1 Status		Cohort B N = 80
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%		57 (71.3)
	BEST OVERALL RESPONSE:	
	COMPLETE REMISSION (CR)	4 (5.0)
	PARTIAL REMISSION (PR)	34 (42.5)
	STABLE DISEASE (SD)	11 (13.8)
	RELAPSED/PROGRESSIVE DISEASE (PD)	5 (6.3)
	UNABLE TO DETERMINE (UTD)	3 (3.8)
	OBJECTIVE RESPONSE RATE (1)	38/57 (66.7%)
	(95% CI)	(52.9, 78.6)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%		6 (7.5)
	BEST OVERALL RESPONSE:	
	COMPLETE REMISSION (CR)	0
	PARTIAL REMISSION (PR)	5 (6.3)
	STABLE DISEASE (SD)	1 (1.3)
	RELAPSED/PROGRESSIVE DISEASE (PD)	0
	UNABLE TO DETERMINE (UTD)	0
	OBJECTIVE RESPONSE RATE (1)	5/6 (83.3%)
	(95% CI)	(35.9, 99.6)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE		17 (21.3)
	BEST OVERALL RESPONSE:	
	COMPLETE REMISSION (CR)	3 (3.8)
	PARTIAL REMISSION (PR)	7 (8.8)
	STABLE DISEASE (SD)	6 (7.5)
	RELAPSED/PROGRESSIVE DISEASE (PD)	1 (1.3)
	UNABLE TO DETERMINE (UTD)	0
	OBJECTIVE RESPONSE RATE (1)	10/17 (58.8%)
	(95% CI)	(32.9, 81.6)

(1) CR+PR, 95% CI based on Clopper and Pearson method

- Efficacy by 9p24.1 Alteration

Chromosome 9p24.1 analyses are presented for Cohort B subjects only according to mutually exclusive categories of 9p24.1 alteration.

Table 21: Objective response per IRRC by baseline chromosome 9p24.1

	9p24.1 Quantifiable Subjects (N=45)	
9p24.1 Alteration Category	Subjects in the Category/Quantifiable Subjects (%)	Responders/All Subjects in the Category (ORR %)
Amplification	12/45 (27.7)	10/12 (83.3)
Copy Gain	26/45 (57.8)	17/26 (65.4)
Polysomy	7/45 (15.6)	5/7 (71.4)

9p24.1 alteration was categorized based on highest observed level of 9p24.1 alteration with amplification being the highest followed by copy gain and polysomy. When amplification was detected from at least 1 R-S cell, subjects were categorized as 'amplification' regardless of copy gain or polysomy. When no amplification was detected, but copy gain was identified from at least 1 R-S cell, subjects were categorized as 'copy gain' regardless of polysomy. When neither amplification nor copy gain were found in at least 1 R-S cell, subjects were categorized as 'polysomy.'

Summary is based on last pre-treatment record with an evaluable result.

Responders = CR+PR

Abbreviations: CR = complete remission; ORR = objective response rate; PR = partial remission; R-S = Reed-Sternberg.

- QoL

Health related Quality of Life (HRQoL) was assessed in CA209205 using the patient reported EQ 5D VAS (QOL) and EORTC-QLQ-C30 (overall health status). Mean EQ-5D VAS scores increased over time. EORTC QLQ-C30 scores remained stable over time with mean changes from baseline trending towards an improvement on treatment across functional and symptom scales.

- Resolution of B-symptoms

Nivolumab treatment resulted in resolution of B-symptoms (median time to resolution of 1.9 months) in most (16/18, 88.9%) of the subjects with B-symptoms at baseline.

Table 22: Time to complete resolution of B-symptoms (Cohort B) – All treated subjects

	Cohort B N=80
Time to Complete Resolution of B-Symptoms (Months)	
Number of Subjects with B-Symptoms Present at Baseline	18
Number of Subjects with Complete Resolution	16
Mean	2.31
Median	1.91
Min, Max	1.8, 5.6
Q1, Q3	1.87, 2.12
Standard Deviation	0.979

Time to complete resolution of B-Symptoms was defined as difference between the date of first dose and the earliest date in which there were no B-symptoms of fever, night sweats, and weight loss.

- **<u>Next line systemic treatment post nivolumab for Cohort B (n=80) - as of 28-Jun-2016</u>**

Information of the next line treatment post nivolumab therapy based on Oct-2015 DBL for the Study CA209205 for Cohort B was submitted. The next line systemic treatment post nivolumab therapy, as of 28-Jun-2016, is presented below.

Of the 80 subjects in Cohort B of CA209205, 37 (46.3 %) subjects are continuing nivolumab therapy, 43 (53.8 %) discontinued nivolumab. Of the 43 subjects,

- No subsequent therapy: n=23
- Subsequent therapy: n=20
- Subjects who had post-nivolumab allogeneic HSCT immediately after nivolumab discontinuation: n=8
- Subjects who had next line systemic cancer treatments: n=12 (10 subjects who discontinue nivolumab due to disease progression and 2 subjects who discontinue nivolumab due to other reason, respectively). Of these, 3 subjects proceeded to allogeneic HCST after receiving systemic cancer treatments. The remaining 9 subjects did not receive allogeneic HCST.

Thus, a total of 11 subjects from Cohort B, at the 28-Jun-2016 DBL had post-nivolumab allogeneic HSCT. Of these 11 subjects, 8 proceeded directly to allogeneic HSCT after nivolumab therapy, while 3 received next line treatment before allogeneic HSCT.

In a post hoc analysis of the 80 patients in CA209205 Cohort B, it was found that 37 had no response to prior brentuximab vedotin treatment. Among these 37 patients, treatment with nivolumab resulted in an ORR of 59.5% (22/37). The median duration of response is 13.14 months (13.14, N.A.) for the 22 responders to nivolumab who had failed to achieve response with prior brentuximab vedotin treatment.

As of the 28-Jun-2016 DBL, 3 out of 12 subjects in Cohort B who had next line systemic treatments died due to disease progression (these 3 subjects are among the 9 subjects who did not receive allogeneic HSCT). Death occurred on Days 284, 309, and 488 from the last dose of nivolumab in these 3 subjects. The median observation time after nivolumab exposure in the 9 subjects who are alive was 10 months (range: 4.3-16.0). The subjects received their first subsequent systemic cancer therapy shortly after the discontinuation of nivolumab, with the median duration of 1.9 months (range: 0.4-7.0). After starting the first subsequent systemic cancer therapy, these subjects were followed up for a median duration of 8.4 months (range: 2.6-15.6).

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 23: Summary of Efficacy for trial CA209205

Study identifier	CA209205			
Design	CA209205 is a non-comparative, parallel-cohort, single-arm Phase 2 study in classical Hodgkin lymphoma (cHL) subjects ≥18 years old who failed autologous stem cell transplant (ASCT).			
	Duration of main phase:		Updated	
Hypothesis	To assess the clinical benefit of nivolumab, as measured by ORR based on IRRC assessment, and defined as proportion of subjects achieving either a PR or CR according to the 2007 IWG criteria.			
Treatments groups	nivolumab		Nivolumab was administered at 3 mg/kg intravenously (IV) over 60 min on the first day of each 14-day cycle (i.e., every 2 weeks [Q2W]).	
Endpoints and definitions	Primary endpoint	**IRRC-assessed ORR**	The ORR was defined as the number of subjects with a best overall response (BOR) of CR or PR based on IRRC assessment according to the 2007 IWG criteria divided by the number of treated subjects	
	Secondary endpoint	**CR rate**	The CR rate was defined as the number of subjects with a BOR of CR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects.	
	Secondary endpoint	**PR rate**	The PR rate was defined as the number of subjects with a BOR of PR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects.	
	Secondary endpoint	**DOR**	DOR was defined as the time from first response (CR or PR) to the date of the first documented tumour progression as determined by the investigator using the 2007 IWG criteria or death due to any cause, whichever occurred first.	
Database lock	DBL date: 19-Apr-2016 (clinical database) and 14-Jun-2016 (IRRC data)			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	final results for Cohort B: subjects after failure of autologous SCT and posttransplant treatment with brentuximab vedotin			
Descriptive statistics and estimate variability	Treatment group	IRRC	Investigator	
	Number of subject	80	80	
	ORR Number (% responders)	54 (67.5)	60 (75)	

	Exact 95% CI	56.1, 77.6	64.1, 84.0	
	DOR events	18/54	15/60	
	Median (95% CI)	13.14 (8.74, NA)	NA (9.56, NA)	
	Subjects with ongoing response (%)	10/54 (18.5)	19/60 (31.7)	
	CR rate Number (%) of Responders	6 (7.5)	26 (32.5)	
	Exact 95% CI	2.8, 15.6	22.4, 43.9	
	PR rate Number (%) of Responders	48 (60.0)	34 (42.5)	
	Exact 95% CI	48.4, 70.8	31.5, 54.1	

Supportive study(ies)

Study CA209039 is a Phase 1, open-label, multi-center, dose-escalation, and multi-dose study of nivolumab as monotherapy and/or nivolumab in combination with ipilimumab or lirilumab in subjects with relapsed/refractory hematologic malignancy, with expansion cohorts in selected hematologic malignancies including cHL. The primary objective of the study was to assess safety and tolerability in subjects treated with nivolumab monotherapy after a minimum follow-up of 18 months. The study includes a nivolumab monotherapy portion. Subjects in the expansion cohorts received nivolumab at 3 mg/kg at Week 1, Week 4, and then every 2 weeks until disease progression or CR or for a maximum of 2 years

- Patients

While this study allowed enrollment for any type of HL including NLPHD, all Hodgkin subjects who enrolled in the nivolumab monotherapy cohort (n =23) had cHL. Subjects with prior allo-SCT transplant or autoimmune disorders were excluded. Of them, 15 subjects (referred as CA209039 ASCT-Bren Failed group) had analogous characteristics to CA209205 Cohort B. Data are based on the 19-Jun-2015 data cutoff after a minimum follow-up of approximately 18 months.

- Endpoints

The investigator-based efficacy endpoints are the primary efficacy endpoints (which was a secondary objective of the study), and the IRRC-based efficacy endpoints are the secondary efficacy endpoints. To assess the preliminary antitumor activity of nivolumab in cHL subjects, efficacy endpoints included objective response rate (ORR), progression free survival (PFS), duration of response (DOR), duration of CR, duration of PR, time to response (TTR), time to CR, time to PR and overall survival (OS). Importantly, investigator assessed BOR in CA209039 was defined as the best response designation over the study as a whole, recorded between the date of first dose and the last efficacy assessment prior to subsequent anticancer therapy. Therefore, BOR may have been identified based on response designations after investigator-assessed initial progression.

Tumor assessments were performed radiographically and by FDG-PET scan at screening and on-treatment at 4, 8, 16, 24 and every 16 weeks thereafter.

- Baseline characteristics

Among all cHL subjects, the median age was 35 years (range 20-54 years).The majority of all cHL subjects were white 20 (87%) non-hispanic or latino 19 (83%) subjects. There was a similar male to

female ratio: 12(52%) male and 11 (48%) female. All subjects had a baseline ECOG PS of 0 or 1. The most common site of lesions other than lymph nodes were lung (34.8%) and other sites included liver (13.0%) and kidney (4.3%). No subjects in the study had CNS disease. The median diameter and range (min-max) of tumour burden for all subjects was 1311.0 mm^2 (180 - 14206 mm^2).

The median number of prior systemic regimens excluding preparative regimens for ASCT was 5 (range: 2-15) in the ASCT-Bren Failed group.

Table 24: End of treatment subjects status-summary of all treated cHL subjects receiving monotherapy nivolumab

	cHL: ASCT-Bren Failed	cHL: Other	cHL: All
SUBJECTS	15	8	23
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	2 (13.3)	1 (12.5)	3 (13.0)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	13 (86.7)	7 (87.5)	20 (87.0)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)			
DISEASE PROGRESSION	5 (33.3)	1 (12.5)	6 (26.1)
STUDY DRUG TOXICITY	2 (13.3)	0	2 (8.7)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	2 (13.3)	0	2 (8.7)
MAXIMUM CLINICAL BENEFIT	3 (20.0)	3 (37.5)	6 (26.1)
OTHER	1 (6.7)	3 (37.5)	4 (17.4)
SUBJECTS CONTINUING IN THE STUDY (%) (A) (B)	14 (93.3)	8 (100.0)	22 (95.7)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (B)	1 (6.7)	0	1 (4.3)
REASON FOR NOT CONTINUING IN THE STUDY (%)			
OTHER	1 (6.7)	0	1 (4.3)

Percentages based on subjects entering period or continuing study.
(A) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period.
(B) Subject status at end of treatment.

- Results

Table 25: Summary of key efficacy results per IRRC and per investigator all treated cHL subjects receiving monotherapy

	Number of Subjects (%)					
Efficacy Parameters	**IRRC Total Subjects (n=23)**	**Investigator Total Subjects (n=23)**	**IRRC ASCT-Bren Failed (n=15)**	**Investigator ASCT-Bren Failed (n=15)**	**IRRC cHL Other (n=8)**	**Investigator cHL Other (n=8)**
ORR	14 (61)	20 (87)	9 (60)	13 (87)	5 (63)	7 (88)
CR	3 (13)	5 (22)	0	2 (13)	3 (38)	3 (38)
PR	11 (48)	15 (65)	9 (60)	11 (73)	2 (25)	4 (50)
SD	7 (30)	3 (13)	5 (33)	2 (13)	2 (25)	1 (13)
Objective Response Achieved						
Within 9 weeks	13 (57)	11 (48)	8 (53)	8 (53)	5 (63)	3 (38)
Within 4 months	13 (57)	16 (70)	8 (53)	11(73)	5 (63)	5 (63)
Within 6 months	14 (61)	18 (78)	9 (60)	13 (87)	5 (63)	5 (63)
Within 12 months	14 (61)	20 (87)	9 (60)	13 (87)	5 (63)	7 (88)
No. of Subj. Evaluated for TTR and DOR (F)	14	18	9	12	5	6
Time to Response (months) Median (Min, Max)	1.2 (0.7, 4.1)	1.7 (0.7, 9.2)	0.8 (0.7, 4.1)	1.7 (0.7, 5.7)	1.6 (0.7, 1.6)	2.6 (1.6, 9.2)
Time to CR (months) Median (Min, Max) (C)	12.5 (5.4, 21.8)	5.3 (1.6, 19.9)	NC	10.8 (1.6, 19.9)	12.4 (5.4, 21.8)	5.3 (4.4, 9.2)
Time to PR (months) Median (Min, Max) (D)	0.8 (0.7, 4.1)	1.7 (0.7, 8.9)	0.82 (0.7, 4.1)	1.7 (0.7, 5.7)	1.17 (0.7, 1.6)	3.5 (1.6, 8.9)
DOR Median (95% CI) (B)	N.A. (7.43, N.A.)	N.A. (15.5, N.A.)	12.0 (1.8, N.A.)	N.A. (8.3, N.A.)	N.A. (1.9, N.A.)	N.A. (17.0, N.A.)
No. of Subj. with DOR of at Least						
12 months	6 (43)	9 (50)	3 (33)	7 (58)	3 (60)	2 (33)
18 months	4 (29)	4 (22)	2 (22)	3 (25)	2 (40)	1 (17)
Ongoing Response (E)	5 (36)	7 (39)	3 (33)	5 (42)	2 (40)	2 (33)

(B) Median computed using Kaplan-Meier Method (C) Subjects with BOR of CR. (D) Subjects with BOR of PR. (E) Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 26 weeks of the clinical cutoff date. (F) Subjects CA209039-1-41 and CA209039-9-29 who had investigator-assessed disease progression per the protocol criteria before achieving response are excluded from calculation.
N.A.: Not available; NC: Not calculated

A total of 12 cHL subjects reported subsequent cancer therapy: 8 were from the cHL ASCT-Bren failed group and 4 from the cHL other group. The subsequent cancer therapies included radiotherapy, immunotherapy, chemotherapy, allo-SCT, ASCT, and steroid treatment. 6 subjects went on to SCT (allo-SCT n=5, ASCT n=1)- following a BOR of CR (n=1), PR (n=4) on study prior to transplant.

Subjects were enrolled in this study regardless of PD-L1 expression status; however, pre-study (baseline) tumor tissue specimens were systematically collected prior to first treatment, in order to conduct pre-planned analyses of efficacy according to PD-L1 expression status. Ten subjects out of 23 had quantifiable PD-L1 expression at baseline. Among these 10 subjects, there were 9 subjects with ≥1% PD-L1 expression and 1 subject with <1% PDL1 expression. Out of the 9 subjects with ≥1% PD-L1 expression, the ORR per investigator was 89% (8/9 subjects): 1 subject with CR, 7 subjects with PR and 1 subject with SD. The 1 subject with <1% PD-L1 expression achieved a PR.

- Efficacy in ASCT-naive Subjects

Of the 23 subjects enrolled in the cHL expansion of CA209039 and treated with nivolumab (3 mg/kg Q2W), 5 were ASCT-naive. The efficacy observed in these ASCT-naive subjects was similar to that in cHL subjects after failure of ASCT and brentuximab. Of these 5 ASCT-naive subjects, 3 were brentuximab-naive and 2 had prior brentuximab. All subjects had at least 2 lines of prior systemic cancer therapy (median: 3; range: 3-8). Two of the 5 subjects had received prior brentuximab.

Two subjects, both responders, elected to discontinue nivolumab treatment and proceeded to subsequent transplant (Subject CA209039-5-57, ASCT; Subject CA209039-9-66, allogeneic SCT).

Out of these 5 ASCT-naive subjects, 4 had an objective response both per IRRC and investigator, (Table 26). Response occurred early during treatment (TTR range per IRRC: 0.7-1.6 months) and the DOR was long in 2 subjects (almost 2 years per IRRC).

Table 26: Summary of BOR, TTR, and DOR - ASCT-naive Subjects

Subject	BOR		TTR Months		DOR Months		Prior Bren	Disposition
	IRRC	INV	IRRC	INV	IRRC	INV		
CA209039-1-49	CR	PR	1.6	1.6	24.0	23.8	YES	Reached maximum clinical benefit per protocol.
CA209039-5-57	SD	PR	NA	3.4	NA	2.3	NO	Elected to stop Nivo after response and underwent subsequent ASCT.
CA209039-9-10	PR	SD	1.6	NA	1.9	NA	NO	DC for disease progression (new lesion). Subsequent therapy: brentuximab and radiotherapy.
CA209039-9-66	CR	CR	1.6	1.6	4.4	3.8	NO	Elected to stop Nivo after response and underwent subsequent allogeneic SCT.
CA209039-12-100	CR	PR	0.7	8.9	21.7	11.9	YES	Still continuing in treatment period.

Abbreviations: ASCT = autologous stem cell transplant; BOR = best overall response; Bren = brentuximab; CR = complete remission; DC = discontinued; DOR = duration of objective response; INV = investigator; IRRC = Independent Radiologic Review Committee; NA = not applicable; PR = partial remission; SCT = stem cell transplant; SD = stable disease; TTR = time to first response.

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

A prospectively planned integrated analysis included a total of 95 cHL subjects from the 2 studies (80 subjects from CA209205 and 15 subjects from CA209039) along with the data from individual studies. All 95 subjects had prior brentuximab treatment after failure of ASCT and were treated with nivolumab 3 mg/kg Q2W. The uniform pre-treatment history of subjects in the studies allowed integration of the efficacy data as assessed by an Independent Radiologic Review Committee (IRRC) using the 2007 revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria).

Table 27: Integrated analysis for cHL subjects studies CA209205 and CA209039

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 95	CA209205 Cohort B N = 80	CA209039 cHL: ASCT-Bren Failed N = 15
BEST OVERALL RESPONSE (1):			
COMPLETE REMISSION (CR)	6 (6.3)	6 (7.5)	0
(95% CI)	(2.4, 13.2)	(2.8, 15.6)	(0.0, 21.8)
PARTIAL REMISSION (PR)	57 (60.0)	48 (60.0)	9 (60.0)
(95% CI)	(49.4, 69.9)	(48.4, 70.8)	(32.3, 83.7)
STABLE DISEASE (SD)	22 (23.2)	17 (21.3)	5 (33.3)
RELAPSED OR PROGRESSIVE DISEASE (PD)	8 (8.4)	7 (8.8)	1 (6.7)
UNABLE TO DETERMINE (UTD)	2 (2.1)	2 (2.5)	0
NO BASELINE CT SCAN AVAILABLE	0	0	0
NOT ELIGIBLE FOR RADIOLOGY REVIEW: OTHER REASON	0	0	0
NO EVIDENCE OF DISEASE	0	0	0
NO POST-BASELINE TUMOR ASSESSMENT AVAILABLE BEFORE OR ON THE DAY OF SUBSEQUENT THERAPY (IF ANY)	2 (2.1)	2 (2.5)	0
ALL POST-BASELINE TUMOR ASSESSMENTS BEFORE OR ON THE DAY OF SUBSEQUENT THERAPY (IF ANY) ARE UNKNOWN	0	0	0
OBJECTIVE RESPONSE RATE (2)	63/95 (66.3%)	54/80 (67.5%)	9/15 (60.0%)
(95% CI)	(55.9, 75.7)	(56.1, 77.6)	(32.3, 83.7)
NUMBER OF SUBJECTS WHO ACHIEVED PR OR CR (%)			
WITHIN THE FIRST 9 WEEKS (3)	40 (42.1)	32 (40.0)	8 (53.3)
WITHIN THE FIRST 4 MONTHS	55 (57.9)	47 (58.8)	8 (53.3)
WITHIN THE FIRST 6 MONTHS	60 (63.2)	51 (63.8)	9 (60.0)

(1) Per Revised International Working Group Criteria for Malignant Lymphoma (2007)
(2) CR+PR, confidence interval based on the Clopper and Pearson method
(3) One week window applied per tumor assessment schedule

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 63	CA209205 Cohort B N = 54	CA209039 cHL: ASCT-Bren Failed N = 9
DURATION OF RESPONSE (MONTHS)			
MIN, MAX (A)	0.0+, 23.1+	0.0+, 14.2+	1.8, 23.1+
MEDIAN (95% CI) (B)	13.14 (9.46, N.A.)	13.14 (8.74, N.A.)	11.96 (1.84, N.A.)
N EVENT/N RESP (%)	22/63 (34.9)	18/54 (33.3)	4/9 (44.4)
DURATION OF COMPLETE REMISSION (MONTHS) (C)			
MIN, MAX (A)	0.7+, 10.4+	0.7+, 10.4+	
MEDIAN (95% CI) (B)	N.A. (4.63, N.A.)	N.A. (4.63, N.A.)	
N EVENT/N RESP (%)	1/6 (16.7)	1/6 (16.7)	
DURATION OF PARTIAL REMISSION (MONTHS) (D)			
MIN, MAX (A)	0.0+, 23.1+	0.0+, 13.4+	1.8, 23.1+
MEDIAN (95% CI) (B)	13.14 (8.74, N.A.)	13.14 (7.79, N.A.)	11.96 (1.84, N.A.)
N EVENT/N RESP (%)	21/57 (36.8)	17/48 (35.4)	4/9 (44.4)
TIME TO RESPONSE (MONTHS)			
NUMBER OF RESPONDERS	63	54	9
MEAN	2.60	2.80	1.40
MEDIAN	2.04	2.10	0.82
MIN, MAX	0.7, 11.1	1.6, 11.1	0.7, 4.1
Q1, Q3	1.84, 2.53	1.87, 2.56	0.72, 1.58
STANDARD DEVIATION	1.820	1.847	1.097

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 63	CA209205 Cohort B N = 54	CA209039 cHL: ASCT-Bren Failed N = 9
TIME TO COMPLETE REMISSION (MONTHS) (C)			
NUMBER OF RESPONDERS	6	6	0
MEAN	4.47	4.47	
MEDIAN	4.11	4.11	
MIN, MAX	3.3, 6.9	3.3, 6.9	
Q1, Q3	3.75, 4.67	3.75, 4.67	
STANDARD DEVIATION	1.311	1.311	
TIME TO PARTIAL REMISSION (MONTHS) (D)			
NUMBER OF RESPONDERS	57	48	9
MEAN	2.60	2.82	1.40
MEDIAN	1.97	2.10	0.82
MIN, MAX	0.7, 11.1	1.6, 11.1	0.7, 4.1
Q1, Q3	1.84, 2.50	1.87, 2.55	0.72, 1.58
STANDARD DEVIATION	1.888	1.928	1.097
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)			
3 MONTHS	51 (81.0)	44 (81.5)	7 (77.8)
6 MONTHS	42 (66.7)	36 (66.7)	6 (66.7)

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 63	CA209205 Cohort B N = 54	CA209039 cHL: ASCT-Bren Failed N = 9
SUBJECTS WITH ONGOING RESPONSE (E)	13/63 (20.6)	10/54 (18.5)	3/9 (33.3)
SUBJECTS WITH ONGOING RESPONSE OF DURATION >= 4 MONTHS (E)	13/63 (20.6)	10/54 (18.5)	3/9 (33.3)
SUBJECTS WITH ONGOING RESPONSE OF DURATION >= 6 MONTHS (E)	13/63 (20.6)	10/54 (18.5)	3/9 (33.3)

	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 95	CA209205 Cohort B N = 80	CA209039 cHL: ASCT-Bren Failed N = 15
# EVENTS / # SUBJECTS (%)	38/95 (40.0)	32/80 (40.0)	6/15 (40.0)
MEDIAN PFS (MONTHS) (95% CI)	14.78 (11.33, N.A.)	14.78 (11.33, N.A.)	12.65 (5.91, N.A.)
PFS RATE (95% CI)			
6 MONTHS	79.5 (69.4, 86.6)	79.8 (68.6, 87.3)	78.0 (45.5, 92.5)
NO. AT RISK	61	52	9
12 MONTHS	57.1 (44.7, 67.7)	54.6 (40.9, 66.4)	69.3 (36.8, 87.5)
NO. AT RISK	29	22	7
18 MONTHS	N.A.	N.A.	49.5 (19.4, 74.0)
NO. AT RISK	4	0	4
24 MONTHS	N.A.	N.A.	N.A.
NO. AT RISK	0	0	0

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two ongoing clinical trials have been submitted to support this application:

- CA209205, is a Phase 2, open-label, non-comparative, multi-cohort, single arm study, investigating the activity of nivolumab monotherapy in cHL subjects
- CA209039 is a Phase 1, open-label, multi-center, dose-escalation, and multi-dose study of nivolumab as monotherapy and/or nivolumab in combination with ipilimumab or lirilumab in subjects with relapsed/refractory hematologic malignancy, with expansion cohorts in selected hematologic malignancies including cHL

The dosing is similar to other indications registered for nivolumab.

Both studies are single arm, open label trials with different cohorts of patients. Overall, patients included in the analyses patients with relapse or refractory cHL after ASCT and brentuximab vedotin (cohort B study CA209205), patients that relapsed followed ASCT (brentuximab vedotin naïve; cohort A study CA209205), patients that relapsed after ASCT but were treated with brentuximab vedotin before and/or after ASCT (cohort C study CA209205) and finally, patients that were ASCT naïve (study CA209039).

In cohort C, 57 out of 100 patients received ASCT followed by brentuximab. Overall, the baseline characteristics seem similar to the patients in cohort B, even though more patients in cohort B received 5 or more previous systemic regimen (49% vs 29%). The median follow-up is almost 9 months (April 2016 DBL).

The data available for assessment included patients after failure of ASCT and brentuximab vedotin (80 patients from cohort B in the study CA209205 along with 15 subjects from the study CA209039) and 100 subjects from the cohort C (study CA209205). Data from cohorts A in the study CA209205 were not available. Only 5 patients ASCT naïve have been treated with nivolumab (study CA209039). In total, data from the 1st interim analysis at 6 months (DBL 20.10.15) and updated data with a 12 month minimum follow up were submitted (DBL 19.04.16). The studies are single arm trials with no comparator arm. The design of the trials are considered acceptable as classic Hodgkin lymphoma is a rare disease with an incidence of 1-5/10 000 and that the treatment is for a last line indication where patients have few remaining options. The endpoints (ORR, DOR, CR, PFS) are also considered relevant for this type of disease. There were no concerns raised with the conduct of the studies. The patients recruited in the cohort B represent a heavily pretreated population. The patients enrolled in the study are representative of the patient population that is seen in the clinic at this stage of the disease.

Efficacy data and additional analyses

With at least 12 months follow up, patients had a high rate of tumour responses with nivolumab (66% IRRC analysis, in the integrated population; n=95), although according to the IRRC review only 6.3% were complete responses. Duration of responses was found to be durable, with a median of 13.14 months in the integrated population. The values were lower with IRRC, however, the trend was similar.

The median time to response was 2 months for study CA209205, whilst in study CA209039, the median was near one month. This could be due to the different time point of the first assessment (at week 4 instead of at week 9 in the CA209205 study).

The PFS results are still too immature to draw any conclusions. Preliminary PFS results show a median of 14.78 months but the number of events is still low (38/95). In comparison, PFS data from the most recent prior systemic cancer therapy prior to the first dose of nivolumab in Study CA209205 showed a median PFS of 5.19 months (95% CI: 4.27, 7.59).

OS data are also too immature to draw any firm conclusions. Among the patients who received subsequent anti-cancer treatment following nivolumab, 40 subjects underwent allo-SCT (35 subjects in study CA209205 and 5 in study CA209039) and only 1 subject (study CA209039) who underwent autologous SCT after discontinuation of nivolumab. Post-SCT efficacy data were currently available for 2 subjects; investigator-assessed response at 100 days from transplant was CR in both subjects.

Patients in cohort C that underwent ASCT followed by brentuximab showed similar results compared to cohort B where ORR was 72% with 12% of CR .Subgroup analysis of patients with treatment of brentuximab before ASCT or before and after ASCT also seem to offer similar results (assuming that the apparently better results in the “before and after” subgroup, could be overestimated due to the low number of patients).

The data seems consistent across the cohorts C and B and it is expected that the durable response observed will lead to a prolonged PFS and eventually a longer survival. The subgroups analyses are also consistent with the results from the whole studied population. Putting the efficacy of nivolumab into context, few efficacy alternatives are available after failure to ASCT and brentuximab. Retreatment with brentuximab vedotin could offer in patients with previous response to brentuximab (CR/PR) an ORR of around 60%, which could be considered similar to nivolumab. Nonetheless, these data come from only 20 evaluable patients. The alternatives generally do not provide response rates above 30-40%. In fact, the ESMO guideline recommends the use of palliative single agent chemotherapy with gemcitabine or bendamustine and/or regional RT in patients with multiple relapses who have no other treatment options.

There was some discordance between the IRRC and investigator assessment of endpoints. It is possible that the discordance in CRs was due mainly to different interpretation (positive or negative) of FDG-PET scans required for confirmation of a CR since the majority (13/19) of investigator-assessed CRs considered not CRs by IRRC were assessed as PRs by IRRC and also since tumour reductions were similar between IRRC and Investigators. This discordance in CRs is not considered to have a meaningful impact on the interpretation of the clinical results (SmPC section 5.1).

Results according to PD-L1 expression (with a designated cutoff value of above or below 1%) do not show any meaningful differences. It is of note that 90% of the quantifiable population (63 subjects) had PD-L1 ≥1%.

Eleven subjects who had progressed based on investigator assessment were considered eligible (per protocol) to receive continued nivolumab therapy. Tumour reduction continued over time in 8/11 subjects despite the appearances of new lesions in some cases. It is unclear whether there is a benefit of treatment continuation beyond progression. Currently the SmPC states that treatment duration of nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Cohort C in the pivotal study will provide initial data in cHL concerning whether discontinuation of nivolumab monotherapy is safe in patients who have remained in CR for one year on nivolumab. Some patients who have achieved CR may remain on study therapy indefinitely unless disease progression occurs. Therefore, the CHMP recommends the MAH to submit efficacy and safety data from study CA209205 cohort C in order to explore whether discontinuation of nivolumab monotherapy is safe in patients who have remained in CR for one year on nivolumab.

The value of TILs, lymphocyte activation and proliferation markers have not been analysed in CA209039 and CA209205 (all cohorts), and will not be further investigated because tumour tissue was exhausted for the studies. Details of the exploratory analysis of the tumour specimens from 45 patients from Study CA209205 were published in The Lancet Oncology (Younes et al, published online July 2016). According to this paper, in all evaluable biopsy specimens, Reed–Sternberg cells had PD-L1 and PD-L2 gene copy number alterations and copy-number-associated increased PD-L1 expression, which is consistent with previous studies on PD-L1 on RS cells. Patients whose RS cells had 9p24.1 amplification and increased PD-1 expression seemed more responsive to PD-L1 blockade; the association between best overall response and H score was significant (p=0,013). Nonetheless, most patients with 9p24.1 polysomy or PD-L1 expression in the first quartile achieved partial remission. Therefore, a clear relationship between 9p24.1 polysomy or PD-L1 expression and efficacy of treatment cannot be made. The applicant is encouraged to aim at further studying the correlation of biomarkers with efficacy in further studies in order to better select the population that responds to treatment. Additional biomarker analyses may lead to improved understanding of the relationship between biomarkers and the efficacy of nivolumab in cHL.

Additionally, secondary efficacy measures were resolution of B-symptoms and quality of life. The median time to B-symptom resolution was 1.9 months in most (16/18, 88.9%) of the subjects with B-symptoms at baseline (SmPC section 5.1). Mean EQ-5D VAS scores increased over time, but the EORTC-QLQ-C30 scores remained stable over time. Importantly, no detrimental effects on QoL were observed.

For ASCT naïve subjects, data was only provided in a very limited number of subjects in study CA209039, which enrolled 5 ASCT-naive subjects that were heavily pre-treated with at least 2 lines of prior systemic cancer therapy. Of these 5 ASCT-naive subjects, 3 were brentuximab-naive and 2 had prior brentuximab. All subjects had at least 2 lines of prior systemic cancer therapy (median: 3; range: 3-8), 2/5 subjects had received prior brentuximab. The efficacy observed in these ASCT-naive subjects seems similar to that in cHL subjects after failure of ASCT and brentuximab (4 out of 5 had an objective response both per IRRC and investigator). Two subjects, both responders, elected to discontinue nivolumab treatment and proceeded to subsequent transplant. The CHMP considered that the claimed indication for the use of nivolumab in the treatment of an ASCT- naive cHL population prior to brentuximab was too broad in light of the limited evidence submitted. In particular, for patients who were not candidates for ASCT, there are other effective treatment options available and the data on nivolumab presented were too scarce to allow for a proper assessment of the benefit. Therefore, the indication was restricted to: "OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin."

2.4.4. Conclusions on the clinical efficacy

Patients treated with nivolumab have shown to achieve a high ORR in a cHL population heavily pre-treated (after ASCT and brentuximab) who had exhausted effective available treatment options. The magnitude of the effect is clinically meaningful. This antitumor activity appears durable, which is expected to delay tumour progression and may potentially result in a prolonged survival benefit. In the setting of patients who are not candidates for ASCT and have other effective treatment options, the level of evidence with nivolumab in this patient population is too limited to draw any firm conclusions.

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

- Annex II condition Post-authorisation efficacy study (PAES): The MAH should submit the final clinical Study report for study CA209205: a Phase 2, non-comparative, multi-cohort, single-arm, open-label study of nivolumab (BMS-936558) in cHL subjects after failure of ASCT. The final clinical study report should be submitted by 30th June 2017

The CHMP recommends the following measures to address issues related to efficacy:

- The additional PD-L1 expression in R-S cells and 9p24.1 status in cHL patients treated with Opdivo from CheckMate CA209205 will be presented in an updated report.
- In order to explore whether discontinuation of nivolumab monotherapy is safe in patients who have remained in CR for one year on nivolumab, update data from Cohort C (study CA209205) should be submitted.

2.5. Clinical safety

Introduction

The safety of nivolumab in cHL is based on safety data from the 2 ongoing studies (CA209205 and CA209039). Safety data from CA209205 (Cohort A+B+C; n= 240) and CA209039 (all cHL, n = 23) were integrated for analyses of safety in cHL (n = 263 subjects), this is the primary **Integrated cHL population.** The applicant has provided data from a database lock (DBL) of 09-Feb-2016 for the CA209205 study and 08-Feb-2016 for the CA209039 study (hereafter, 120-day SUR DBL). In 120-day SUR DBL, the number of the safety population increased from 263 to 266 because the last three subjects started the first dose of nivolumab after the cut-off date for DBL. In addition, safety is presented for the population of all subjects analysed for efficacy. The **Integrated Efficacy (SCE) Population** was the

population of 95 subjects who received brentuximab vedotin treatment following failure of ASCT (80 subjects in CA209205 Cohort B + 15 subjects in CA209039).

In addition to presenting safety data for the integrated cHL population, also presents safety data for the following smaller subgroups:

- CA209205 Cohort A+B+C: 243 subjects in 120-day SUR DBL
  - Cohort A: 63 subjects with autologous stem cell transplant (ASCT) failure who have not received prior therapy with brentuximab vedotin
  - Cohort B: 80 subjects who received brentuximab vedotin treatment following failure of ASCT, supporting the proposed indication
  - Cohort C: 100 subjects (April 2016 DBL) adult patients with cHL failing ASCT who received prior treatment with brentuximab vedotin at any time (as initial therapy, salvage therapy before ASCT, and/or after ASCT [eg, salvage and maintenance therapy after ASCT]).
- CA209039 all cHL: n =23 subjects
  - 15 subjects who received brentuximab vedotin treatment following failure of ASCT (same population as Cohort B)
  - 8 subjects who had an alternative history of prior treatment
    - 5 ASCT-naive subjects (3 also naive to brentuximab vedotin)
    - 3 Other: 2 brentuximab vedotin-naive subjects; 1 subject who received brentuximab before ASCT

The population of 'All SCS Subjects' was defined as all CA209205 (Cohort A+B+C) and CA209039 cHL subjects who received at least 1 dose of nivolumab monotherapy.

Safety data were further integrated across studies in multiple indications using the approved dosage and administration of nivolumab monotherapy. The 9 studies included in the analyses for nivolumab monotherapy (3 mg/kg Q2W) were CA209205 (Cohort A+B+C) and CA209039 (all cHL) in cHL, CA209025 in RCC, CA209037, CA209066, and CA209067 (monotherapy arm) in melanoma, CA209063, CA209017, and CA209057 in NSCLC.

Patient exposure

In the safety database, the majority of cHL subjects (76.7%) received ≥90% of the planned nivolumab dose intensity, the median number of nivolumab doses received was 16 (Table 28).

Table 28: Cumulative Dose and Relative Dose Intensity Summary - All SCS Subjects (120-day SUR DBL)

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266	CA209205 Cohort A+B+C N = 243	CA209205 Cohort B + CA209039 cHL: ASCT-Rsn Failed N = 95	CA209039 all cHL N = 23
NUMBER OF DOSES RECEIVED				
MEAN (SD)	17.7 (9.44)	17.1 (8.38)	22.0 (10.92)	23.7 (16.07)
MEDIAN (MIN - MAX)	16.0 (1 - 53)	16.0 (1 - 35)	25.0 (3 - 52)	18.0 (6 - 53)
CUMULATIVE DOSE (MG/KG)				
MEAN (SD)	52.47 (27.922)	50.78 (24.885)	65.46 (32.282)	70.35 (47.045)
MEDIAN (MIN - MAX)	47.15 (3.0 - 153.8)	47.13 (3.0 - 105.1)	70.64 (9.0 - 149.0)	53.97 (18.0 - 153.8)
RELATIVE DOSE INTENSITY				
>= 110%	0	0	0	0
90% TO < 110%	204 (76.7)	186 (76.5)	71 (74.7)	18 (78.3)
70% TO < 90%	57 (21.4)	52 (21.4)	21 (22.1)	5 (21.7)
50% TO < 70%	5 (1.9)	5 (2.1)	3 (3.2)	0
< 50%	0	0	0	0

Adverse events

A summary of safety in the Integrated cHL Population and CA209205 Cohort B is presented in Table 29.

Table 29: Summary of Safety - Integrated cHL Population and CA209205 Cohort B

	CA209205 Cohort A+B+C & CA209039 all cHL N = 263			CA209205 Cohort B N = 80		
DEATHS						
NUMBER OF SUBJECTS WHO DIED (%)	12 (4.6)			3 (3.8)		
WITHIN 30 DAYS OF LAST DOSE	4 (1.5)			1 (1.3)		
WITHIN 100 DAYS OF LAST DOSE	5 (1.9)			1 (1.3)		
STUDY DRUG TOXICITY	1 (0.4)			0		
	Any Grade	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
ALL AES	246 (93.5)	79 (30.0)	3 (1.1)	79 (98.8)	32 (40.0)	1 (1.3)
MOST FREQUENTLY REPORTED AES (≥ 20% OF SUBJECTS)						
FATIGUE	73 (27.8)	3 (1.1)	0	29 (36.3)	0	0
PYREXIA	64 (24.3)	2 (0.8)	0	25 (31.3)	1 (1.3)	0
DIARRHOEA	61 (23.2)	2 (0.8)	0	21 (26.3)	0	0
COUGH	54 (20.5)	0	0	22 (27.5)	0	0
NAUSEA	45 (17.1)	0	0	19 (23.8)	0	0
PRURITUS	44 (16.7)	0	0	18 (22.5)	0	0
RASH	39 (14.8)	3 (1.1)	0	17 (21.3)	2 (2.5)	0
UPPER RESPIRATORY TRACT INFECTION	35 (13.3)	1 (0.4)	0	19 (23.8)	1 (1.3)	0
INFUSION RELATED REACTION	32 (12.2)	1 (0.4)	0	16 (20.0)	0	0
ARTHRALGIA	29 (11.0)	0	0	17 (21.3)	0	0
NASOPHARYNGITIS	27 (10.3)	0	0	16 (20.0)	0	0
DRUG-RELATED AES	188 (71.5)	42 (16.0)	3 (1.1)	72 (90.0)	20 (25.0)	1 (1.3)
MOST FREQUENTLY REPORTED DRUG-RELATED AES (≥ 10% OF SUBJECTS)						
FATIGUE	42 (16.0)	1 (0.4)	0	20 (25.0)	0	0
INFUSION RELATED REACTION	32 (12.2)	1 (0.4)	0	16 (20.0)	0	0
DIARRHOEA	29 (11.0)	1 (0.4)	0	8 (10.0)	0	0
NAUSEA	29 (11.0)	0	0	10 (12.5)	0	0
RASH	27 (10.3)	2 (0.8)	0	13 (16.3)	1 (1.3)	0
PYREXIA	24 (9.1)	0	0	11 (13.8)	0	0
PRURITUS	23 (8.7)	0	0	8 (10.0)	0	0
ARTHRALGIA	17 (6.5)	0	0	11 (13.8)	0	0
ALL SAES	55 (20.9)	33 (12.5)	3 (1.1)	20 (25.0)	10 (12.5)	1 (1.3)
DRUG-RELATED SAES	26 (9.9)	9 (3.4)	3 (1.1)	5 (6.3)	0	1 (1.3)
ALL AES LEADING TO DC	11 (4.2)	7 (2.7)	2 (0.8)	3 (3.8)	2 (2.5)	1 (1.3)
DRUG-RELATED AES LEADING TO DC	11 (4.2)	7 (2.7)	2 (0.8)	3 (3.8)	2 (2.5)	1 (1.3)

MedDRA Version: 18.0; CTC Version 4.0; Except for deaths, includes events reported between first dose and 30 days after last dose of study therapy.

A summary of safety in Integrated cHL Population and CA209205 Cohort B (120-day SUR DBL by severity is presented in Table 30.

Table 30: Summary of any adverse events by worst CTC grade (any grade, grade 3-4, grade 5) CA209205 Cohort A+B+C & CA209039 all cHL, CA209205 Cohort B – All SCS subjects (120-day Safety Update)

System Organ Class (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B N = 80		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	261 (98.1)	93 (35.0)	3 (1.1)	80 (100.0)	37 (46.3)	1 (1.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	160 (60.2)	9 (3.4)	0	54 (67.5)	2 (2.5)	0
FATIGUE	86 (32.3)	5 (1.9)	0	31 (38.8)	0	0
PYREXIA	72 (27.1)	1 (0.4)	0	27 (33.8)	1 (1.3)	0
INFECTIONS AND INFESTATIONS	157 (59.0)	17 (6.4)	0	61 (76.3)	7 (8.8)	0
UPPER RESPIRATORY TRACT INFECTION	47 (17.7)	1 (0.4)	0	22 (27.5)	1 (1.3)	0
NASOPHARYNGITIS	38 (14.3)	0	0	18 (22.5)	0	0
PNEUMONIA	22 (8.3)	5 (1.9)	0	13 (16.3)	2 (2.5)	0
GASTROINTESTINAL DISORDERS	150 (56.4)	11 (4.1)	0	51 (63.8)	3 (3.8)	0
DIARRHOEA	77 (28.9)	2 (0.8)	0	25 (31.3)	0	0
NAUSEA	53 (19.9)	0	0	19 (23.8)	0	0
VOMITING	46 (17.3)	2 (0.8)	0	14 (17.5)	1 (1.3)	0
CONSTIPATION	32 (12.0)	1 (0.4)	0	13 (16.3)	0	0
ABDOMINAL PAIN	26 (9.8)	2 (0.8)	0	11 (13.8)	2 (2.5)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	132 (49.6)	9 (3.4)	0	44 (55.0)	4 (5.0)	0
COUGH	69 (25.9)	0	0	24 (30.0)	0	0
DYSPNOEA	28 (10.5)	4 (1.5)	0	13 (16.3)	3 (3.8)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	112 (42.1)	5 (1.9)	0	40 (50.0)	3 (3.8)	0
PRURITUS	48 (18.0)	0	0	18 (22.5)	0	0
RASH	47 (17.7)	3 (1.1)	0	19 (23.8)	2 (2.5)	0
INVESTIGATIONS	107 (40.2)	33 (12.4)	1 (0.4)	39 (48.8)	14 (17.5)	1 (1.3)
LIPASE INCREASED	22 (8.3)	13 (4.9)	0	10 (12.5)	7 (8.8)	0
ALANINE AMINOTRANSFERASE INCREASED	19 (7.1)	7 (2.6)	0	5 (6.3)	2 (2.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	17 (6.4)	5 (1.9)	0	7 (8.8)	3 (3.8)	0

System Organ Class (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B N = 80		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	98 (36.8)	5 (1.9)	0	35 (43.8)	3 (3.8)	0
ARTHRALGIA	39 (14.7)	0	0	21 (26.3)	0	0
BACK PAIN	26 (9.8)	2 (0.8)	0	10 (12.5)	1 (1.3)	0
MYALGIA	26 (9.8)	0	0	9 (11.3)	0	0
NERVOUS SYSTEM DISORDERS	85 (32.0)	3 (1.1)	0	31 (38.8)	1 (1.3)	0
HEADACHE	40 (15.0)	1 (0.4)	0	9 (11.3)	1 (1.3)	0
NEUROPATHY PERIPHERAL	22 (8.3)	0	0	10 (12.5)	0	0
METABOLISM AND NUTRITION DISORDERS	65 (24.4)	13 (4.9)	0	22 (27.5)	3 (3.8)	0
HYPERGLYCAEMIA	25 (9.4)	2 (0.8)	0	9 (11.3)	1 (1.3)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	62 (23.3)	21 (7.9)	0	17 (21.3)	9 (11.3)	0
ANAEMIA	30 (11.3)	6 (2.3)	0	9 (11.3)	2 (2.5)	0
THROMBOCYTOPENIA	22 (8.3)	4 (1.5)	0	2 (2.5)	0	0
NEUTROPENIA	19 (7.1)	8 (3.0)	0	7 (8.8)	4 (5.0)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	46 (17.3)	1 (0.4)	0	18 (22.5)	0	0
INFUSION RELATED REACTION	35 (13.2)	1 (0.4)	0	16 (20.0)	0	0
ENDOCRINE DISORDERS	36 (13.5)	0	0	14 (17.5)	0	0
HYPOTHYROIDISM	23 (8.6)	0	0	8 (10.0)	0	0
PSYCHIATRIC DISORDERS	33 (12.4)	0	0	12 (15.0)	0	0
INSOMNIA	17 (6.4)	0	0	8 (10.0)	0	0
EYE DISORDERS	30 (11.3)	0	0	13 (16.3)	0	0
VASCULAR DISORDERS	30 (11.3)	1 (0.4)	0	14 (17.5)	1 (1.3)	0
RENAL AND URINARY DISORDERS	18 (6.8)	1 (0.4)	0	3 (3.8)	0	0
CARDIAC DISORDERS	17 (6.4)	4 (1.5)	1 (0.4)	8 (10.0)	3 (3.8)	0
EAR AND LABYRINTH DISORDERS	14 (5.3)	0	0	5 (6.3)	0	0
IMMUNE SYSTEM DISORDERS	14 (5.3)	1 (0.4)	0	3 (3.8)	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	13 (4.9)	0	0	5 (6.3)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	12 (4.5)	5 (1.9)	1 (0.4)	8 (10.0)	3 (3.8)	0
HEPATOBILIARY DISORDERS	6 (2.3)	3 (1.1)	0	3 (3.8)	1 (1.3)	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0

In CA209205 Cohort B, frequencies of all-causality AEs (any grade and Grade 3-4) were slightly higher than in the Integrated cHL Population, consistent with the longer duration of exposure and follow up in CA209205 Cohort B.

Drug-related Adverse Events

The frequency, type, and severity of drug-related AEs as assessed by the investigator (any grade and grade 3-4) are shown in Table 31.

- Drug-related AEs of any grade were reported in 77.1% of subjects. The most frequently reported drug-related AEs (≥10% of subjects) were fatigue (19.9%), infusion-related reaction (12.8%), diarrhea (13.5%), nausea (10.2%), and rash 12.0%).
- Drug-related Grade 3-4 AEs were reported in 19.5% of subjects. The most frequently reported Grade 3-4 drug-related AEs (≥1% of subjects) were lipase increased (3.8%), ALT increased (2.3%), AST (1.5%), amylase increased (1.5%) and neutropenia (2.3%).

Table 31: Summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) CA209205 Cohort A+B+C & CA209039 all cHL, CA209205 Cohort B- All SCS subjects 120—day safety update

System Organ Class (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B N = 80		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	205 (77.1)	52 (19.5)	0	72 (90.0)	23 (28.8)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	87 (32.7)	3 (1.1)	0	34 (42.5)	0	0
FATIGUE	53 (19.9)	2 (0.8)	0	22 (27.5)	0	0
PYREXIA	23 (8.6)	0	0	11 (13.8)	0	0
GASTROINTESTINAL DISORDERS	82 (30.8)	5 (1.9)	0	31 (38.8)	2 (2.5)	0
DIARRHOEA	36 (13.5)	1 (0.4)	0	10 (12.5)	0	0
NAUSEA	27 (10.2)	0	0	9 (11.3)	0	0
VOMITING	20 (7.5)	1 (0.4)	0	6 (7.5)	0	0
ABDOMINAL PAIN	14 (5.3)	2 (0.8)	0	6 (7.5)	2 (2.5)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	66 (24.8)	3 (1.1)	0	26 (32.5)	2 (2.5)	0
RASH	32 (12.0)	2 (0.8)	0	14 (17.5)	1 (1.3)	0
PRURITUS	26 (9.8)	0	0	9 (11.3)	0	0
INVESTIGATIONS	61 (22.9)	22 (8.3)	0	25 (31.3)	12 (15.0)	0
LIPASE INCREASED	17 (6.4)	10 (3.8)	0	8 (10.0)	6 (7.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	14 (5.3)	4 (1.5)	0	6 (7.5)	3 (3.8)	0
ALANINE AMINOTRANSFERASE INCREASED	13 (4.9)	6 (2.3)	0	4 (5.0)	2 (2.5)	0
AMYLASE INCREASED	8 (3.0)	4 (1.5)	0	4 (5.0)	2 (2.5)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	7 (2.6)	1 (0.4)	0	3 (3.8)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	43 (16.2)	1 (0.4)	0	22 (27.5)	1 (1.3)	0
ARTHRALGIA	20 (7.5)	0	0	12 (15.0)	0	0
MYALGIA	14 (5.3)	0	0	7 (8.8)	0	0
BACK PAIN	4 (1.5)	0	0	2 (2.5)	0	0
NERVOUS SYSTEM DISORDERS	42 (15.8)	3 (1.1)	0	16 (20.0)	1 (1.3)	0
HEADACHE	14 (5.3)	0	0	2 (2.5)	0	0
NEUROPATHY PERIPHERAL	8 (3.0)	0	0	3 (3.8)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	42 (15.8)	1 (0.4)	0	15 (18.8)	1 (1.3)	0
COUGH	11 (4.1)	0	0	3 (3.8)	0	0
PNEUMONITIS	9 (3.4)	0	0	1 (1.3)	0	0
DYSPNOEA	5 (1.9)	1 (0.4)	0	3 (3.8)	1 (1.3)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	35 (13.2)	1 (0.4)	0	16 (20.0)	0	0
INFUSION RELATED REACTION	34 (12.8)	1 (0.4)	0	16 (20.0)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	32 (12.0)	9 (3.4)	0	7 (8.8)	4 (5.0)	0
NEUTROPENIA	14 (5.3)	6 (2.3)	0	7 (8.8)	4 (5.0)	0
THROMBOCYTOPENIA	13 (4.9)	0	0	1 (1.3)	0	0
ANAEMIA	6 (2.3)	1 (0.4)	0	2 (2.5)	0	0
ENDOCRINE DISORDERS	28 (10.5)	0	0	12 (15.0)	0	0
HYPOTHYROIDISM	16 (6.0)	0	0	7 (8.8)	0	0
PRIMARY HYPOTHYROIDISM	8 (3.0)	0	0	3 (3.8)	0	0
HYPERTHYROIDISM	4 (1.5)	0	0	1 (1.3)	0	0
METABOLISM AND NUTRITION DISORDERS	24 (9.0)	3 (1.1)	0	7 (8.8)	0	0
DECREASED APPETITE	9 (3.4)	0	0	2 (2.5)	0	0
HYPERGLYCAEMIA	6 (2.3)	0	0	5 (6.3)	0	0
INFECTIONS AND INFESTATIONS	22 (8.3)	3 (1.1)	0	14 (17.5)	1 (1.3)	0
RESPIRATORY TRACT INFECTION	3 (1.1)	0	0	3 (3.8)	0	0
UPPER RESPIRATORY TRACT INFECTION	3 (1.1)	0	0	3 (3.8)	0	0
EYE DISORDERS	10 (3.8)	0	0	6 (7.5)	0	0
IMMUNE SYSTEM DISORDERS	8 (3.0)	1 (0.4)	0	2 (2.5)	0	0
HYPERSENSITIVITY	6 (2.3)	1 (0.4)	0	1 (1.3)	0	0
VASCULAR DISORDERS	8 (3.0)	0	0	5 (6.3)	0	0
PSYCHIATRIC DISORDERS	7 (2.6)	0	0	5 (6.3)	0	0
HEPATOBILIARY DISORDERS	5 (1.9)	3 (1.1)	0	2 (2.5)	1 (1.3)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (1.1)	1 (0.4)	0	2 (2.5)	0	0

Select Adverse Events

Endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Hypersensitivity/infusion reactions are also considered AEs of special clinical interest that are potentially associated with the use of nivolumab. Hypersensitivity/infusion reactions were analysed along with the select AE.

Endocrine Events

Endocrine selected AEs (all causality, any grade) were reported in 16.2% of subjects. The majority of endocrine select AEs were considered drug-related by the investigator. For the 31 subjects (11.7%) with drug-related endocrine select AEs, all events were thyroid disorders, with hypothyroidism and primary hypothyroidism as the most frequently reported terms (> 2% of subjects). All events were Grade 1-2. The incidence of immune-related endocrinopathies has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 32: Summary of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) – All SCS and SCE subjects (120-day safety update)

Sub Category (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	43 (16.2)	1 (0.4)	0	20 (21.1)	0	0
THYROID DISORDER	40 (15.0)	0	0	19 (20.0)	0	0
HYPOTHYROIDISM	23 (8.6)	0	0	12 (12.6)	0	0
PRIMARY HYPOTHYROIDISM	8 (3.0)	0	0	3 (3.2)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	6 (2.3)	0	0	3 (3.2)	0	0
HYPERTHYROIDISM	4 (1.5)	0	0	1 (1.1)	0	0
THYROIDITIS	2 (0.8)	0	0	2 (2.1)	0	0
DIABETES	2 (0.8)	1 (0.4)	0	0	0	0
DIABETES MELLITUS	2 (0.8)	1 (0.4)	0	0	0	0
ADRENAL DISORDER	1 (0.4)	0	0	1 (1.1)	0	0
ADRENAL INSUFFICIENCY	1 (0.4)	0	0	1 (1.1)	0	0

Table 33: Summary of drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) - Integrated cHL population and SCE population – 120-day Safety Update

Sub Category (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	31 (11.7)	0	0	15 (15.8)	0	0
THYROID DISORDER	31 (11.7)	0	0	15 (15.8)	0	0
HYPOTHYROIDISM	16 (6.0)	0	0	9 (9.5)	0	0
PRIMARY HYPOTHYROIDISM	8 (3.0)	0	0	3 (3.2)	0	0
HYPERTHYROIDISM	4 (1.5)	0	0	1 (1.1)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	3 (1.1)	0	0	1 (1.1)	0	0
THYROIDITIS	2 (0.8)	0	0	2 (2.1)	0	0

Gastrointestinal Events

The frequency of GI selected AEs (all causality, any grade) was 28.9%. For the 36 subjects (13.5%) with drug-related GI select AEs, all subjects reported diarrhoea and 1 subject also reported colitis. The majority of events were Grade 1-2; there was 2 Grade 3-4 event (diarrhoea) reported. There was no Grade 5 events reported. The incidence of immune-related colitis has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 34: Summary of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) – All SCS and SCE subjects (120-day safety update)

Select Adverse Events Category: GASTROINTESTINAL ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	77 (28.9)	2 (0.8)	0	32 (33.7)	1 (1.1)	0
DIARRHOEA	77 (28.9)	2 (0.8)	0	32 (33.7)	1 (1.1)	0
COLITIS	1 (0.4)	0	0	0	0	0

Table 35: Summary of drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) Integrated cHL population (CA209205 Cohort A+B+C & CA209039 all cHL), and SCE population- 120—day safety update

Select Adverse Events Category: GASTROINTESTINAL ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	36 (13.5)	1 (0.4)	0	12 (12.6)	0	0
DIARRHOEA	36 (13.5)	1 (0.4)	0	12 (12.6)	0	0
COLITIS	1 (0.4)	0	0	0	0	0

Hepatic Events

The frequency of hepatic selected AEs (all causality, any grade) was 13.5%, of which the majority were considered drug-related by the investigator. For the 23 subjects (8.6%) with drug-related hepatic select AEs, ALT increased, AST increased, and blood ALP increased were the most frequently reported terms (>2.0% of subjects). The majority of events were Grade 1-2. Grade 3-4 events were reported in 13 subjects (GGT increased was the only Grade 4 event and was reported in 1 subject). There were no Grade 5 events reported. The incidence of immune-related hepatitis has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 36: Summary of any Select AEs by worst CTC grade (any grade, grade 3-4, grade 5) – All SCS and SCE subjects (120-day Safety Update)

Summary of Any Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5)
All SCS and SCE Subjects

Select Adverse Events Category: HEPATIC ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	36 (13.5)	13 (4.9)	0	14 (14.7)	5 (5.3)	0
ALANINE AMINOTRANSFERASE INCREASED	19 (7.1)	7 (2.6)	0	7 (7.4)	2 (2.1)	0
ASPARTATE AMINOTRANSFERASE INCREASED	17 (6.4)	5 (1.9)	0	8 (8.4)	3 (3.2)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	15 (5.6)	4 (1.5)	0	6 (6.3)	1 (1.1)	0
BLOOD BILIRUBIN INCREASED	4 (1.5)	1 (0.4)	0	2 (2.1)	0	0
AUTOIMMUNE HEPATITIS	2 (0.8)	2 (0.8)	0	1 (1.1)	1 (1.1)	0
LIVER FUNCTION TEST ABNORMAL	2 (0.8)	1 (0.4)	0	1 (1.1)	0	0
TRANSAMINASES INCREASED	2 (0.8)	1 (0.4)	0	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
HEPATITIS	1 (0.4)	1 (0.4)	0	0	0	0
HEPATOTOXICITY	1 (0.4)	0	0	0	0	0

Table 37: Summary of drug-related select AEs by worst CTC grade (any grade, grade 3-4, Grade 5) Integrated cHL population (CA209205 cohort A+B+C & CA209039 all cHL), and SCE population- 120—day safety update

Select Adverse Events Category: HEPATIC ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	23 (8.6)	9 (3.4)	0	11 (11.6)	4 (4.2)	0
ASPARTATE AMINOTRANSFERASE INCREASED	14 (5.3)	4 (1.5)	0	6 (6.3)	3 (3.2)	0
ALANINE AMINOTRANSFERASE INCREASED	13 (4.9)	6 (2.3)	0	4 (4.2)	2 (2.1)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	7 (2.6)	1 (0.4)	0	4 (4.2)	0	0
AUTOIMMUNE HEPATITIS	2 (0.8)	2 (0.8)	0	1 (1.1)	1 (1.1)	0
BLOOD BILIRUBIN INCREASED	2 (0.8)	0	0	2 (2.1)	0	0
TRANSAMINASES INCREASED	2 (0.8)	0	0	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
HEPATITIS	1 (0.4)	1 (0.4)	0	0	0	0
HEPATOTOXICITY	1 (0.4)	0	0	0	0	0
LIVER FUNCTION TEST ABNORMAL	1 (0.4)	0	0	1 (1.1)	0	0

Pulmonary Events

The frequency of pulmonary selected AEs (all causality, any grade) was 4.9%. The majority of pulmonary select AEs were considered drug-related by the investigator. The incidence of immune-related pulmonitis has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 38: Summary of Any Select AEs by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) – All SCS and SCE Subjects (120-day Safety Update)

Select Adverse Events Category: PULMONARY ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	13 (4.9)	1 (0.4)	0	4 (4.2)	0	0
PNEUMONITIS	11 (4.1)	0	0	3 (3.2)	0	0
ACUTE RESPIRATORY DISTRESS SYNDROME	1 (0.4)	1 (0.4)	0	0	0	0
LUNG INFILTRATION	1 (0.4)	0	0	1 (1.1)	0	0

Table 39: Summary of Drug-Related Select AEs by Worst CTC Grade (Any Grade, grade 3-4, Grade 5) Integrated cHL population (CA209205 Cohort A+B+C & CA209039 all cHL), and SCE Population- 120—day Safety Update

Select Adverse Events Category: PULMONARY ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	10 (3.8)	0	0	2 (2.1)	0	0
PNEUMONITIS	9 (3.4)	0	0	1 (1.1)	0	0
LUNG INFILTRATION	1 (0.4)	0	0	1 (1.1)	0	0

Renal Events

The frequency of renal selected AEs (all causality, any grade) was 3.8%. For the 4 subjects (1.5%) with drug-related renal select AEs: Elevations in serum creatinine levels and autoimmune nephritis were reported.

The majority of events were Grade 1-2. One Grade 3 event (autoimmune nephritis) was reported. There were no Grade 5 events reported. The 1 event of autoimmune nephritis led to discontinuation of study

therapy. The incidence of immune-related nephritis and renal dysfunction has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 40: Summary of Any Select AEs by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) – All SCS and SCE Subjects (120-day Safety Update)

Select Adverse Events Category: RENAL ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	10 (3.8)	1 (0.4)	0	6 (6.3)	0	0
BLOOD CREATININE INCREASED	9 (3.4)	0	0	6 (6.3)	0	0
AUTOIMMUNE NEPHRITIS	1 (0.4)	1 (0.4)	0	0	0	0

Table 41: Summary of Drug-Related Select AEs by Worst CTC Grade (Any Grade, grade 3-4, Grade 5) Integrated cHL population (CA209205 Cohort A+B+C & CA209039 all cHL), and SCE Population- 120—day Safety Update

Select Adverse Events Category: RENAL ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	4 (1.5)	1 (0.4)	0	2 (2.1)	0	0
BLOOD CREATININE INCREASED	3 (1.1)	0	0	2 (2.1)	0	0
AUTOIMMUNE NEPHRITIS	1 (0.4)	1 (0.4)	0	0	0	0

Skin Events

The frequency of skin select AEs (all causality, any grade) was 33.8%. The majority of skin select AEs were considered drug-related by the investigator. For the 56 subjects (21.1%) with drug-related skin select AEs, rash, pruritus, and rash maculo-papular were the most frequently reported terms. The majority of events were Grade 1-2. Grade 3 events were reported in 3 subjects (rash in 2 subjects, rash maculo-papular in 1 subject). The incidence of immune-related rash has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 42: Summary of Any Select AEs by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) – All SCS and SCE Subjects (120-day Safety Update)

Select Adverse Events Category: SKIN ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	90 (33.8)	4 (1.5)	0	43 (45.3)	3 (3.2)	0
PRURITUS	48 (18.0)	0	0	24 (25.3)	0	0
RASH	47 (17.7)	3 (1.1)	0	25 (26.3)	2 (2.1)	0
RASH MACULO-PAPULAR	8 (3.0)	1 (0.4)	0	4 (4.2)	1 (1.1)	0
RASH PRURITIC	3 (1.1)	0	0	2 (2.1)	0	0
URTICARIA	3 (1.1)	0	0	1 (1.1)	0	0
ERYTHEMA	2 (0.8)	0	0	1 (1.1)	0	0
RASH PAPULAR	2 (0.8)	0	0	1 (1.1)	0	0
DERMATITIS	1 (0.4)	0	0	1 (1.1)	0	0
DERMATITIS EXFOLIATIVE	1 (0.4)	0	0	1 (1.1)	0	0
ECZEMA	1 (0.4)	0	0	0	0	0
PHOTOSENSITIVITY REACTION	1 (0.4)	0	0	0	0	0
PSORIASIS	1 (0.4)	0	0	1 (1.1)	0	0
RASH MACULAR	1 (0.4)	0	0	1 (1.1)	0	0
SKIN EXFOLIATION	1 (0.4)	0	0	0	0	0
SKIN HYPOPIGMENTATION	1 (0.4)	0	0	1 (1.1)	0	0

Table 43: Summary of Drug-Related Select AEs by Worst CTC Grade (Any Grade, grade 3-4, Grade 5) Integrated cHL population (CA209205 Cohort A+B+C & CA209039 all cHL), and SCE Population- 120—day Safety Update

Select Adverse Events Category: SKIN ADVERSE EVENT

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	56 (21.1)	3 (1.1)	0	29 (30.5)	2 (2.1)	0
RASH	32 (12.0)	2 (0.8)	0	17 (17.9)	1 (1.1)	0
PRURITUS	26 (9.8)	0	0	13 (13.7)	0	0
RASH MACULO-PAPULAR	6 (2.3)	1 (0.4)	0	3 (3.2)	1 (1.1)	0
RASH PRURITIC	3 (1.1)	0	0	2 (2.1)	0	0
ERYTHEMA	2 (0.8)	0	0	1 (1.1)	0	0
ECZEMA	1 (0.4)	0	0	0	0	0
RASH PAPULAR	1 (0.4)	0	0	0	0	0
SKIN HYPOPIGMENTATION	1 (0.4)	0	0	1 (1.1)	0	0
URTICARIA	1 (0.4)	0	0	1 (1.1)	0	0

Hypersensitivity/Infusion Reactions

The frequency of hypersensitivity/infusion reactions (all causality, any grade) were 16.9%. The majority of hypersensitivity/infusion reactions were considered drug-related by the investigator. The most frequently reported events were infusion-related reactions (13.2%, 35/45 subjects). The majority of events were Grade 1-2. Two Grade 3-4 events were reported (infusion related reaction and hypersensitivity). No Grade 5 events were reported. The incidence of infusion reactions has been updated and is depicted as selected adverse reaction in the SmPC section 4.4 and 4.8.

Table 44: Summary of Any Select AEs by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) – All SCS and SCE Subjects (120-day Safety Update)

Select Adverse Events Category: HYPERSENSITIVITY/INFUSION REACTION

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	45 (16.9)	2 (0.8)	0	20 (21.1)	0	0
INFUSION RELATED REACTION	35 (13.2)	1 (0.4)	0	17 (17.9)	0	0
HYPERSENSITIVITY	8 (3.0)	1 (0.4)	0	1 (1.1)	0	0
BRONCHOSPASM	5 (1.9)	0	0	4 (4.2)	0	0

Table 45: Summary of Drug-Related Select AEs by Worst CTC Grade (Any Grade, grade 3-4, Grade 5) Integrated cHL population (CA209205 Cohort A+B+C & CA209039 all cHL), and SCE Population- 120—day Safety Update

Select Adverse Events Category: HYPERSENSITIVITY/INFUSION REACTION

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B & CA209039 cHL: ASCT-Bren Failed N = 95		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	40 (15.0)	2 (0.8)	0	19 (20.0)	0	0
INFUSION RELATED REACTION	34 (12.8)	1 (0.4)	0	17 (17.9)	0	0
HYPERSENSITIVITY	6 (2.3)	1 (0.4)	0	1 (1.1)	0	0
BRONCHOSPASM	1 (0.4)	0	0	1 (1.1)	0	0

Other Events of Special Interest

There were 6 subjects that had OESIs (3 with pancreatitis, 3 with a uveitis event [2 uveitis, 1 iritis], and 1 with encephalitis). One subject had a Grade 3 SAE of encephalitis, which was not treated with immune-modulating medication and was not considered related to study drug by the investigator.

Increased lipase level (any Grade or Grade 3/4) as an AE of abnormal investigation was higher frequency in the Integrated cHL Population than the Pooled Population of the subjects who were treated with nivolumab monotherapy. However, not all nivolumab monotherapy Phase 2 and 3 studies systematically monitored lipase test. Thus, an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown.

Increased lipase as AE (any grade) was reported more frequently in cHL subjects than in the pooled nivolumab safety population (6.8% versus 3.1% and drug-related 4.9% versus 2.1%). Approximately 50% was grade 3-4 in both populations.

Table 46: Increased Lipase Level Reported as an AE of Abnormal Investigation

		Integrated SCS cHL Population n=263	Pooled Population* N=1991
Lipase Increased reported as AE (All Causality)	Any grade	18 (6.8 %)	61 (3.1%)
	Grade 3-4	10 (3.8 %)	34 (1.7%)
Lipase Increased reported as AE (Drug-related)	Any grade	13 (4.9 %)	42 (2.1%)
	Grade 3-4	7 (2.7 %)	24 (1.2%)

*Comprised of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039.

Table 47: Frequency of Worsened Lipase Relative to Baseline On-Treatment Worst CTC Grade Laboratory Parameters

	Integrated SCS cHL population n=246	Pooled Population* N=660
Worsened to Grade 1-4	39 (15.9%)	149 (22.6%)
Worsened to Grade 3-4	16 (6.5%)	49 (7.4%)

*Comprised of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209205 and CA209039

However, not all nivolumab monotherapy Phase 2 and 3 studies systematically monitored lipase.

Pancreatitis was reported in 2 subjects in the cHL integrated population and 10 subjects in the pooled population, with a similar incidence (0.8% versus 0.5%). Lipase increase and pancreatitis are reported in the SmPC section 4.8.

Systemic Inflammatory Response Syndrome

Another event of special interest first observed in RCC Study CA209025 was systemic inflammatory response syndrome. In the Integrated cHL Population, no events of systemic inflammatory response syndrome were reported.

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) was identified as an event of special interest based on 3 cases with fatal outcome identified in ongoing studies in the nivolumab program (1 case occurred on nivolumab monotherapy; 1 case occurred on subsequent Bactrim after discontinuation from nivolumab and

ipilimumab [1 dose] due to ulcerative colitis; 1 case occurred on subsequent ipilimumab after discontinuation from nivolumab due to erythema multiforme).

In the Integrated cHL Population, no events of TEN were reported.

Serious adverse event / deaths / other significant events

The frequency, type, and severity of drug-related SAEs (any grade and Grade 3-4) are reported in Table 48.

Table 48: Summary of Drug-Related Serious Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) CA209205 Cohort A+B+C & CA209039 all cHL, CA209205 Cohort B- All SCS Subjects 120—day safety update

System Organ Class (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B N = 80		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	27 (10.2)	13 (4.9)	0	5 (6.3)	1 (1.3)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (1.9)	1 (0.4)	0	2 (2.5)	0	0
INFUSION RELATED REACTION	5 (1.9)	1 (0.4)	0	2 (2.5)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (1.9)	0	0	0	0	0
PNEUMONITIS	3 (1.1)	0	0	0	0	0
PLEURAL EFFUSION	2 (0.8)	0	0	0	0	0
GASTROINTESTINAL DISORDERS	4 (1.5)	2 (0.8)	0	0	0	0
PANCREATITIS	2 (0.8)	1 (0.4)	0	0	0	0
ABDOMINAL PAIN	1 (0.4)	0	0	0	0	0
DIARRHOEA	1 (0.4)	1 (0.4)	0	0	0	0
NAUSEA	1 (0.4)	0	0	0	0	0
VOMITING	1 (0.4)	0	0	0	0	0
INFECTIONS AND INFESTATIONS	3 (1.1)	2 (0.8)	0	1 (1.3)	0	0
MENINGITIS	1 (0.4)	0	0	1 (1.3)	0	0
PNEUMONIA	1 (0.4)	1 (0.4)	0	0	0	0
SEPSIS	1 (0.4)	1 (0.4)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	3 (1.1)	3 (1.1)	0	0	0	0
GLUCOSE TOLERANCE IMPAIRED	1 (0.4)	1 (0.4)	0	0	0	0
HYPERCALCAEMIA	1 (0.4)	1 (0.4)	0	0	0	0
HYPONATRAEMIA	1 (0.4)	1 (0.4)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.8)	0	0	1 (1.3)	0	0
PYREXIA	2 (0.8)	0	0	1 (1.3)	0	0
INVESTIGATIONS	2 (0.8)	2 (0.8)	0	1 (1.3)	1 (1.3)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.4)	1 (0.4)	0	1 (1.3)	1 (1.3)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.4)	0	0	0	0	0
LYMPH NODE PAIN	1 (0.4)	0	0	0	0	0
CARDIAC DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
PERICARDIAL EFFUSION	1 (0.4)	1 (0.4)	0	0	0	0
HEPATOBILIARY DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
AUTOIMMUNE HEPATITIS	1 (0.4)	1 (0.4)	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.4)	1 (0.4)	0	0	0	0
MYELODYSPLASTIC SYNDROME	1 (0.4)	1 (0.4)	0	0	0	0
NERVOUS SYSTEM DISORDERS	1 (0.4)	0	0	0	0	0
SEIZURE	1 (0.4)	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
RASH	1 (0.4)	1 (0.4)	0	0	0	0

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

- Drug-related SAEs of any grade were reported in 10.2% of subjects. The most frequently reported drug-related SAEs (≥1% of subjects) were infusion-related reaction (1.9%) and pneumonitis (1.1%).

- Drug-related Grade 3-4 SAEs were reported in 4.9% of subjects.

Deaths

A total of 18 subjects (6.8%) died (Table 49). 3.4% of the death was due to disease progression and one death (within 30 days of last dose) was attributed to a reason of "study drug toxicity "grade 5 SAE atypical pneumonia), this was changed by the investigator to unrelated post database lock. One subject whose death was attributed to disease progression had a Grade 5 drug-related SAE of dyspnea 2 days prior to his death. Eight deaths (3.0%) were attributed to a reason of "other". One death (within 30 days of last dose) was attributed to a reason of "unknown" (subject was lost to follow up).

Table 49: Death Summary - All SCS Subjects and SCE Subjects – 120 Day Safety Update

	CA209205 Cohort A+B+C & CA209039 all cHL N = 266	CA209205 Cohort A+B+C N = 243	CA209205 Cohort B + CA209039 cHL: ASCT-Bren Failed N = 95	CA209039 all cHL N = 23
NUMBER OF SUBJECTS WHO DIED (%)	18 (6.8)	13 (5.3)	7 (7.4)	5 (21.7)
PRIMARY REASON FOR DEATH (%)				
DISEASE PROGRESSION	9 (3.4)	7 (2.9)	3 (3.2)	2 (8.7)
STUDY DRUG TOXICITY	1 (0.4)	1 (0.4)	0	0
UNKNOWN	0	0	0	0
OTHER	8 (3.0)	5 (2.1)	4 (4.2)	3 (13.0)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	5 (1.9)	5 (2.1)	1 (1.1)	0
PRIMARY REASON FOR DEATH (%)				
DISEASE PROGRESSION	2 (0.8)	2 (0.8)	0	0
STUDY DRUG TOXICITY	1 (0.4)	1 (0.4)	0	0
UNKNOWN	0	0	0	0
OTHER	2 (0.8)	2 (0.8)	1 (1.1)	0
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	8 (3.0)	8 (3.3)	1 (1.1)	0
PRIMARY REASON FOR DEATH (%)				
DISEASE PROGRESSION	4 (1.5)	4 (1.6)	0	0
STUDY DRUG TOXICITY	1 (0.4)	1 (0.4)	0	0
UNKNOWN	0	0	0	0
OTHER	3 (1.1)	3 (1.2)	1 (1.1)	0

In the SCE Subjects (cohort B + 15 patients from CA209039), 3 deaths were attributed to a reason of "other", 1 from CA209205 study and 2 from the 15 subjects of CA209039 study who received brentuximab vedotin treatment following failure of ASCT. The one subject in study CA2090205 was found to have died from Epstein Barr virus (EBV) positive peripheral T cell lymphoma which was deemed unrelated to study drug. The 2 deaths from study CA209039 were related to GVHD and complications associated with allo-SCT 224 days after the last dose of nivolumab.

Laboratory findings (Integrated cHL Population)

The incidence of laboratory abnormalities has been updated and is depicted as selected adverse reaction in the SmPC section 4.8.

Hematology

The majority of subjects did not have on-study worsening in hematology, the majority of hematology laboratory abnormalities were Grade 1-2. The only Grade 3-4 hematologic abnormality reported in ≥ 5% of subjects was decreased absolute lymphocytes (8.3%). Treated subjects (n = 263) who experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality were as follows: 3 (1.1%) subjects with decreased hemoglobin (Grade 3), 5 (1.9%) subjects with decreased platelet count (3 Grade 3, 2 Grade 4), seven (2.7%) subjects with decreased leukocytes (6 Grade 3, 1 Grade 4), 5 (1.9%) subjects

with decreased lymphocytes (4 Grade 3, 1 Grade 4), 9 (3.4%) subjects with decreased absolute neutrophil count (6 Grade 3, 3 Grade 4).

Table 50: Summary of on-treatment worst CTC grade haematology tests that worsened relative to baseline - SI Units - integrated cHL population

	Number of Subjects (%)					
	CA209205 Cohort A+B+C & CA209039 all cHL SCS Population (CSR OCT 2015 DBL)			CA209205 Cohort A+B+C & CA209039 all cHL 120-day SUR Feb 2016 DBL		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	253	56 (22.1)	7 (2.8)	265	67 (25.3)	7 (2.6)
PLATELET COUNT	253	71 (28.1)	6 (2.4)	265	92 (34.7)	8 (3.0)
LEUKOCYTES	253	83 (32.8)	9 (3.6)	265	97 (36.6)	12 (4.5)
LYMPHOCYTES (ABSOLUTE)	252	61 (24.2)	21 (8.3)	265	82 (30.9)	28 (10.6)
ABSOLUTE NEUTROPHIL COUNT	253	74 (29.2)	9 (3.6)	265	86 (32.5)	13 (4.9)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as denominator.
(B) Per Anemia criteria in CTC version 4.0 there is no grade 4 for hemoglobin.

Liver Function Tests

The majority of subjects did not have on-study worsening in liver function tests. Most abnormalities in liver function were Grade 1-2. Grade 3-4 increases in the following liver function tests occurred in ≥ 2% of subjects: AST (2.4%) and ALT (2.0%). The number of treated subjects (n = 263) who experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality was low: 2 (0.8%) subjects for ALP increased (Grade 3), 6 (2.3%) subjects for AST increased (5 Grade 3, 1 Grade 4), 4 (1.5%) subjects for ALT increased (3 Grade 3, 1 Grade 4), 1 (0.4%) subject for total bilirubin increased (Grade 3), 3/255 (1.2%) subjects had concurrent ALT or AST elevation > 3 x ULN with concurrent (within 1 day) total bilirubin > 2 x ULN.

In CA209205 and CA209039, 3 subjects met the protocol-specified criteria for drug-induced liver injury (DILI; concurrent [within 1 day] ALT or AST > 3 x ULN and total bilirubin > 2 x ULN within 100 days of the last dose of nivolumab).

Kidney Function Tests

The majority of subjects had normal serum creatinine values during the reporting period; serum creatinine that worsened relative to baseline (any grade) was reported in 10.3% of subjects. There were no Grade 3-4 abnormalities in serum creatinine.

Thyroid Function Tests

The majority of subjects had normal TSH levels at baseline and throughout the treatment period. 16.3% of subjects had elevated on-study TSH (> ULN) with normal baseline TSH (≤ ULN). 5.9% of subjects had low on-study TSH (< LLN) with normal baseline TSH (≥ LLN).

Safety in special populations

In the Integrated cHL Population, the frequencies of all-causality and drug-related AEs for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population.

In the integrated cHL cohort only 7 subjects were ≥65 years. The limited experience with elderly has updated the SmPC (SmPC section 4.8 and 5.1).

Table 51: Summary of on-treatment AEs by age group - All treated subjects - Integrated cHL population

MedDRA Terms	Number of Subjects (%)			
	Age < 65 years (N = 256)	Age 65-74 years (N = 7)	Age 75-84 years (N = 0)	Age 85+ years (N = 0)
Total AEs	239 (93.4)	7 (100.0)	0	0
Serious AEs -Total	55 (21.5)	0	0	0
Fatal	4 (1.6)	0	0	0
Hospitalization/prolong existing hospitalization	52 (20.3)	0	0	0
Life-threatening	1 (0.4)	0	0	0
Cancer	0	0	0	0
Disability/incapacity	0	0	0	0
AEs leading to drop-out	10 (3.9)	1 (14.3)	0	0
Psychiatric disorders	21 (8.2)	0	0	0
Nervous system disorders	69 (27.0)	3 (42.9)	0	0
Accidents and Injuries	9 (3.5)	0	0	0
Cardiac disorders	13 (5.1)	0	0	0
Vascular disorders	21 (8.2)	1 (14.3)	0	0
Cerebrovascular disorders	1 (0.4)	0	0	0
Infections and infestations	115 (44.9)	2 (28.6)	0	0
Anticholinergic syndrome	86 (33.6)	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	9 (3.5)	0	0	0

MedDRA Version: 18.0; CTC version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Abbreviations: AE: adverse event; HLGT: MedDRA High-Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Queries; SAE: serious adverse event; SOC: System Organ Class.

Table 52: Summary of on-treatment AEs by age group - All treated subjects - Nivolumab monotherapy data integrated across indications

MedDRA Terms	Number of Subjects (%)			
	Monotherapy Data Integrated Across Indications[a]			
	Age < 65 years (N = 1301)	Age 65-74 years (N = 504)	Age 75-84 years (N = 165)	Age 85+ years (N = 21)
Total AEs	1260 (96.8)	492 (97.6)	162 (98.2)	21 (100.0)
Serious AEs -Total	501 (38.5)	236 (46.8)	82 (49.7)	12 (57.1)
Fatal	104 (8.0)	45 (8.9)	21 (12.7)	3 (14.3)
Hospitalization/prolong existing hospitalization	445 (34.2)	209 (41.5)	73 (44.2)	8 (38.1)
Life-threatening	20 (1.5)	7 (1.4)	2 (1.2)	0
Cancer	13 (1.0)	11 (2.2)	9 (5.5)	1 (4.8)
Disability/incapacity	1 (<0.1)	1 (0.2)	0	0
AEs leading to drop-out	153 (11.8)	77 (15.3)	38 (23.0)	5 (23.8)
Psychiatric disorders	222 (17.1)	78 (15.5)	26 (15.8)	6 (28.6)
Nervous system disorders	449 (34.5)	180 (35.7)	57 (34.5)	13 (61.9)
Accidents and injuries	88 (6.8)	46 (9.1)	14 (8.5)	3 (14.3)
Cardiac disorders	113 (8.7)	51 (10.1)	13 (7.9)	5 (23.8)
Vascular disorders	195 (15.0)	91 (18.1)	26 (15.8)	9 (42.9)
Cerebrovascular disorders	9 (0.7)	9 (1.8)	1 (0.6)	1 (4.8)
Infections and infestations	493 (37.9)	215 (42.7)	62 (37.6)	10 (47.6)
Anticholinergic syndrome	439 (33.7)	160 (31.7)	56 (33.9)	9 (42.9)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	128 (9.8)	68 (13.5)	24 (14.5)	4 (19.0)

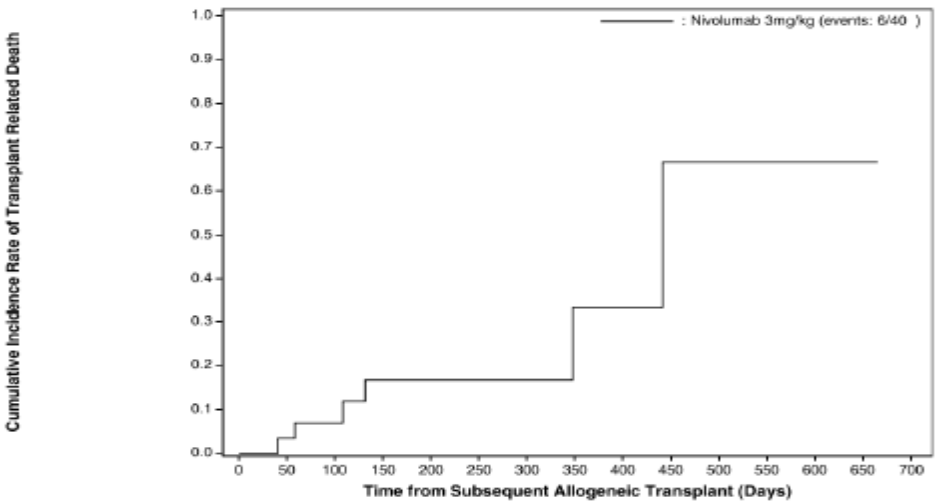
[a] Includes nivolumab monotherapy data from studies CA209039, CA209205, CA209025, CA209063, CA209017, CA209057, CA209037, CA209066, and CA209067 (monotherapy arm only).
MedDRA Version: 18.0; CTC version 4.0. Events reported within 30 days after last dose of study therapy.
Abbreviations: AE: adverse event; HLGT: MedDRA High-Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Queries; SAE: serious adverse event; SOC: System Organ Class.

Subjects receiving subsequent stem cell transplantation (SCT)

Information on the updated outcome of 17 subjects having post-nivolumab allogenic SCT was reported. Out of 266 cHL subjects who were treated with nivolumab monotherapy (an additional 7 subjects since the database lock for the SCS (10 subjects, 5 subjects in a Phase 1 (CA209039) and 2 (CA209205) trial, respectively).

The median age at HSCT was 33 (range: 18 - 56). Most subjects received a non-myeloablative regimen prior to SCT (15 of the 17 subjects). A median of 9 doses (range 4-16) nivolumab were administered prior to allo-SCT with a time from last nivolumab dose to SCT ranging from 11 to 94 days. Acute GvHD was reported in 14 subjects, of which 5 patients with grade 3-4. Six out of the 17 subjects died from complications post nivolumab alloSCT. Two subjects experienced hyperacute graft-versus-host disease (GVHD), defined as occurring within the first 14 days after stem cell infusion. Two subjects experienced encephalitis (1 case of grade 3 lymphocytic encephalitis without an identified infectious cause and 1 case of grade 3 suspected viral encephalitis). One subject was reported with hepatic veno-occlusive disease (sinusoidal obstruction syndrome) who received reduced-intensity conditioning and died due to multiorgan GVHD. From the updated safety data, an additional 23 subjects receiving alloSCT after nivolumab were submitted. In the 23 new cases only 2 subjects developed a grade 3- 4 GvHD, while of the previous 17 subjects 5 patients developed a grade 3- 4 GvHD. There were no cases of treatment related mortality (TRM) among the 23 newly reported patients, leaving the total number of TRM events at 6.

Figure 9: Plot of Cumulative Incidence Rate of Transplant Related Death -CA209039 all cHL and CA209205 Cohort A+B+C - All Treated Subjects who underwent Subsequent Allogeneic Transplant



A multivariate analysis for transplant related death was performed applying a standard Cox PH model to study the effects of the covariates. Again, since all the deaths are transplant-related mortality (TRM) and no progression dates were collected after allogeneic HSCT for the 40 subjects, the competing risk model was not used.

Acute GVHD after allogeneic HSCT (n=40)

The incidence and grade of acute GVHD reported from the 40 subjects are described in Table 53. Two subjects experienced hyperacute GVHD, defined as occurring within the first 14 days after stem cell infusion. For this analysis, subjects with unknown grade of acute GVHD were imputed to Grade 4. In the 40 subjects who received allogeneic HSCT after nivolumab from CA209039 and CA209205, the overall frequencies of Grade 2-4 and Grade 3-4 acute GVHD was 32.5% and 17.5%. As cited in literature[7], the frequency of moderate to severe acute GVHD was approximately 40% of all recipients of allogeneic HSCT.

Table 53: Incidence and grade of acute GVHD in the 40 subjects who received allogeneic HSCT after nivolumab treatment at any timepoint after allogeneic HSCT

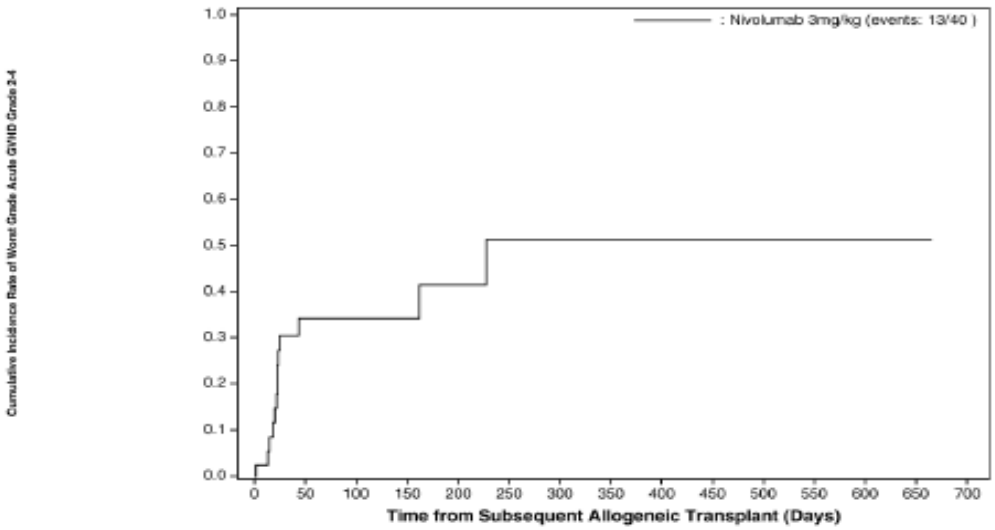
	Any grade	≥Grade 2	≥Grade 3
All subjects n=40	18 (45%)	13 (32.5%)	7* (17.5%)

*Two subjects (CA209205-4-50 and CA209205-17-138) with unknown grade of acute GVHD was imputed to Grade 4

Grade 2-4 Acute GVHD after allogeneic HSCT

Cumulative incidence rate of Grade 2-4 acute GVHD from subsequent allogeneic HSCT was calculated using Kaplan-Meier method. The cumulative incidence rate of Grade 2-4 acute GVHD (95% CI) at Day 100, 6 months, and 1 year are 34.2 % (20.5, 53.4), 41.5 % (24.7, 63.7) and 51.2 % (30.3, 76.1), respectively.

Figure 10: Plot of Cumulative Incidence Rate of Worst Grade Acute GVHD Grade 2-4 from Subsequent Allogeneic Transplant - CA209039 all cHL and CA209205 Cohort A+B+C - All Treated Subjects who underwent Subsequent Allogeneic Transplant



CA209039-4-50 reported worst acute GVHD on 01MAY2014 with missing grade. Therefore grade was imputed to Grade 4.
CA209205-17-138 reported worst acute GVHD on 23MAR2016 with missing grade. Therefore grade was imputed to Grade 4.
CA209205-26-269 reported acute GVHD grade 2 with missing onset date that has been imputed to his allogeneic transplant date (17MAR2016).
PROGRAM SOURCE:/gbs/prod/clin/programs/ca/209/000/csrfa02/rpt/039-205/ema/20160830-allo/rg-efkm2dt-v02.sas RUN DATE: 12SEP2016 10:51

A multivariate analysis for Grade 2-4 acute GVHD was performed applying a standard Cox PH model to study the effects of the covariates. The number of prior systemic cancer therapy prior to nivolumab was associated with an increased risk for Grade 2-4 acute GVHD. Subjects with more prior systemic cancer therapies (i.e. more advanced) were more likely to experience acute GVHD. No association with Grade 2-4 acute GVHD was detected for time from last dose of nivolumab to allogeneic HSCT, number of nivolumab doses received, and age at allogeneic HSCT was not associate. The non-significance of these covariates may be due to a small sample size and small number of events.

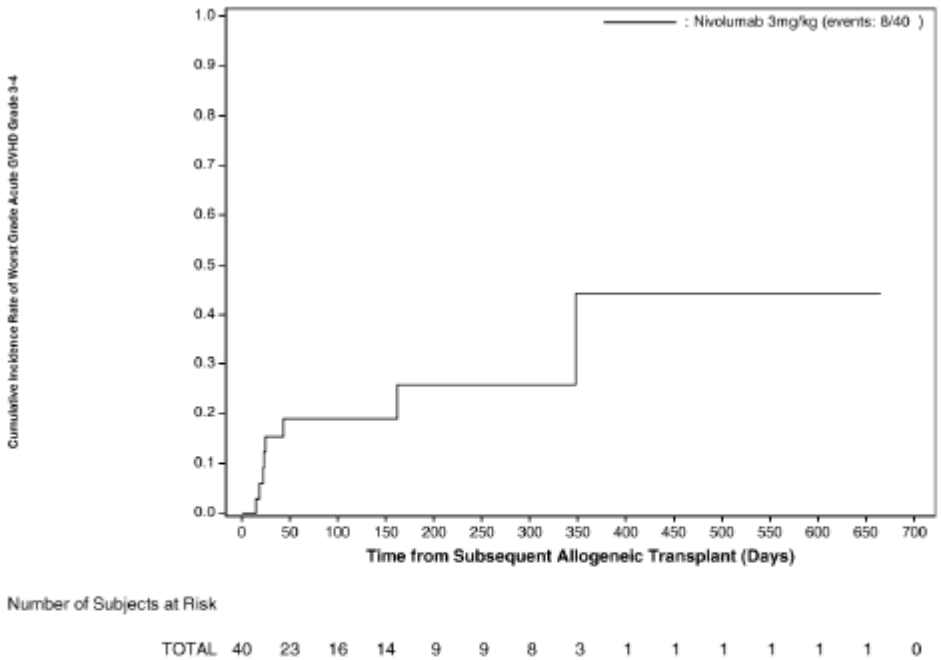
Grade 3-4 Acute GVHD after allogeneic HSCT

Cumulative incidence rate of Grade 3-4 acute GVHD from subsequent allogeneic HSCT was calculated in the same method as for Grade 2 -4 acute GVHD.

There is one subject who had a death without Grades 3-4 acute GVHD. The cumulative incidence rate of Grade 3-4 acute GVHD (95% CI) at Day 100, 6 months, and 1 year are 19.0 % (9.0, 37.6), 25.7 % (12.4, 48.7) and 44.3 % (18.5, 81.2), respectively (Figure 11).

The median time from transplant to Grade 3-4 acute GVHD (including two subjects with unknown grade of acute GVHD) cannot be estimated due to the small number of the subjects (n=7). The range of the onset of Grade 3-4 acute GVHD in 5 subjects (all Grade 4) was 14-43 days from transplant date. The onset of acute GVHD in the 2 subjects with unknown grades of acute GVHD was 22 and 162 days, respectively, from transplant date.

Figure 11: Plot of Cumulative Incidence Rate of Worst Grade Acute GVHD Grade 3-4 from Subsequent Allogeneic Transplant - CA209039 all cHL and CA209205 Cohort A+B+C - All Treated Subjects who underwent Subsequent Allogeneic Transplant



CA209039-4-50 reported worst acute GVHD on 01MAY2014 with missing grade. Therefore grade was imputed to Grade 4.
CA209205-17-138 reported worst acute GVHD on 23MAR2016 with missing grade. Therefore grade was imputed to Grade 4.
CA209039-5-95 had Grade 2 GVHD and died, and was counted as an event in the analysis.
PROGRAM SOURCE:/gbs/prod/clin/programs/ca/209/000/csrfa02/rpt/039-205/ema/20160830-allo/rg-efhm3dt-v02.sas RUN DATE: 12SEP2016 10:52

Other complications following allogeneic HSCT:

- One subject was reported with hepatic veno-occlusive disease (VOD) who received reduced-intensity conditioning and died due to multiorgan GVHD. The onset of hepatic VOD was 11 days after allogeneic HSCT.
- Chronic GVHD was reported in 2 subjects; both are limited stage of chronic GVHD.
- Steroid-responsive febrile syndrome, defined as fever (which may have been accompanied by skin, joint, or liver symptoms) without infection, which responded to steroids, was reported for 6 subjects.
- Two subjects experienced encephalitis: 1 case of grade 3 lymphocytic encephalitis which occurred and resolved on corticosteroids, and 1 case of grade 3 suspected viral encephalitis which resolved with antiviral therapy.

Discontinuation due to adverse events

Dose Delays and Interruptions

The majority of subjects received all doses of nivolumab without any infusion interruptions (95.1%) or dose delays (62.4%). Infusion interruptions were reported for 4.9% (n=13) of subjects. Of the doses interrupted (15/3140, 0.5%), 53.3% (8/15) were interrupted due to a hypersensitivity reaction.

Dose delays were reported for 37.6% of subjects, dose delays due to AEs were reported for 3.3% (96/2877) of all doses received. 98,4% of the delays were restarted within 42 days (47,2% within 4-7 days).

Table 54: Dose modification summary - All SCS subjects

	CA209205 Cohort A+B+C & CA209039 all cHL N = 263	CA209205 Cohort A+B+C N = 240	CA209205 Cohort B N = 80	CA209039 all cHL N = 23
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	13 (4.9)	10 (4.2)	5 (6.3)	3 (13.0)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)				
0	250 (95.1)	230 (95.8)	75 (93.8)	20 (87.0)
1	12 (4.6)	10 (4.2)	5 (6.3)	2 (8.7)
2	0	0	0	0
3	1 (0.4)	0	0	1 (4.3)
>= 4	0	0	0	0
TOTAL NUMBER DOSES INTERRUPTED/ TOTAL NUMBER DOSES RECEIVED	15/3140 (0.5)	10/2607 (0.4)	5/1288 (0.4)	5/ 533 (0.9)
REASON FOR INFUSION INTERRUPTION (A)				
HYPERSENSITIVITY REACTION	8 (53.3)	4 (40.0)	1 (20.0)	4 (80.0)
INFUSION ADMIN ISSUES	2 (13.3)	1 (10.0)	0	1 (20.0)
OTHER	5 (33.3)	5 (50.0)	4 (80.0)	0
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	99 (37.6)	88 (36.7)	48 (60.0)	11 (47.8)
NUMBER OF DOSES DELAYED PER SUBJECT (%)				
0	164 (62.4)	152 (63.3)	32 (40.0)	12 (52.2)
1	57 (21.7)	53 (22.1)	22 (27.5)	4 (17.4)
2	27 (10.3)	25 (10.4)	18 (22.5)	2 (8.7)
3	7 (2.7)	3 (1.3)	1 (1.3)	4 (17.4)
>= 4	8 (3.0)	7 (2.9)	7 (8.8)	1 (4.3)
TOTAL NUMBER DOSES DELAYED/ TOTAL NUMBER DOSES RECEIVED (B)	176/2877 (6.1)	148/2367 (6.3)	97/1208 (8.0)	28/ 510 (5.5)
REASON FOR DOSE DELAY (C)				
ADVERSE EVENT	96 (54.5)	80 (54.1)	53 (54.6)	16 (57.1)
OTHER	79 (44.9)	67 (45.3)	44 (45.4)	12 (42.9)
NOT REPORTED	1 (0.6)	1 (0.7)	0	0
LENGTH OF DELAY (C)				
4 - 7 DAYS	83 (47.2)	72 (48.6)	54 (55.7)	11 (39.3)
8 - 14 DAYS	58 (33.0)	48 (32.4)	28 (28.9)	10 (35.7)
15 - 42 DAYS	32 (18.2)	27 (18.2)	14 (14.4)	5 (17.9)
> 42 DAYS	3 (1.7)	1 (0.7)	1 (1.0)	2 (7.1)

A dose was considered as actually delayed if the delay is exceeding 3 days.
(A) Percentages are computed out of the total number of Dose Interrupted.
(B) Total number doses received is excluding first cycle.
(C) Percentages are computed out of the total number of doses delayed.

In the Integrated cHL Population, AEs leading to dose delay were reported in 60/263 (22.8%) subjects.

CA209205 Cohort A+B+C: AEs leading to dose delay were reported in 60/240 (25.0%) subjects. The most frequently reported AEs leading to dose delay (≥1% of subjects) were diarrhea (2.5%), ALT increased (1.7%), bronchopneumonia (1.7%), anemia (1.7%), neutropenia (1.3%), and pyrexia (1.3%).

- CA209039 all cHL: no subjects had AEs leading to dose delay.

In CA209205 Cohort B, AEs leading to dose delay were reported in 32/80 (40.0%) subjects.

All AEs Leading to Discontinuation (All Causality)

Table 55: Summary of adverse events leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) CA209205 Cohorts A+B+C & CA209039 all cHL, CA209205 Cohort B - All SCS subjects (120-day safety update)

System Organ Class (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B N = 80		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	14 (5.3)	10 (3.8)	1 (0.4)	4 (5.0)	3 (3.8)	1 (1.3)
INVESTIGATIONS	4 (1.5)	3 (1.1)	1 (0.4)	3 (3.8)	2 (2.5)	1 (1.3)
ASPARTATE AMINOTRANSFERASE INCREASED	3 (1.1)	3 (1.1)	0	2 (2.5)	2 (2.5)	0
ALANINE AMINOTRANSFERASE INCREASED	2 (0.8)	2 (0.8)	0	1 (1.3)	1 (1.3)	0
EPSTEIN-BARR VIRUS TEST POSITIVE	1 (0.4)	0	1 (0.4)	1 (1.3)	0	1 (1.3)
HEPATOBILIARY DISORDERS	2 (0.8)	2 (0.8)	0	1 (1.3)	1 (1.3)	0
AUTOIMMUNE HEPATITIS	1 (0.4)	1 (0.4)	0	1 (1.3)	1 (1.3)	0
HEPATITIS	1 (0.4)	1 (0.4)	0	0	0	0
INFECTIONS AND INFESTATIONS	2 (0.8)	2 (0.8)	0	0	0	0
PNEUMONIA	2 (0.8)	2 (0.8)	0	0	0	0
ATYPICAL PNEUMONIA	1 (0.4)	1 (0.4)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.8)	0	0	0	0	0
PLEURAL EFFUSION	1 (0.4)	0	0	0	0	0
PNEUMONITIS	1 (0.4)	0	0	0	0	0
CARDIAC DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
PERICARDIAL EFFUSION	1 (0.4)	1 (0.4)	0	0	0	0
GASTROINTESTINAL DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
PANCREATITIS	1 (0.4)	1 (0.4)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.4)	0	0	0	0	0
PYREXIA	1 (0.4)	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.4)	1 (0.4)	0	0	0	0
MYELODYSPLASTIC SYNDROME	1 (0.4)	1 (0.4)	0	0	0	0
NERVOUS SYSTEM DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
SYNCOPE	1 (0.4)	1 (0.4)	0	0	0	0
RENAL AND URINARY DISORDERS	1 (0.4)	0	0	0	0	0
AUTOIMMUNE NEPHRITIS	1 (0.4)	0	0	0	0	0

Drug-related Adverse Events Leading to Discontinuation

Table 56: Summary of drug-related adverse events leading to discontinuation by worst CTC grade (any grade, grade 3-4, gcrade 5) CA209205 Cohort A+B+C & CA209039 all cHL, CA209205 Cohort B- All SCS subjects 120—day safety update

System Organ Class (%) Preferred Term (%)	CA209205 Cohort A+B+C & CA209039 all cHL N = 266			CA209205 Cohort B N = 80		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	11 (4.1)	9 (3.4)	0	3 (3.8)	3 (3.8)	0
INVESTIGATIONS	3 (1.1)	3 (1.1)	0	2 (2.5)	2 (2.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	3 (1.1)	3 (1.1)	0	2 (2.5)	2 (2.5)	0
ALANINE AMINOTRANSFERASE INCREASED	2 (0.8)	2 (0.8)	0	1 (1.3)	1 (1.3)	0
HEPATOBILIARY DISORDERS	2 (0.8)	2 (0.8)	0	1 (1.3)	1 (1.3)	0
AUTOIMMUNE HEPATITIS	1 (0.4)	1 (0.4)	0	1 (1.3)	1 (1.3)	0
HEPATITIS	1 (0.4)	1 (0.4)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.8)	0	0	0	0	0
PLEURAL EFFUSION	1 (0.4)	0	0	0	0	0
PNEUMONITIS	1 (0.4)	0	0	0	0	0
CARDIAC DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
PERICARDIAL EFFUSION	1 (0.4)	1 (0.4)	0	0	0	0
GASTROINTESTINAL DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
PANCREATITIS	1 (0.4)	1 (0.4)	0	0	0	0
INFECTIONS AND INFESTATIONS	1 (0.4)	1 (0.4)	0	0	0	0
PNEUMONIA	1 (0.4)	1 (0.4)	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.4)	1 (0.4)	0	0	0	0
MYELODYSPLASTIC SYNDROME	1 (0.4)	1 (0.4)	0	0	0	0
NERVOUS SYSTEM DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
SYNCOPE	1 (0.4)	1 (0.4)	0	0	0	0
RENAL AND URINARY DISORDERS	1 (0.4)	0	0	0	0	0
AUTOIMMUNE NEPHRITIS	1 (0.4)	0	0	0	0	0

Immunogenicity

In study CA209205, there was 1/159 (0.6%) subject who was ADA positive and who was not considered persistent positive or neutralizing ADA positive. The highest titer value observed in this ADA-positive subject was 4. Of the 159 subjects with a baseline and least 1 post-baseline ADA measurement, 26 subjects experienced select AEs in the hypersensitivity/infusion reaction category and all were ADA negative.

In study CA209039, there was 1/19 (5.3%) subject who was ADA positive and who was not considered persistent positive or neutralizing ADA positive. The highest titer value observed in this ADA-positive subject was 32. Of the 19 subjects with a baseline and least 1 post-baseline ADA measurement, a total of 4 subjects experienced select AEs in the hypersensitivity/infusion reaction category and all were ADA negative.

An integrated analysis of nivolumab immunogenicity assessments was performed with data across indications from subjects treated with 3 mg/kg Q2W nivolumab (Studies CA209037, CA209063, CA209066, CA209017, CA209057, CA209067 [nivolumab monotherapy arm only]), CA209025, CA209205, and CA209039. Of 1586 subjects who were treated with nivolumab 3 mg/kg Q2W and evaluable for the presence of ADA, 157 subjects (9.9%) tested positive for treatment-emergent ADA. Only 2 subjects (0.1% of the total) were persistent positive, and neutralizing antibodies were detected in only 9 (0.6% of the total) of the ADA positive subjects. There were no acute infusion reactions, hypersensitivity events, or new or additional AEs observed in patients with neutralizing antibodies.

The incidence of immunogenicity has been updated and is depicted as selected adverse reaction in the SmPC section 4.8.

Table 57: Summary of hypersensitivity/infusion reactions by nivolumab ADA status across studies - All treated subjects receiving nivolumab monotherapy with ADA positive or ADA negative

Select AE Category: Hypersensitivity/Infusion Reaction	Number of Subjects (%)	
	Nivolumab ADA Positive (N = 167)	Nivolumab ADA Negative (N = 1468)
Total Subjects with an Event	4 (2.4)	105 (7.2)
Anaphylactic Shock	0	1 (0.07)
Bronchospasm	1 (0.6)	10 (0.7)
Hypersensitivity	1 (0.6)	42 (2.9)
Infusion Related Reaction	2 (1.2)	58 (4.0)

Integrated data from studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067 (monotherapy arm), CA209025, CA209205 (Cohort A+B+C) and CA209039 (all cHL).

ADA positive: subject with at least 1 ADA positive sample relative to baseline at any time after start of treatment.

ADA negative: subject with no ADA positive sample after the start of treatment. Post-baseline are assessments reported after initiation of treatment.

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved across multiple countries, including the US and the EU, and for other indications (eg, metastatic NSCLC, advanced RCC). Based on routine pharmacovigilance activities conducted by the MAH Pharmacovigilance and Epidemiology, review of postmarketing data confirms the clinical trial data for nivolumab. To date, no new significant safety concerns have been identified based on the global postmarketing reports.

2.5.1. Discussion on clinical safety

The safety of nivolumab monotherapy was assessed primarily based on the data from the integrated CHL population (CA209205 cohort A+B+C (n=240) and CA209039 all cHL (n=23 subjects). The median extent of follow-up was prolonged from 5.55 months to 9.49 months, the median number of doses received increased from 10.0 to 16.0, and the number of the subjects who had at least 12 months follow-up has been changed from 10 to 88.The safety data from the separate studies were in line with the data from integrated analysis. The frequencies of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, infusion reactions, laboratory abnormalities and immunogenicity have been updated in section 4.8 of the SmPC.

Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL, thus a warning has been included in section 4.4 of the SmPC. In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential risk-benefit on an individual basis.

All-causality AEs and drug-related AEs were slightly higher in cohort B study CA209205 which is likely due to the longer exposure duration and follow-up. In general, the types and frequencies of AEs were consistent with prior nivolumab experience from other indications. In the 120-day safety update, the majority of subjects (76.5%) received ≥90% of the planned nivolumab dose intensity, the median number of nivolumab doses received was 16.

All-causality AEs of any grade were reported in 98.1% of subjects. The most frequently reported AEs (≥20% of subjects) were fatigue (32.3%), diarrhoea (28.9%), pyrexia (27.1%) and cough (25.9%).

Drug-related AEs of any grade were reported in 77.1% of subjects. The most frequently reported drug-related AEs (≥10% of subjects) were fatigue (19.9%), infusion-related reaction (12.8%), diarrhoea (13.5%), nausea (10.2%), and rash (12.0%).

All-causality Grade 3-4 AEs were reported in 35.0% of subjects. The most frequently reported Grade 3-4 AEs (≥2% of subjects) were lipase increased (4.9%), neutropenia (3.0%), alanine aminotransferase increased (2.6%) and anaemia (2.3%).

Drug-related Grade 3-4 AEs were reported in 19.5% of subjects. The most frequently reported Grade 3-4 drug-related AEs (≥ 1% of subjects) were lipase increased (3.8%), ALT increased (2.3%), neutropenia (2.3%), amylase increased (1.5%) and AST (1.5%).

Increased lipase as AE (any grade) was reported more frequently in cHL subjects than in the pooled nivolumab safety population (6.8% versus 3.1% and drug-related 4.9% versus 2.1%). Approximately 50% was grade 3-4 in both populations. The reported higher frequency of increased lipase in cHL population was possibly due to systematic monitoring of serum lipase in the Phase 1 (CA209039) and Phase 2 (CA209205) studies.

Pancreatitis was reported in 2 subjects in the cHL integrated population and 10 subjects in the pooled population, with a similar incidence (0.8% versus 0.5%). Lipase increase and pancreatitis are reported in the SmPC section 4.8.

The increased frequency of neutropenia is likely attributed to the cHL patient population since the majority of subjects had previous exposure to high-dose chemotherapy and ASCT.

Among the most frequently reported AEs pyrexia was reported more frequently (> 5% difference) in cHL than in RCC, melanoma, and NSCLC, this could be attributed to the underlying disease.

All-causality SAEs of any grade were reported in 23.3% of subjects. The most frequently reported SAEs (≥1% of subjects) were infusion-related reaction (1.9%), pneumonia (1.9%), pleural effusion (1.5%), pyrexia (1.5%), malignant neoplasm progression (1.5%), dyspnoea (1.1%) and pneumonitis (1.1%).

Drug-related SAEs of any grade were reported in 10.2% of subjects. The most frequently reported drug-related SAEs (≥1% of subjects) were infusion-related reaction (1.9%) and pneumonitis (1.1%)

All-causality Grade 3-4 SAEs were reported in 15.4% of subjects. The most frequently reported Grade 3-4 SAEs (≥1% of subjects) were pneumonia (1.1%), dyspnoea (1.1%) and malignant neoplasm progression (1.1%).

Drug-related Grade 3-4 SAEs were reported in 4.9% of subjects.

The frequencies of Select AEs (endocrine, gastrointestinal, hepatic, pulmonary, renal, and dermatological events) showed similar frequencies as other indications.

A higher incidence of drug-related infusion reactions was observed in cHL versus other tumour types, this is likely due to a high rate of reporting at one single site. The infusion-related reactions were reported at higher frequencies in cHL (13.2%) compared with other tumour types: RCC (5.2%), melanoma (4.8%), and NSCLC (2.2%). In the Integrated cHL Population -120-day safety update, the frequency of hypersensitivity/infusion reactions (all causality, any grade) was 16.9%. Therefore, these hypersensitivity/infusion reactions are not considered significantly clinically relevant to nivolumab treatment.

In the integrated analysis, 18 subjects (6.8%) died, 3.4% of the death was due to disease progression and one death (within 30 days of last dose) was attributed to a reason of "study drug toxicity", eight deaths (3.0%) were attributed to a reason of "other" and 0.4% due to study drug toxicities.

Interpretation of the frequencies in the ≥65 years age group is limited for the total nivolumab monotherapy group due to the small number of subjects. In the integrated cHL cohort only 7 subjects were ≥65 years. The limited experience with elderly has been reflected in the SmPC.

There was am increase in number of cases with (moderate and severe) acute GvHD (87%), and alloSCT associated death observed after nivolumab treatment which is of concern since it exceeds the percentage of similar cases published in the literature (which has been reported close to 40%). The MOA as well as limited published non-clinical and clinical studies suggest a relation between nivolumab and aGVHD. It is notable that among the new cases reported in the safety update, there was a remarkable lower incidence of acute GVHD and TRM. When comparing the median observation time after alloSCT, i.e. 308 days for the initial 17 subjects and 41 days for the additional 23 subjects, the shorter follow-up in the additionally reported patients is likely the most important factor contributing to the lower incidence rates for aGvHD and TRM. Multivariate analysis results showed that for both aGvHD and OS, no relevant association between transplant procedures and nivolumab treatment could be found. However, patient number is small and the patient population is very heterogeneous, particular regarding follow-up duration. Based on these data, a relationship between an increased risk for aGvHD and TRM following alloSCT after previous exposure to nivolumab cannot be excluded. Therefore, acute GvHD has been included as an important potential safety concern in the RMP and will be managed through routine pharmacovigilance (warning in section 4.4 of the SmPC) and additional risk minimisation activities with updated educational material. In addition, the CHMP has requested for the MAH to perform a registry study in patients who underwent post-nivolumab allogenic HSCT.

2.5.2. Conclusions on clinical safety

The overall safety of nivolumab monotherapy in cHL appears to be consistent with the safety in approved indications. In heavily pretreated cHL patients who received prior ASCT and brentuximab vedotin, the safety profile of nivolumab monotherapy was consistent with the Integrated cHL Population, with higher AE frequencies. The SmPC has been updated with the pooled frequencies for the adverse reactions. No new safety concerns have been raised except for the increased risk for acute GvHD and TRM following alloSCT after nivolumab exposure (see RMP). Because of the limited data available, it is not possible to exclude causality between aGvHD and nivolumab following alloSCT. Therefore, complications of allogeneic HSCT following nivolumab therapy has been included as an important potential risk and risk minimisation measures will be put in place. There are few data on the safety of elderly patients with cHL ≥ 65 years of age, which has been include as missing information in the RMP.

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

- PASS: A registry study in patients who underwent post-nivolumab allogeneic hematopoietic stem cell transplantation (HSCT) should be carried out.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 03/01/2017.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the RMP version 5.0 (dated 05 October 2015) could be acceptable if the

applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur Updated assessment report dated 09 June 2016.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as requested by the PRAC the CHMP.

The CHMP endorsed the Risk Management Plan version 5.3 (dated 12 October 2016) with the following content:

Safety concerns

Table 58: Summary of the safety concerns

Important identified risks	• Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis • Immune-related nephritis and renal dysfunction • Immune-related endocrinopathies • Immune-related rash • Other immune-related ARs • Severe infusion reactions
Important potential risks	• Embryofetal toxicity • Immunogenicity • Cardiac arrhythmias (previously treated melanoma indication, only) • Complications of allogeneic HSCT following nivolumab therapy
Missing information	• Pediatric patients <18 years of age • Elderly patients with cHL ≥ 65 years of age • Patients with severe hepatic and/or renal impairment • Patients with autoimmune disease • Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Table 59: Ongoing and planned additional PV Studies / Activities in the Pharmacovigilance Plan

Study / Activity Type Title and Category (1-3	**Objectives**	**Safety concern addressed**	**Status**	***Estimated date for submission of interim or final study report***
CA209835: A registry study in patients who underwent post-nivolumab allogeneic HSCT Category 3	To assess transplant-related complications following prior nivolumab use	Post-marketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	Planned	Final CSR submission: 4Q 2022

CA209234: Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice. Category 3	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Post-marketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, and myasthenic syndrome), and infusion reactions	Started	Final CSR submission: 4Q2024

Risk Minimisation Measures

Table 60: Summary table of the risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
• Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis • Immune-related nephritis and renal dysfunction • Immune-related endocrinopathies • Immune related rash • Other immune-related ARs	SmPC wording in section 4.2, 4.4,4.8	To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan. The Plan comprising 2 tools to be distributed to potential prescribers at launch by BMS: • Adverse Reaction Management Guide • Patient Alert Card
Severe infusion reactions	SmPC wording in section 4.4,4.8	None
Important Potential Risks		
Embryofetal Toxicity	SmPC wording in section 4.6, 5.3	None
Immunogenicity	SmPC wording in section 4.8	None
Cardiac arrhythmias (previously treated melanoma indication, only)	SmPC wording in section 4.8	None
Complications of allogeneic HSCT following nivolumab therapy	SmPC wording in section 4.4, 4.8	Adverse Reaction Management Guide
Missing Information		
Pediatric patients	SmPC wording in section 4.2	None
Elderly patients with cHL ≥ 65 years of age	SmPC wording in section 4.8, 5.1	None
Severe hepatic and/or renal impairment	SmPC wording in section 4.2, 5.2	None
Patients with autoimmune disease	SmPC wording in section 4.4	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Patients already receiving systemic immunosuppressants before starting nivolumab	SmPC wording in section 4.4, 4.5	None

2.7. Update of the Product information

As a consequence of this new indication, section 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. New warnings on interstitial lung disease and complications of allogenic HSCT post-nivolumab treatment have been included. The Package Leaflet has been updated accordingly. For further details, please refer to the full PI in attachment.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Croatia.

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 applicant and has been found acceptable. This variation does not involved major changes to the PI or impact the readability of the PL.

3. Benefit-Risk Balance

Benefits

The application for an extension of indication in cHL is based on the clinical data derived from two ongoing single arm, open label studies, the phase II study CA209205 (in patients having progressed after ASCT with different cohorts having received or not brentuximab vedotin) and phase I study CA209039 (with expansion cohorts studying different types of hematologic malignancies patients). Overall, patients relapse or refractory after ASCT and brentuximab vedotin (cohort B study CA209205), patients having progressed after ASCT but not treated with brentuximab vedotin (brentuximab naïve; cohort A study CA209205), patients having progressed after ASCT but treated with brentuximab before and/or after ASCT (cohort C study CA209205) and finally, patients not eligible for ASCT (ASCT naïve:; study CA209039) have been included in the analyses.

Beneficial effects

- Nivolumab treatment after ASCT and treatment with brentuximab vedotin

In the integrated population (n=90) from study CA209205 (n=80) (cohort B) and CA209039 (n=15), treatment of patients with nivolumab led to an ORR of 66.3% (IRRC analysis) with a CR of 6.3% and median DOR of 13.14 months. Data from cohort C in patients with the same previous sequence of treatment than in the cohort B (n=57) are consistent with the efficacy showed in the integrated population. The efficacy results from this cohort look similar to cohort B, ORR was 72% (vs 66.3% in cohort B Oct 2015 DBL) with 12% of CR (vs 9% CR in cohort B). Median time to reach a response was 2 months, according to the phase II trial results, and almost 1 month when the phase I study is observed but the difference could just be due to differences in the time point for assessment within studies (at week 4 in the phase I instead of week 9 in the CA209205 study).

Regarding the subgroups analyses (by age, gender, race, region, smoking status, B-symptoms at initial diagnosis, baseline ECOG performance status, time from initial diagnosis to first transplant, time from

recent transplant to first subsequent therapy, and number of prior lines of cancer therapy excluding preparative regimens) the results are in line with those of the whole study population, even when the previous response to brentuximab is included in the analysis.

Analysis of biomarkers such as 9p24.1 showed that patients with 9p24.1 amplification and increased PD-1 expression seemed more responsive to PD-L1 blockade; the association between best overall response and H score was significant (p=0.013).

This antitumor activity appears to translate into a delay in the tumour progression, with a median PFS of 14.78 months. However, the number of events is still low (38/95 in the integrated population) and there is no OS data.

- Nivolumab treatment after at least 2 prior therapies in patients who are not candidates for ASCT

Study CA209039 enrolled 5 ASCT-naive subjects (3 were brentuximab-naive and 2 had prior brentuximab treatment) that were heavily pre-treated with at least 2 lines of prior systemic cancer therapy. Four out of five ASCT naive subjects had an objective response both per IRRC and investigator. Two subjects, both responders, were elected to discontinue nivolumab treatment and preceded to subsequent transplant.

Uncertainty in the knowledge about the beneficial effects

In patients heavily pre-treated (ASCT and brentuximab), mature PFS and OS data are still unavailable. Therefore, the CHMP has requested the MAH to submit PFS and OS data from study CA209205 as part of an Annex II condition.

Results from PD-L1 expression according to the pre-specified cutoff of 1%, do not show meaningful differences, although 90% of the quantifiable population (63 subjects) had PD-L1 ≥1%.

The value of TILs, lymphocyte activation and proliferation markers have not been analysed in CA209039 and CA209205 (all cohorts). Analysis of patients with 9p24.1 polysomy or PD-L1 expression showed that in the first quartile were able to achieve partial remission and as such a clear relation between 9p24.1 polysomy or PD-L1 expression and efficacy of treatment can currently not be made. At this stage the number of biopsies is small and analyses seem exploratory. The applicant is encouraged to aim at further studying the correlation of biomarkers with efficacy in further studies. Additional biomarker analyses may lead to improved understanding of biomarkers and the efficacy of nivolumab in cHL. Therefore, the CHMP recommends for the MAH to pursue biomarker analysis in the context of cHL.

In ASCT-naive subjects with a median of 2 prior treatments, although efficacy was shown in 4/5 subjects, the sample size was too limited for any meaningful conclusion and comparative data to a brentuximab vedotin treatment arm was lacking. The CHMP had concerns that there were too few data to support an expanded indication in patients that were ASCT- naïve at this time considering that there are currently other effective treatment options for this patient population.

It is unknown whether discontinuation of nivolumab monotherapy is safe in patients who have discontinued and remained in CR for one year on nivolumab. Currently the SmPC states that treatment duration of nivolumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. For cHL, this would mean that some patients who have achieved CR may remain on therapy for a prolonged period of time until disease progression occurs. Therefore, the CHMP recommends the MAH to submit efficacy and safety data from study CA209205 cohort C in order to explore whether discontinuation of nivolumab monotherapy is safe in patients who have remained in CR for one year on nivolumab.

Risks

Unfavourable effects

The safety profile of nivolumab monotherapy was assessed primarily based on the data from the integrated CHL population (CA209205 cohort A+B+C (n=240) and CA209039 all cHL (n=23 subjects). Drug-related AEs of any grade were reported in 77.1% of subjects. The most frequently reported drug-related AEs (≥10% of subjects) were fatigue (19.9%), infusion-related reaction (12.8%), diarrhoea (13.5%), nausea (10.2%), and rash (12.0%). Drug-related Grade 3-4 AEs were reported in 19.5% of subjects. The most frequently reported Grade 3-4 drug-related AEs (≥ 1% of subjects) were lipase increased (3.8%), ALT increased (2.3%), neutropenia (2.3%), amylase increased (1.5%) and AST (1.5%). Lipase increased and neutropenia were the only Grade 3-4 AE reported more frequently (>1% difference) in cHL than in the other tumour types.

In the integrated cHL Population (120-day safety update), there was a low frequency of AEs leading to discontinuation (5.3% of subjects). Drug-related AEs leading to discontinuation of any grade were reported in 4.1% of subjects. Drug-related Grade 3-4 AEs leading to discontinuation were reported in 3.4% of subjects.

In the integrated analysis (120-day Safety update), 18 subjects (6.8%) died. 3.4% of the death was due to disease progression and one death (within 30 days of last dose) and 0.4% due to study drug toxicities. Eight deaths (3.0%) were attributed to a reason of "other" and not thought to be related to the treatment.

The immunogenic potential of nivolumab monotherapy is low (0,6% in CA209205 and 5,3% in CA209039). The incidence of infusion-related reactions is numerically higher in the cHL population than in the nivolumab monotherapy treatment group. Delayed hypersensitivity can be observed beyond 6 months from the first dose of nivolumab at a very low frequency. Therefore, these hypersensitivity/infusion reactions are not considered significantly clinically relevant to nivolumab treatment.

Uncertainty in the knowledge about the unfavourable effects

Fatal events have occurred in patients who received allogeneic Stem Cell Transplantation (allo-SCT) after nivolumab and there were a higher than expected number of patients who suffered aGvHD and TRM compared to historical controls. The data is still preliminary and further follow up of patients undergoing allogeneic HSCT after previous exposure to nivolumab would be needed to ascertain this risk. Nevertheless, complications of allogeneic HSCT following nivolumab therapy has been included as an important potential risk in the RMP and will be monitored through routine pharmacovigilance (SmPC section 4.4). Additional risk minimisation activities have been included with an update to the educational material on the risk of complications of allogenic HSCT following nivolumab therapy. In addition, the CHMP has requested the MAH to follow up patients who underwent post-nivolumab allogeneic hematopoietic stem cell transplantation (HSCT) in a registry study.

Interpretation of the frequencies in the ≥65 years age group is limited for the total nivolumab monotherapy group due to the small number of subjects. The limited experience with elderly has been reflected in the updated SmPC and added to the RMP as missing information.

Effects Table

Table 61: Effects Table for Nivolumab in cHL adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. (data cut-off: April 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR (Integrated population)	% of patients with BOR of CR or PR according to the 2007 IWG criteria (IRRC assessment)	%	66.3	No control	Data from 2 single arm studies with only 95 patients / Results seem robust regardless of the study and subgroup analyses	See Clinical efficacy
DOR (Integrated population)	Time from the 1st response to date of progression or death (IRRC assessment)	months	13.14		Data not mature enough (subjects with ongoing response 13/63)	
PFS (Integrated population)	Time from the 1st dosing date to date of progression or death	Median (months)	14.78		Data not mature	
OS (Integrated population)	Time from 1st dosing date to death	Median (months)	NA		Data not mature	
Unfavourable Effects						
All AEs	Adverse events regardless causality	%	98.1	No control	Limited safety dataset	No new safety concerns with nivolumab monotherapy treatment were identified in cHL, except the transplant-related deaths after nivolumab treatment
Fatigue	Most frequent drug-related AE	%	19.9			
Infusion related reaction	Most frequent drug-related AE	%	12.8			
Diarrhoea	Most frequent drug-related AE	%	13.5			
nausea	Most frequent drug-related AE	%	10.2			
AEs Grade 3-4	Percentage of Adverse events grade 3-4 regardless causality	%	35			
All SAEs	Percentage of serious Adverse events regardless causality	%	23.3			
Drug-related SAEs	Percentage of drug-related serious Adverse events	%	10.2			
All AEs leading to Dose Delay	frequency of AEs leading to discontinuation %	%	5.3			
Drug-related AEs leading to Dose Delay	frequency of drug-related AEs leading to discontinuation %	%	4.1			

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The treatment of cHL patients with nivolumab showed an ORR with a high order of magnitude which in itself is considered clinically meaningful. In the group of patients heavily pretreated (after ASCT and brentuximab) and with limited treatment options available, tumour responses following treatment with nivolumab are considered clinically relevant. In addition, support for this outcome is observed in the prolonged durability of the responses. It is realistic to assume that the delay in tumour progression will result in a higher PFS and longer OS in the long term. This is supported by the analysis from the most recent prior systemic cancer therapy in Study CA209205 and comparing those to the median PFS offered by nivolumab (14.78 months vs 5.19 months).

From a safety point of view, data are limited but so far no unexpected AEs have been identified. Nonetheless, the potential complications (acute GvHD and TRM) in patients pretreated with nivolumab and then with alloScT are uncertain, since the patient number is small and the patient population is very heterogenous, especially regarding follow-up duration. This will be follow up by routine and additional pharmacovigilance activities.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

Hodgkin Lymphoma is a potentially curable disease in patients at first line, with a cure rate of approximately 80% with the use of modern therapies. For patients who relapse, treatment of choice consists of a chemotherapy regimen (different than that used in the first line) followed by high dose chemotherapy and autologous stem cell rescue with or without radiation therapy. Once a subject undergoes ASCT and subsequently relapses, the outcomes are generally poor and efficacious therapeutic options are limited. The median OS of patients who relapse after ASCT was initially reported to be < 1 year; more recent data suggests that the median OS is evolving and may be closer to 2 years because of the availability of newer therapies like brentuximab.

Data from the clinical development of nivolumab in cHL come from two small open label single arm studies. In spite of the uncertainties generated by the lack of control group, the tumour response rates achieved with nivolumab in a heavily pre-treated population (including ASCT and brentuximab, with a median of number of prior systemic regimens excluding preparative regimen of 4) are considered outstanding. Few efficacy alternatives are available after failure to ASCT and brentuximab vedotin. Retreatment with brentuximab vedotin in those patients with a previous response to brentuximab (CR/PR) appears to show an ORRs around 60%[8], which could be considered similar to nivolumab. The rest of alternatives can hardly provide response rates above 30-40%. In fact, the ESMO guideline recommends the use of palliative single agent chemotherapy with gemcitabine or bendamustine and/or regional RT in patients with multiple relapses who have no other treatment options.

It is clear that in a relapse/refractory population heavily pre-treated with ASCT and brentuximab, the treatment with nivolumab is able to provide high and durable tumour responses. This improvement in antitumour activity is expected to translate into a clinical benefit in terms of PFS and OS, however, the data are immature at this stage to draw any conclusions. As a follow up, the CHMP has request the MAH to submit PFS and OS data from study CA209205.

It is of note that a higher than expected number of cases with (moderate and severe) acute GvHD, and alloSCT-related deaths occurred after nivolumab treatment. As nivolumab releases the regulatory breaks

that keep the immune system under control, the relationship between nivolumab and aGVHD cannot be ruled out. According to the current guidelines, as alloSCT is currently not the preferred approach in the post- autoSCT setting, nivolumab use prior to alloSCT does not result in a loss of chance per se. The decision of treating patients with nivolumab following alloAST should be taken following careful consideration to the potential benefits of SCT and the possible increased risk of transplant related complications. This decision should be made on a case by case. Close monitoring of patients undergoing alloSCT for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid requiring febrile syndrome, hepatic veno-occlusive disease, and other transplant related complications is recommended.

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

- Annex II condition Post-authorisation efficacy study (PAES): The MAH should submit the final clinical Study report for study CA209205: a Phase 2, non-comparative, multi-cohort, single-arm, open-label study of nivolumab (BMS-936558) in cHL subjects after failure of ASCT. The final clinical study report should be submitted by 30th June 2017
- PASS: A registry study in patients who underwent post-nivolumab allogeneic hematopoietic stem cell transplantation (HSCT) should be carried out.

4. Recommendations

Outcome

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

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

Extension of Indication to include the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin; as a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed new indication, add a warning that patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL, and update the safety and pharmacodynamic information. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.0. Moreover, the updated RMP version 5.3 was agreed during the procedure.

This recommendation is subject to the following amended condition:

Conditions and requirements of the marketing authorisation

- **Additional risk minimisation measures**

Prior to launch of OPDIVO in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness about the potential immune mediated adverse events associated with OPDIVO use, how to manage them and to enhance the awareness of patients or their caregivers on the signs and symptoms relevant to the early those adverse events.

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 following educational package:

- Physician educational material
- Patient alert card

The physician educational material should contain:

- The Summary of Product Characteristics
- Adverse Reaction Management Guide

The Adverse Reaction Management Guide shall contain the following key elements:

- Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable) for the following safety concerns:
    - Immune-related pneumonitis
    - Immune-related colitis
    - Immune-related hepatitis
    - Immune-related nephritis or renal dysfunction
    - Immune-related endocrinopathies
    - Immune related rash
    - Other immune-related ARs
    - Potential risk of 'Complications including acute graft-versus-host-disease and transplant related mortality of allogeneic Haematopoietic Stem Cell Transplant following nivolumab therapy'
- Details on how to minimise the safety concern through appropriate monitoring and management
- **The patient alert 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 or renal dysfunction
    - Immune-related endocrinopathies
    - Immune related rash
    - 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

The recommendation is further subject to the following new condition:

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

Description	**Due date**
3. Post-authorisation efficacy study (PAES): The MAH should submit the final Study report for study CA209205: a Phase 2, non-comparative, multi-cohort, single-arm, open-label study of nivolumab (BMS-936558) in cHL subjects after failure of ASCT.	The final clinical study report should be submitted by 30th June 2017

Appendix

1. CHMP AR on similarity dated 11 May 2016

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[2] Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in Patients With Relapsed/Refractory Hodgkin's Lymphoma After Autologous Stem-Cell Transplantation: Results of a Phase II Study. J Clin Oncol. 2012;13(18):2197-203.

[3] Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol. 2010;85(5):320-24.

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[5] Venkatesh H, Di Bella N, Flynn TP, et al. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's lymphoma. Clin Lymphoma. 2004; 5(2):110-115.

[6] Younes A, Romaguera J, Hagemeister F, et al. A Pilot Study of Rituximab in Patients with Recurrent, Classic Hodgkin Disease. Cancer. 2003; 98(2):310-14.

[7]The 2012 revised edition of the EBMT-ESH Handbook onHaematopoietic Stem Cell Transplantation. Chapter 13. Editors: J.Apperley, E. Carreras, E. Gluckman, T. Masszi.

[8]http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf