28 January 2021
EMA/97222/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: **pembrolizumab**

Procedure No. EMEA/H/C/003820/II/0090

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	Antidrug antibodies
AE(s)	Adverse event(s)
AEOSI	Adverse event(s) of special interest
Allo-SCT	Allogeneic stem cell transplant
ASaT	All Subjects as Treated
AUC	Area under the concentration-time curve
Auto-SCT	Autologous-stem cell transplant
BICR	Blinded independent central radiology review
BOR	Best Overall Response
BV	Brentuximab vedotin
cHL	Classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRR	Complete remission rate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
EC50	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D	European Quality of Life Five Dimensions Questionnaire
EU	European Union
FDA	Food and Drug Administration
GHS	Global health status
GVHD	Graft versus host disease
HL	Hodgkin lymphoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio

IA	Interim analysis
IFNγ	Interferon gamma
IgG4	Immunoglobulin G4
IL-2	Interleukin-2
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
mAb	Monoclonal antibody
MCC	Merkel cell carcinoma
MSI-H	Microsatellite instability-high
NOS	Not otherwise specified
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
PRO	Patient-reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rrcHL	Relapsed/refractory classical Hodgkin lymphoma
SAE	Serious adverse event(s)
SCLC	Small-cell lung cancer

SCT	Stem cell transplant
SoC	Standard of care
TNFα	Tumor necrosis factor alpha
TRAE	Treatment-related adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 13 May 2020 an application for a variation.

The following variation was requested:

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

Extension of the currently approved therapeutic indication for the treatment of relapsed or refractory classical Hodgkin lymphoma (rrcHL) in adults to an earlier line of therapy and to include paediatric patients - as follows:
KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) following at least one prior therapy when ASCT is not a treatment option.
The indication is based on the study KEYNOTE-204, a randomized, open-label, Phase 3 trial evaluating KEYTRUDA monotherapy versus Brentuximab Vedotin (BV) for the treatment of patients with rrcHL and supportive data from updated analysis of KEYNOTE-087, which was the pivotal study supporting the initial rrcHL indication. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The revised RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics 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 EMA Decisions P/0008/2018 and P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0008/2018 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

Scientific Advice (SA) related to clinical development of pembrolizumab in relapsed/refractory cHL, including phase III study KN-204 was received from the CHMP (see procedure EMEA/H/SA/2437/9/2015/II).

Further SA was received on the proposed extrapolation approach to support the registration in paediatric patients with r/r cHL (see procedure EMEA/H/SA/2437/28/2019/PED/II).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	13 May 2020
Start of procedure:	20 June 2020
CHMP Rapporteur's preliminary assessment report circulated on:	19 August 2020
CHMP Co- Rapporteur's preliminary assessment report circulated on:	13 August 2020
PRAC Rapporteur's preliminary assessment report circulated on:	26 August 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	3 September 2020
CHMP Rapporteurs' (Joint) Assessment Report circulated on:	11 September 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	17 September 2020
MAH's responses submitted to the CHMP on:	9 October 2020
CHMP Rapporteurs' (Joint) preliminary assessment report on the MAH's responses circulated on:	19 November 2020
2nd request for supplementary information and extension of timetable adopted by the CHMP on:	10 December 2020
MAH's responses submitted to the CHMP on:	18 December 2020
CHMP Rapporteurs' (Joint) preliminary assessment report on the MAH's responses circulated on:	13 January 2021
CHMP opinion adopted on:	28 January 2021
The CHMP adopted a report on similarity of Keytruda with Adcetris on:	28 January 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Classical Hodgkin Lymphoma (cHL); the claimed therapeutic indication was for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory cHL who have failed autologous stem cell transplant (ASCT) or following at least one prior therapy when ASCT is not a treatment option. Following the assessment, the agreed indication was for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory cHL who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Epidemiology

cHL is a B cell lymphoproliferative disease with distinct clinic and biologic features; it accounts for approximately 10% of all lymphomas, 0.6% of all cancers and 0.2% of all cancer deaths. The incidence in Europe is approximately 2.4 cases per 100.000 persons, with a characteristic bimodal age distribution: one peak in young adults (median age of onset 20 years) and a second peak in older adults (median age of onset 65 years). Overall, the majority of patients are young adults, with a peak incidence between 15 and 35 years and a slightly higher prevalence in males. The actual incidence pattern is known to vary, however, according to race and region.

Biologic features

cHL is characterised by the presence of Reed-Sternberg (RS) cells (i.e. CD30+, CD15+, CD45- bi-nucleate B cells with a typical "owl's eyes" morphology) in the context of a mixed inflammatory background, which comprises lymphocytes (T-cells are usually predominant), eosinophils, neutrophils, macrophages, plasma cells and fibroblasts. The specific inflammatory pattern has prognostic value, further classifying cHL into 4 distinct histologic subtypes: nodular sclerosis (70%), mixed cellularity (20-25%), lymphocyte-rich (5%) and lymphocyte-depleted (<1%) cHL. The rare lymphocyte depleted variant is associated with the most aggressive behaviour and worst prognosis. The disease has similar biology and natural history in both children and adults age groups.

Together with NFkB, JAK-STAT signalling is usually hyperactivated in cHL, with a significant impact on the differentiation, proliferation, and survival of neoplastic lymphocytes. In particular, dysregulated JAK-STAT signalling results in PD-L1 and PD-L2 hyperexpression: binding to PD1 on T cells, PD-L1 and PD-L2 are implicated in the "exhaustion" of cytotoxic cells and contribute to cHL cells survival. Alterations in the PD-L1 and/or PD-L2 genetic loci resulting in increased PD-1 ligands expression (e.g. amplification or polysomy of chromosome 9p24.1) are also common in cHL, further highlighting how immune evasion is a key element in cHL pathogenesis.

EBV infection, obesity, high birthweight, smoking, immunosuppression, HLA-A1 and autoimmune disorders have all been associated with an increased risk of developing cHL, and in some cases a familial predisposition has been reported.

Clinical presentation and prognosis

cHL usually presents with asymptomatic enlarged lymph nodes or as a neoplastic mediastinal/abdominal mass. Systemic "B" symptoms (i.e. fever, night sweats, unintended weight loss, recurrent infections) are present in approximately 40% of patients at the time of diagnosis. Pruritus is also common in cHL (~10 to 15% of patients) and can precede the diagnosis by months or longer.

Staging of cHL is based on the Lugano classification, which is derived from the Ann Arbor staging system. Early stages (I and IIA) are characterised by limited lymph node involvement, while advanced stage disease (IIB-IV) is defined by high disease burden in terms of extensive nodal and/or extranodal involvement or bulky disease (e.g. a mediastinal mass ≥ 10 cm or with a ≥0.33 ratio of the maximum width of the mass and the maximum intrathoracic diameter).

Prognosis is evaluated by the international prognostic score (IPS) based on serum albumin and haemoglobin levels, male gender, age, disease stage and white blood cell/absolute lymphocyte counts. Subjects with no risk factors are predicted to have a 5-year progression-free survival (PFS) and overall survival (OS) of 88% and 98%, respectively. Conversely, for patients with 5 or more risk factors the 5-year PFS and OS are 62% and 67%, respectively.

Management

Localised, early stage cHL is usually treated with a combination of abbreviated chemotherapy and low dose involved-site radiation therapy and high cure rates (~90%) are usually observed. Advanced stage cHL is treated with upfront combination chemotherapy (e.g. ABVD, BEACOPP or STANFORD-V) ± involved-field radiation therapy (e.g. in presence of bulky disease and/or residual mass). Brentuximab vedotin (BV), an immunotoxin comprised of a CD30-directed antibody linked to an anti-tubulin agent (MMAE), has been recently authorised in combination with doxorubicin, vinblastine and dacarbazine (AVD) for the treatment of adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL), with an overall response rate (ORR) and complete remission rate (CRR) as high as 86% and 73%, respectively, and a 82.2% 2-year modified PFS rate (see Connors JM et al, NEJM 2017). Although the majority of patients with advanced stage cHL are able to obtain disease remission with combination chemotherapy, treatment failures are not uncommon, with relapsed/refractory disease rates as high as 30-40% in some high-risk settings.

Salvage therapy is currently based on the use of non cross-resistant chemotherapy regimens (i.e. DHAP, IGeV, GemOX plus dexamethasone, ICE etc.) and is able to re-induce disease remission in approximately 50% of patients. Long-term disease control following conventional therapy alone is uncommon and further consolidation is usually needed: younger and fit patients are candidate for high dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT), which can allow for long-term disease control/cure in approximately 50% of patients. The German Hodgkin's Lymphoma Study Group (GHSG) has identified three adverse risk factors predictive of second relapse following salvage therapy and ASCT: time to first recurrence ≤12 months, stage III or IV and/or low haemoglobin levels at first relapse (i.e. <10.5 g/dL for females or <12.0 g/dL for males, see Josting A et al, JCO 2002). The long-term prognosis of patients not eligible ASCT, or who have failed ASCT, is poor: three-year survival rate is 31% (see e.g. Böll B et al, JCO 2013).

BV is approved for the treatment of adult patients with relapsed or refractory (r/r) cHL following ASCT or at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, or as a "consolidation" for the treatment of adult patients at increased risk of relapse or progression following ASCT. In a phase II trial in which 102 patients with r/r cHL after prior ASCT were treated with BV (1.8 mg/kg every three weeks for up to 16 cycles) the ORR was 75% (CRR 34%). 5-year OS was 41% (65% for patients who obtained a CR) and 5-year PFS was 22% (52% for patients in CR). Treatment with BV is

not devoid of toxicities, with peripheral sensory neuropathy (42%) being the most common non-hematologic adverse event (AE). BV also proved to be an effective "bridge" to transplant (see e.g. Chen R et al, Blood 2016; Younes A et al, JCO 2012).

Prognosis after failure of salvage chemotherapy, including BV, is poor. A selected subset of patients might be eligible to allogeneic hematopoietic stem cell transplant (allo-HSCT), which might still result in long-term remission in a subset of fit patients. However, transplant-related mortality and toxicity is not negligible.

Treatment of rrcHL in children and adolescents follows adult-based strategies, with multi-agent chemotherapy followed by myeloablative high-dose chemotherapy with auto-SCT. In patients who have previously been refractory to or relapsed from 1 or 2 lines of chemotherapy, particularly those with high-risk disease, these existing treatment options are not satisfactory, leaving little expectation of potential benefit, but unavoidable additional toxicity. Therefore, the disease burden caused by paediatric cancers remains an area with significant unmet need.

2.1.2. About the product

Keytruda (pembrolizumab, MK-3475) is a humanized monoclonal antibody designed to block the interaction between the programmed death-1 (PD-1) receptor and its ligands PD-L1 and PD-L2. The PD-1 immune checkpoint inhibition results in increased functional activity of cytotoxic lymphocytes which facilitates immune-mediated anti-tumour activity. The increased expression of PD-L1 and PD-L2 cHL Reed-Sternberg cells makes PD-1 an attractive target in r/r cHL. Pembrolizumab is currently approved as monotherapy for the treatment of adult patients with r/r cHL who have failed ASCT and BV, or who are transplant-ineligible and have failed BV on the basis of uncontrolled studies KN-087 and KN-013 in subjects with cHL in advanced stages of relapse.

In this application the initially claimed indication was in adult and paediatric patients who have failed autologous stem cell transplant (ASCT) or following at least one prior therapy when ASCT is not a treatment option.

The approved indication is "KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option".

The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 3 years and older with cHL is 2 mg/kg bodyweight (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received SA from the CHMP on the clinical development of pembrolizumab in r/r cHL (EMEA/H/SA/2437/9/2015/II). In particular, the adequacy of phase 3 study KN204 was discussed in terms of patient population, comparator and magnitude of target effect. The feedback received by the CHMP was partially taken into account.

In addition, a SA was adopted by the CHMP (EMEA/H/SA/2437/28/2019/PED/II) on the proposed approach to support the registration of a new indication for paediatric patients with r/r cHL. The proposed extrapolation concept was in principle considered acceptable

2.1.4. General comments on compliance with GLP, GCP

The MAH confirmed that all clinical studies were conducted following appropriate Good Clinical Practice (GCP) standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

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

An environmental risk assessment has not been included. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) in all cases, except for Type I variations and renewal applications, an ERA or a justification for its absence should be provided. Vitamins, electrolytes, amino acids, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Pembrolizumab (MK-3475) is a humanized monoclonal antibody of the IgG4/kappa isotype; being a protein, it is exempt from ERA requirements.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

*Table 1**: Summary of Studies in the Hodgkin Lymphoma Clinical Development Program***

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KN-013 Ongoing (N=31 rrHL)	Single-arm Phase 1b	Approximately 156 participants with MDS, HL NHL, PMBCL, and MM. N=31 r/r cHL	Pembrolizumab 10 mg/kg Q2W	ORR for MDS, MM, NHL, and PMBCL CR for HL
KN-087 Ongoing (N=210)	Single-arm Phase 2	Cohort 1: participants with r/r cHL who failed to achieve a response or progressed after ASCT and BV Cohort 2: participants with r/r cHL who failed salvage chemotherapy and were ineligible for ASCT (unable to achieve a complete or partial response to salvage chemotherapy) and failed BV therapy Cohort 3: participants with r/r cHL who failed to achieve a response or progressed after ASCT and who did not receive BV post ASCT. These participants could have received BV as part of primary or salvage treatment.	Pembrolizumab 200 mg Q3W	ORR
KN-204 Ongoing (N=304; 1:1 randomization)	Randomized, open-label Phase 3 vs BV	Participants with r/r cHL who have not had previous treatment with BV or who had prior treatment with response to BV or BV-containing regimen, and 1) have failed to achieve a response or progressed after ASCT, or 2) are not ASCT candidates and have received at least 2 prior multi-agent chemotherapy regimens	Pembrolizumab 200 mg Q3W or BV 1.8 mg/kg intravenously on Day 1 every 3 weeks	PFS (according to the IWG response criteria as assessed by BICR) and OS
KN-051 Ongoing (N=162 enrolled)	Single-arm, open-label, Phase 1/2	Up to 310 participants 6 months to <18 years of age with advanced melanoma; r/r cHL; advanced, relapsed/refractory PD-L1 positive solid tumor or other lymphoma; or advanced relapsed/refractory MSI-H solid tumor.	Dose finding was conducted in Part I, with pembrolizumab doses of 1-10 mg/kg Q3W	Part I: DLTs Parts I and II: Safety, ORR
KN-667 **Ongoing (N=11 as of 31Mar2020)**	Parallel-group open-label Phase 2	Approximately 440 participants 3 to 25 years of age with newly diagnosed cHL or with inadequate early response to frontline chemotherapy	Group 1: 2 cycles ABVD induction chemotherapy followed by pembrolizumab in SERs. Group 2: 2 cycles of OEPA induction chemotherapy followed by pembrolizumab in SERs. Pembrolizumab dosing in both groups: 2 mg/kg up to a max of 200 mg (3 to 17 years of age) or 200 mg (18 to 25 years of age) Q3W	ORR

ABVD= Adriamycin, bleomycin, vinblastine, dacarbazine; auto-SCT=autologous-stem cell transplant; BV=brentuximab vedotin; CR = complete remission; HL=Hodgkin lymphoma; IWG=International Working Group; MDS=myelodysplastic syndrome; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; OEPA= vincristine sulfate, etoposide phosphate, prednisone, doxorubicin hydrochloride; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-free Survival; PMBCL=primary mediastinal B-cell lymphoma; Q2W=every 2 weeks; Q3W=every 3 weeks; rrHL=relapsed; refractory Hodgkin lymphoma; SER=slow early responder.

2.3.2. Pharmacokinetics

Clinical pharmacology results are available from two clinical studies (KEYNOTE-013 and KEYNOTE-087), already included in the previous application to support 200 mg Q3W of pembrolizumab in rrcHL patients and are further informed by results obtained in study KEYNOTE-051 to support the inclusion of a paediatric indication.

The updated clinical pharmacology results specific to this submission include:

- PK data of pembrolizumab in paediatric patients with an advanced solid tumor or lymphoma treated with2mg/kg Q3W in KN051 study
- Update of the existing population pharmacokinetic model with additional paediatric data from KN051 and adult classical Hodgkin lymphoma (cHL) data from KN204
- Comparison of pembrolizumab pharmacokinetics and exposures in different age groups of paediatric patients to those obtained in adult patients to justify paediatric dose regimens
- Extrapolation of adult data from KEYNOTE-204 and KEYNOTE-087 along with the results of KEYNOTE-051 to support the inclusion of a paediatric indication.

Absorption

As pembrolizumab is administered intravenously, bioavailability is 100%.

Distribution

Pooled pop PK analysis (all age ranges and several cancer indications) including cHL PK data from KN051, KN013, KN087, KN204 estimated the central volume of distribution to 3.37 L (19 %CV) and peripheral volume of distribution to 2.61 L (19% CV). Body weight (alpha = 0.540), was selected as predictive covariate on both volumes. Age (< 18 years) and value: 0.292; Albumin (value: -0.258), Gender (value: -0.123) were selected as predictive covariate for Vc.

Median central volume of distribution ranged from 0.8 L (2-6 years of age), over 1.3 L (6-12 years of age) and 2.3 L (12-18 years of age) to 3.3 L (> 18 years).

Elimination

Pooled pop PK analysis (all age ranges and several cancer indications) including cHL PK data from KN051, KN013, KN087, KN204 estimated clearance to 0.252 L/day. Weight (alpha = 0.604), Cancer type (HL: -0.197), Age (< 18 years; value: 0.538), Albumin (value: -0.86), Baseline ECOG (0.065), Bilirubin (value: -0.0398), Baseline tumour size (solid tumours only) with value of 0.0985, eGFR (value 0.116), and Gender were selected as statistical significant covariates on CL.

Median clearance ranged with age from 0.047 L/d (2-6 years of age), over 0.092 L/d (6-12 years of age) and 0.152 L/d (12-18 years of age) to 0.295 L/d (> 18 years).

Dose proportionality and time dependencies

Clinical pharmacology of pembrolizumab in participants with rrcHL was described in the KEYNOTE-087 application to support 200 mg Q3W as the recommended monotherapy dose of pembrolizumab in this patient population.

Following administration of pembrolizumab 200 mg Q3W in participants with cHL (KEYNOTE-087), the observed median Cmin at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in median Cmax between cHL and other tumour types.

Following 2 mg/kg Q3W (paediatrics patients, KN051) steady state is overall reached by 15 weeks post-dose, with a slight trend in ongoing accumulation (PK data by week 81).

Pharmacokinetics in the target population

Participants with rrcHL in KEYNOTE-204 and KEYNOTE-087 and paediatric participants with rrcHL in KEYNOTE-051 comprise the primary participant populations for this application.
A description of the clinical pharmacology of pembrolizumab in participants with rrcHL was included in the KEYNOTE-087 application to support 200mg Q3W as the recommended monotherapy dose of pembrolizumab in this patient population in adults. Following administration of pembrolizumab 200 mg Q3W in participants with cHL enrolled in KEYNOTE-087, the observed median Cmin at steady-state was up to 40% higher than that in other tumor types treated with the same dosage; however, the range of trough concentrations was similar as well as there were no notable differences in median Cmax between cHL and other tumor types.

Previously, a pooled population PK analysis using KN001, KN002, KN006, and KN010 studies was performed to characterize serum concentrations over time based on a dataset including 2841 subjects across the melanoma and NSCLC indications.
A first extension of the previous population PK analysis was conducted primarily to assess the pharmacokinetics of pembrolizumab in adult patients with classical Hodgkin Lymphoma and in paediatric patients with solid tumors. For this purpose, paediatric PK data from study KN051 and data from adult patients with classical Hodgkin Lymphoma (cHL) from studies KN013 and KN087 were added to the dataset to enhance the relevance of the model for non-solid tumor indications.
A second extension of the population PK analysis was conducted as outlined in this report with additional paediatric data in solid tumors and cHL from KN051 and adult cHL data from KN204 to increase robustness of the first extension analysis.
Based on the extended dataset, the model was refined with a focus on an optimal characterization of the pembrolizumab concentration-time data in paediatric patients.
The final model was subsequently used in simulations of pembrolizumab PK parameters and exposure parameters in different age groups of paediatric patients and compared to the estimates in adult patients to support pembrolizumab dose regimen selection in paediatric patients.

Pembrolizumab PK data from KEYNOTE-051 study *(Paediatric patients)*

KEYNOTE-051 was an ongoing Phase I/II Study of Pembrolizumab (MK-3475) in Children with Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumor or Lymphoma (KEYNOTE-051). As of the data cutoff date for the submitted report (10-JAN-2020), 162 participants (N=22 rrcHL patients) were enrolled out of a total of up to 310 participants that was planned to be enrolled.

Table 2 Overview of cancer types included in the KN-051 PK analysis

Cancer type	Number of Subjects [a]	Total	PK Data Cutoff
Melanoma (MEL)	8	152	13-Aug-2018
Wilms Tumor Nephroblastoma	3		
Renal cell carcinoma (RCC)	2		
Hodgkin's Lymphoma (HL)	17		
Neuroblastoma, CNS primary tumor, Astrocytoma, Gliobastoma multiforme, Medulloblastoma, Ependymoma	43		
Solid Tumor	29		
Soft tissue neoplasm, alveolar soft part sarcoma	13		
Osteosarcoma	10		
Adrenocortical carcinoma	4		
Diffuse large B cell lymphoma, Precursor T Lymphoblastic Lymphoma, Lymphoma	2		
Hepatoblastoma, Hepatocellular carcinoma	8		
Rhabdomyosarcoma	7		
Atypical Teratoid Rhabdoid Tumor	4		
Non Rhabdomyosarcoma Soft Tissue Sarcoma Nos	1		
Other	1		

[a] Number of unique subject numbers in dataset

Nos: Not otherwise specified

Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

PK samples in KN051 were scheduled as follow: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 8 and every 4 cycles (12 weeks) thereafter. Post-dose serum concentrations (Cmax) were drawn within approximately 30-minutes after the end of the infusion in Cycle 1 and Cycle 8. Additional PK samples were drawn in Cycle 1 between 72 to 168 hours (4-8 days) post-dose and at 264 to 408 hours (12-18 days)-post-dose. Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.

For the pharmacokinetic analysis, serum pembrolizumab concentrations with an early PK cut-off date of 13-Aug-2018 were used from the bioanalytical report. Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.

In total, there were 151 participants in KEYNOTE-051 with evaluable PK samples. Observed PK concentrations in paediatric participants receiving 2 mg/kg Q3W were within the range of values for adults administered 2 mg/kg Q3W.

Table 3 Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in paediatric subjects from KN051

Summary Statistics of Pembrolizumab Predose (Ctrough), Postdose (Cmax) and Post Cycle 1 Serum Concentration Values Following Administration of Multiple I.V. Doses of 2 mg/kg Q3W in KN051

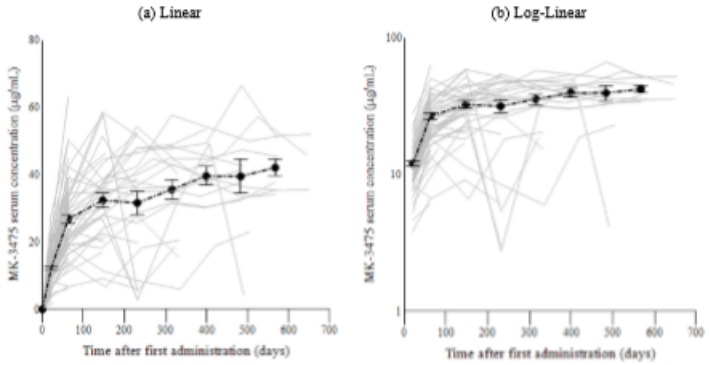
Cycle	NOMTAFD day	N	GM (%CV)	GM (SD)	AM (SD) (µg/mL)	Min	Median	Max
Predose (C_{trough})								
Cycle 2 (Week 3)	21	123	11.1 (47)	11.1 (5)	12.1 (5)	1.84	11.6	28.1
Cycle 4 (Week 9)	63	64	24.5 (48)	24.5 (11)	26.8 (11)	6.05	26.5	63.0
Cycle 8 (Week 21)	147	36	29.5 (52)	29.5 (13)	32.4 (13)	6.62	32.9	58.7
Cycle 12 (Week 33)	231	24	24.0 (116)	24.0 (17)	31.6 (17)	2.75	35.4	54.3
Cycle 16 (Week 45)	315	19	32.2 (58)	32.2 (13)	35.6 (13)	5.98	36.6	57.7
Cycle 20 (Week 57)	399	12	38.3 (30)	38.3 (10)	39.7 (10)	18.8	38.7	53.6
Cycle 24 (Week 69)	483	11	33.6 (87)	33.6 (17)	39.5 (17)	4.20	41.6	66.6
Cycle 28 (Week 81)	567	8	41.6 (18)	41.6 (7)	42.1 (7)	34.1	41.6	51.8
Postdose (C_{max}) (within 30 min post end of infusion)								
Cycle 1 (Week 0)	0	143	43.6 (28)	43.6 (14)	45.4 (14)	21.3	44.5	145
Cycle 8 (Week 21)	147	36	77.7 (30)	77.7 (24)	81.1 (24)	41.3	79.3	143
Post Cycle 1								
72-168 hours post C1	7	136	17.4 (40)	17.4 (6)	18.5 (6)	2.04	18.4	42.5
336 hours post C1	14	136	12.4 (49)	12.4 (5)	13.4 (5)	0.520	13.2	31.2

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean;
CV% = Geometric Coefficient of Variation;
SD = Standard Deviation;
AM = Arithmetic Mean;
Results reported for time points with N ≥ 3.

Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

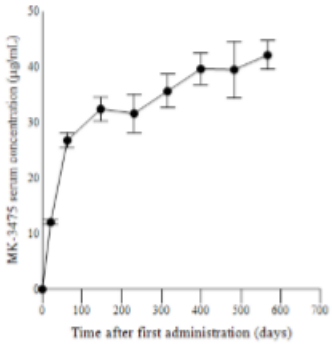
Figure 1 individual and mean pre-dose concentration-time profiles

Individual and Arithmetic Mean (SE) Pembrolizumab Predose Concentration -Time Profiles Following Multiple I.V. Doses of 2 mg/kg Q3W in Study KN051 (a) Linear scale, (b) Log scale



Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE (Standard Error).
Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

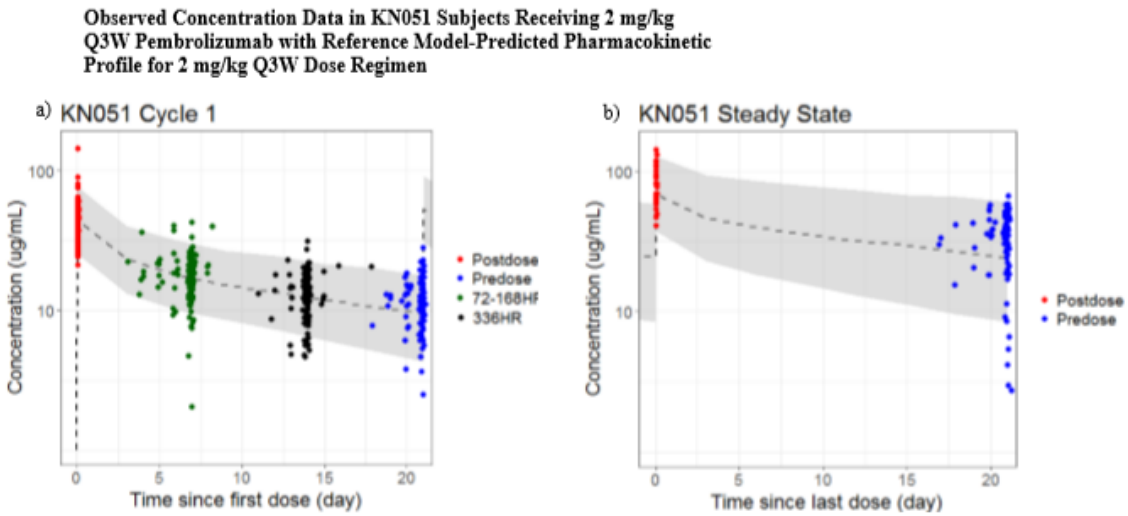
Arithmetic Mean (SE) Pembrolizumab Predose Concentration -Time Profiles Following Multiple I.V. Doses of 2 mg/kg Q3W to Subjects in Study KN051 (Linear scale)



Note: This plot is Arithmetic Mean with Standard Error (SE).
Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration at post-dose cycle 1 and at steady state (at and after cycle 8) are illustrated in the following figure:

Figure 2 Observed concentration data in KN051subjects receiving 2 mg/kg Q3W pembrolizumabwith reference model – predicted PK profile for 2 mg/kg Q3W dose regimen



a) After 1st dose on log scale; b) At and after cycle 8 (21 weeks) on log scale. Symbols are individual observed data (actual time) from subjects in KN051; black dashed line is median predicted concentrations from the model for a regimen of 2 mg/kg Q3W and the grey shaded area represents the 90% prediction interval.

Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

Based on the existing robust characterization of pembrolizumab PK, a comparison was conducted between the observed PK of pembrolizumab in children from study KEYNOTE-051 and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024). New "overlay" figures at Cycle 1 and steady state are generated for KEYNOTE-051 paediatric participants and KEYNOTE-204 adult cHL participants based on the updated popPK model including adult cHL participants and paediatric participants with solid tumours and cHL. Observed data shown in blue refer to cHL participants and data shown in green refer to paediatric participants with solid tumors.

Figure 3

Observed Concentration Data in Subjects Receiving 2 mg/kg Q3W Pembrolizumab at Cycle 1 With Updated Model-Predicted Pharmacokinetic Profile for 2 mg/kg Q3W Dos Regimen

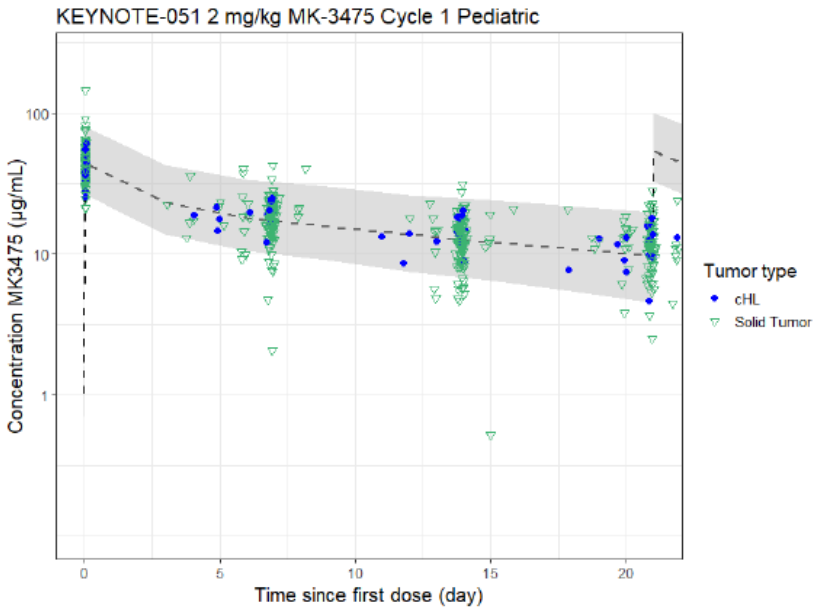
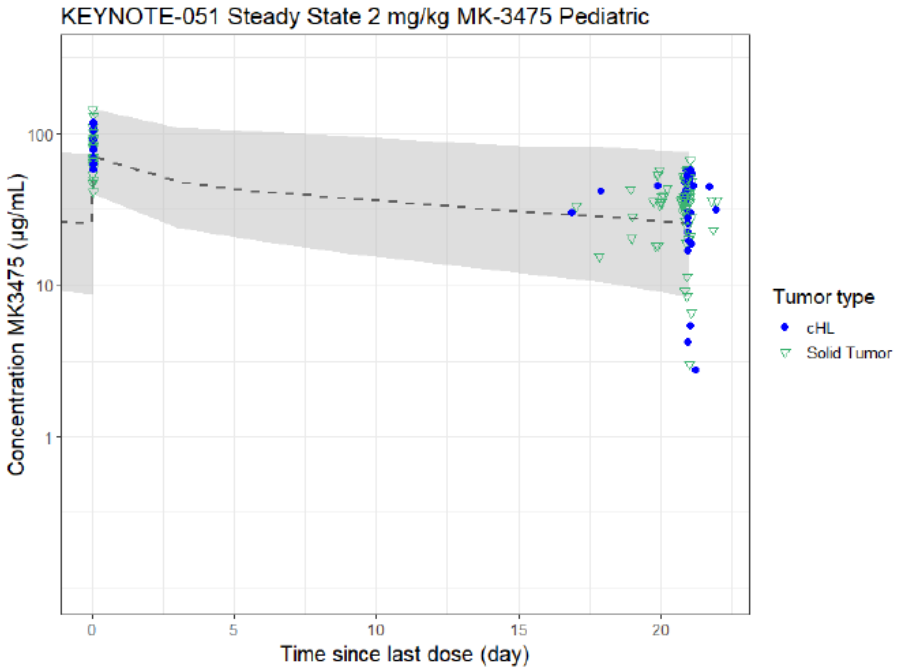


Figure 4

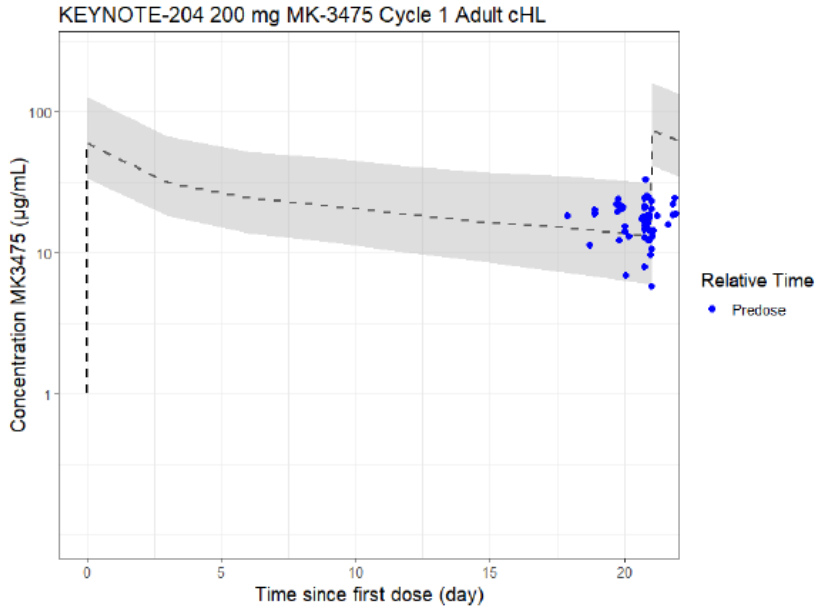
Observed Concentration Data in Subjects Receiving 2 mg/kg Q3W Pembrolizumab at Steady State With Updated Model-Predicted Pharmacokinetic Profile for 2 mg/kg Q3W Dose Regimen



*Data cutoff: August, 2018

Figure 5

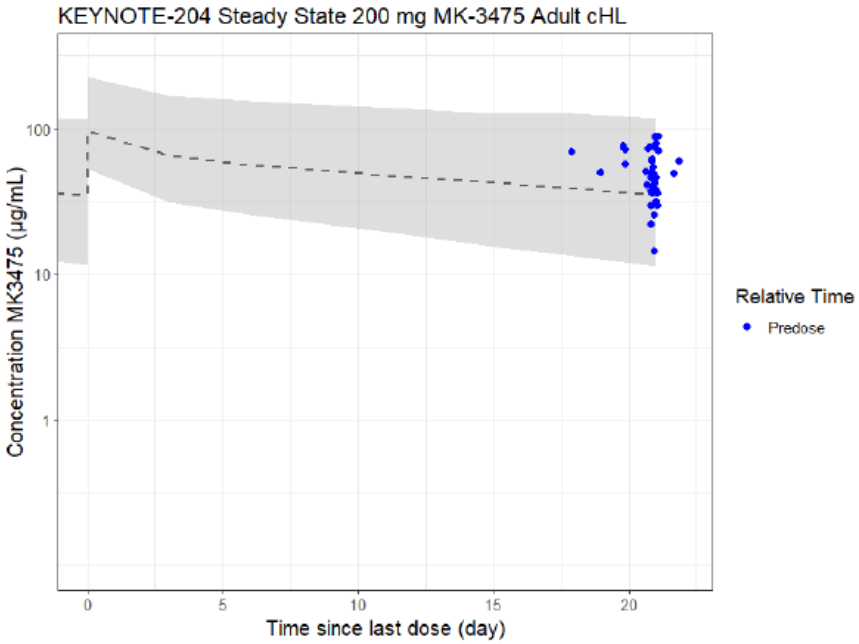
Observed Concentration Data in Subjects Receiving 200 mg Q3W Pembrolizumab at Cycle 1 With Updated Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen



*Data cutoff: November, 2017

Figure 6

Observed Concentration Data in Subjects Receiving 200 mg Q3W Pembrolizumab at Steady State With Updated Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen



*Data cutoff: November, 2017

Overview of bio-analytical methods and assay validation

Analytical methods

The validation performance of the bioanalytical assay for the quantitation of serum concentrations of pembrolizumab were summarized. PK and immunogenicity data included in this submission were exclusively generated at PPD laboratories using appropriately validated assays.

The concomitantly administered compounds MK-1308, MK-7684, and GSK3174998 were evaluated for potential interference. Data met the acceptance criteria specified in the method validation plan addendum, indicating no effect of the stated compounds on the quantitation of MK-3475 in human serum at the levels evaluated. Results from analyte interference studies presented indicate there is no effect on the quantitation of MK-3475 in human serum fortified with concomitantly administered compounds (MK-1308, MK-7684, GSK3174998) to the stated concentrations. Results from all samples were within the pre-specified acceptance criteria. Analysis of Variance (ANOVA) was conducted and the validation intra- and inter-assay data for both the fresh and frozen preparations met the acceptance criteria.

The addendum provides data on analyte stability in frozen matrix and on conjugated reagent stability.

Stability was demonstrated after 842 days and at 1218 days (in this case an intermediate calibrator was diluted in matrix to the high-level concentration prior the analysis).

Data from the analysis of MK-3475 stability samples in frozen human serum stored for up to 1217 days at -25 °C ± 5 °C and for up to 1218 days at -80 °C ± 10 °C met the criteria for demonstrating stability.

Data from the analysis of QCs using conjugated reagents stored for up to 1135 days at -80 °C ± 10 °C and for up to 30 days at 2-8 °C met the criteria; The results of selectivity assessment in small cell lung cancer human serum are reported in this validation report amendment. Results from all samples were within the pre-specified acceptance criteria.

2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Primary and secondary pharmacology

Immunogenicity

There were no cases of positive immunogenicity status after pembrolizumab treatment in paediatric participants (0%), while the incidence rate (2.1%) of treatment-emergent positive immunogenicity status in adults (Report 052J8M) is low. No additional analyses were performed for the current KEYNOTE-051 CSR. The details of the immunogenicity analysis are available in the prior version of the CSR of study KN051 and reported below.

The table below presents an overview of the immunogenicity status of all assessable subjects. To evaluate immunogenicity, the overall immunogenicity was defined as the proportion of emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

Table 4

Summary of Subject Immunogenicity Results after Pembrolizumab Therapy in Children, 2 mg/kg Q3W (KN051)

Stratified by treatment						
Immunogenicity status	All indications	Indication				
		Hodgkin's Lymphoma	Brain / CNS-related Tumors	Solid Tumors	Soft Tissue Neoplasm	Other
Assessable subjects[a]	133	17	38	24	12	42
Inconclusive subjects[b]	8	2	3	2	0	1
Evaluable subjects[c]	**125**	**15**	**35**	**22**	**12**	**41**
Negative[d]	123 (98.4%)	15 (100%)	34 (97.1%)	22 (100%)	12 (100%)	40 (97.6%)
Non-Treatment emergent positive[d]	2 (1.6%)	0	1 (2.9%)	0	0	1 (2.4%)
Neutralizing negative[d]	2 (1.6%)	0	1 (2.9%)	0	0	1 (2.4%)
Neutralizing positive[d]	0	0	0	0	0	0
Treatment emergent positive[d]	0	0	0	0	0	0
Neutralizing negative[d]	0	0	0	0	0	0
Neutralizing positive[d]	0	0	0	0	0	0

CNS: Central Nervous System
a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.

Data source [052J8M: analysis-p051pkada0pip2018v4]

Out of the 133 subjects included in the immunogenicity assessment, 125 subjects were evaluable. The evaluable subject group contains 2 subjects with non-treatment emergent positive status (1.6%), and 123 with negative immunogenicity status (98.4%). There were no subjects with a treatment emergent positive status observed.

2.3.4. PK/PD modelling

PK Bridging Analysis

Model parameters including covariate effects were re-estimated with a focus on an optimal characterization of the potential effects of age and body weight in the paediatric population.

Reliability and robustness of the subsequent final model was assessed by a range of goodness of fit plots. Post-hoc parameter estimates from the final model were used to compare pharmacokinetic parameters as well as individual pembrolizumab exposure estimates between paediatric and adult populations.

Simulations from the final model were performed to assess the exposure to pembrolizumab in paediatric patients at the dose regimens of 2 mg/kg Q3W or 200 mg Q3W and compare to the exposures in adult patients. Paediatric covariate information for simulations was obtained from an external dataset (171 paediatric oncology subjects) in combination with the paediatric subjects from the pembrolizumab dataset (152 subjects).

Evaluation and qualification of model

The established population PK model for pembrolizumab had a two-compartment model structure with a linear clearance from the central compartment, parameterized in terms of clearance (CL), inter-compartmental clearance (Q), central compartment volume of distribution (Vc), and peripheral

compartment volume of distribution (Vp). All PK parameters were allometrically scaled based on body weight with separate exponents estimated for the clearance (CL, Q) and volume (Vc, Vp) parameters.
Additionally, a time-dependent component was estimated on the pembrolizumab clearance. The change in clearance over time (TDPK(t)) was described according to an Emax function.
In addition to body weight, the existing population PK model contained several more covariate relationships, which were established through a stepwise covariate search. Specifically, the following covariates were included in the model: Age, Gender and Albumin on CL and Vc; Bilirubin, eGFR, Baseline tumor size , ECOG performance status and Cancer type on CL.
No formal full covariate evaluation was planned as part of this new analysis. Rather, the previously established covariate relationships were re-estimated and a focused reassessment of specific covariates was performed. Statistical criteria for forward addition ($P<0.01$) and backward deletion ($P<0.001$) were identical to previously conducted stepwise covariate model building.

Model Performance.

The following goodness-of-fit plots were utilized to assess the adequacy of the structural model to describe the pooled dataset. All plots included a specific highlighting of the data from paediatric patients through the use of different markers to enable an assessment of the adequacy of the model specifically for this patient group.

- Observations versus population and individual predictions log-log plots overall and by study
- Population and individual weighted residuals versus time by study
- Population weighted residuals versus population predictions
- Conditional weighted residuals versus population predictions
- Individual weighted residuals versus individual predictions

Comparison Paediatrics vs Adults

Following finalization of the population PK model on the pooled dataset, the final model was used to enable comparisons of the pharmacokinetics of pembrolizumab between paediatric and adult patients. The following comparisons were included in this assessment: 1) Comparison of individual posthoc parameter estimates, through boxplots and descriptive statistics of individual parameters; 2) Comparison of derived individual PK parameters (Cmax at Cycle 1, AUC6wks, t1/2, Cmin at Cycle 1) for selected dose regimens between different populations by means of boxplots and tabular summaries of descriptive statistics.

Simulations in Paediatrics

In order to project distributions of pembrolizumab PK parameters and exposures in a broader paediatric population, a set of simulations was performed. A dataset of individual patient covariate information was constructed from which simulation datasets were obtained through resampling.
The resampling dataset consisted of the subjects included in the analysis dataset. However, since only a relatively small number of paediatric subjects in the younger age groups were available in the pembrolizumab dataset and since no relevant public database containing the required covariate information was readily available, the resampling dataset was augmented with a paediatric oncology dataset from another program including 171 subjects aged 0.5 – 17 years.
The simulation dataset consisted of a total of 1000 paediatric and 500 adult patients sampled with replacement from the covariate dataset. As no baseline tumor size data was available for the paediatric population, no covariate effect of baseline tumor size was assumed for the paediatric subjects. Also, a 50/50 distribution of ECOG values 0 or 1 was assumed for the paediatric population. In terms of indication, the paediatric subjects were classified as either solid tumor or non-solid tumor type, with the first having the typical clearance associated with the melanoma and other indications in the model and the second having the typical clearance associated with the cHL indication.

The final population PK model was used to predict the pembrolizumab concentrations following single dose and at steady state for the patients in the simulation dataset. Distributions of the PK parameters CL0 (Clearance estimate at t=0), Vc, AUC6wks (derived from CL0) as well as of the steady-state Cmax (Cmax,ss) and Cmin (Cmin,ss) estimates derived from the simulated concentration-time profiles were characterized through box-plots and descriptive statistics, according to the following age groups: - <2 years / ≥2-<6 years / ≥6 -<12 years / ≥12 -<18 years / ≥18 years and < 3years / ≥3-<6 years / ≥6 -<12 years / ≥12 -<18 years / ≥18 years.

RESULTS

The final analysis data set comprised of a total of 19488 pembrolizumab concentrations from 3293 patients. Of these, 2654 concentrations were available from 301 adult cHL patients and 775 concentrations were available from 152 paediatric patients aged < 18 years with solid tumors and cHL.

Table 5 Number of subjects and PK observations by dose and study in the pooled analysis dataset

Numbers of Subjects and Observations by Dose and Dosing Regimen in the Pooled Analysis Dataset (KN001, KN002, KN006, KN010, KN051, KN013, KN087 and KN204)

Doses	N of subjects	% of subjects	N of PK observations	% of PK observations
1mg/kg Q2W (Adults solid tumors)	4	0.12	43	0.22
1mg/kg Q3W (Adults solid tumors)	6	0.18	10	0.05
2mg/kg Q3W (Adults solid tumors)	761	23.11	4077	20.92
3mg/kg Q2W (Adults solid tumors)	3	0.09	55	0.28
10mg/kg Q2W (Adults solid tumors)	660	20.04	4117	21.13
10mg/kg Q3W (Adults solid tumors)	1406	42.7	7879	40.43
10mg/kg Q2W (Adults cHL)	29	0.88	157	0.81
200mg Q3W (Adults cHL)	272	8.26	2375	12.19
2mg/kg Q3W (Pediatrics solid tumors)	136	4.13	653	3.35
2mg/kg Q3W (Pediatrics cHL)	16	0.49	122	0.63

Note: some subjects received more than one dose levels under dose escalation cohorts
Reviewed per SOP-QP2-005

Table 6 Covariate distribution in adult and paediatric populations in the analysis dataset

Covariate	Population	Min	Q1	Median	Mean	Q3	Max	N	Missing
Body weight (kg)	Adults solid tumors	35.7	64	75.1	77.2	88	209.5	2840	0 (0.0%)
	Adults cHL	33.1	60	71.4	74.6	87	185	301	0 (0.0%)
	Pediatrics solid tumors	8.4	23.1	41.5	42.1	55.1	120	136	0 (0.0%)
	Pediatrics cHL	32.5	44.5	50.8	58.8	69.4	103.4	16	0 (0.0%)
Age (years)	Adults solid tumors	18	53	62	61.1	70	94	2840	0 (0.0%)
	Adults cHL	18	27	34	38.6	48	79	301	0 (0.0%)
	Pediatrics solid tumors	1	7.8	13	11.1	15	17	136	0 (0.0%)
	Pediatrics cHL	11	13.8	15	14.7	16	17	16	0 (0.0%)
Albumin (g/L)	Adults non-HL	15	37	40	39.6	43	59	2787	53 (1.9%)
	Adults cHL	21	35.6	39	39	43	52	293	8 (2.7%)
	Pediatrics non-HL	25	38	41	40.5	43	53	136	0 (0.0%)
	Pediatrics cHL	33	39	42	41.8	45	47	16	0 (0.0%)
Bilirubin (µmol/L)	Adults solid tumors	1	5.5	8	8.9	10.4	87.2	2804	36 (1.3%)
	Adults cHL	1.2	5.1	7	7.9	10	35	300	1 (0.3%)
	Pediatrics solid tumors	0	4.9	6.4	7.2	9	22	136	0 (0.0%)
	Pediatrics cHL	1.7	4.9	6.5	7.1	10.1	12	16	0 (0.0%)
Baseline tumor size (mm for solid tumors. mm^2 for cHL)	Adults solid tumors	10	45.4	84.5	109.5	145.9	895	2588	252 (8.9%)
	Adults cHL	13.6	256.2	2300.6	3144.6	3714.9	34659.3	301	0 (0.0%)
	Pediatrics solid tumors	10	34.5	57.1	76.4	101.2	411	134	2 (0.7%)
	Pediatrics cHL	NA	NA	NA	NA	NA	NA	NA	16 (100%)
eGFR ($ml/min/1.73\ m^2$)	Adults solid tumors	25.4	73.4	88.7	91.1	104.8	402.9	2814	26 (0.9%)
	Adults cHL	41.8	89.4	110.2	114.4	131.5	332.1	300	1 (0.3%)
	Pediatrics solid tumors	50	94.4	121.6	126	148.5	229.2	133	3 (2.2%)
	Pediatrics cHL	75.6	94.7	110.9	114	140.9	152.8	16	0 (0.0%)

Reviewed per SOP-QP2-005

Table 7 Summary of categorical covariates in paediatric and adult populations

Covariate	Category	Pediatric solid tumors		Pediatric cHL		Adults solid tumors		Adults cHL	
		N	N%	N	N%	N	N%	N	N%
Baseline ECOG Performance	0 Asymptomatic	84	61.76	13	81.25	1479	52.08	142	47.18
	1 Symptomatic	50	36.76	3	18.75	1356	47.75	130	43.19
	Missing	2	1.47	0	0	5	0.18	29	9.63
Gender	Female	67	49.26	5	31.25	1150	40.49	142	47.18
	Male	69	50.74	11	68.75	1690	59.51	159	52.82
Cancer type	Melanoma	9	6.62	0	0	1611	56.73	0	0
	HL	0	0	16	100	0	0	301	100
	NSCLC	0	0	0	0	1207	42.5	0	0
	Other type of solid tumor	127	93.38	0	0	22	0.77	0	0

Reviewed per SOP-QP2-005

Population PK Model

The existing population PK model for pembrolizumab was used as a basis for an update of the model with the addition of data from paediatric patients with solid tumors and cHL and adult cHL patients.

A comparison of parameter estimates of the final model using the integrated dataset (i.e. KN001, KN002, KN006, KN010, KN051, KN013, KN087 and KN204) and the dataset used in (Report 04LL90) are shown in the table reported below. The values of parameters estimates are very similar and %RSE are within the expected range (i.e. <50%). All the previously added covariate parameters are precisely estimated on the updated dataset as well.

Table 8

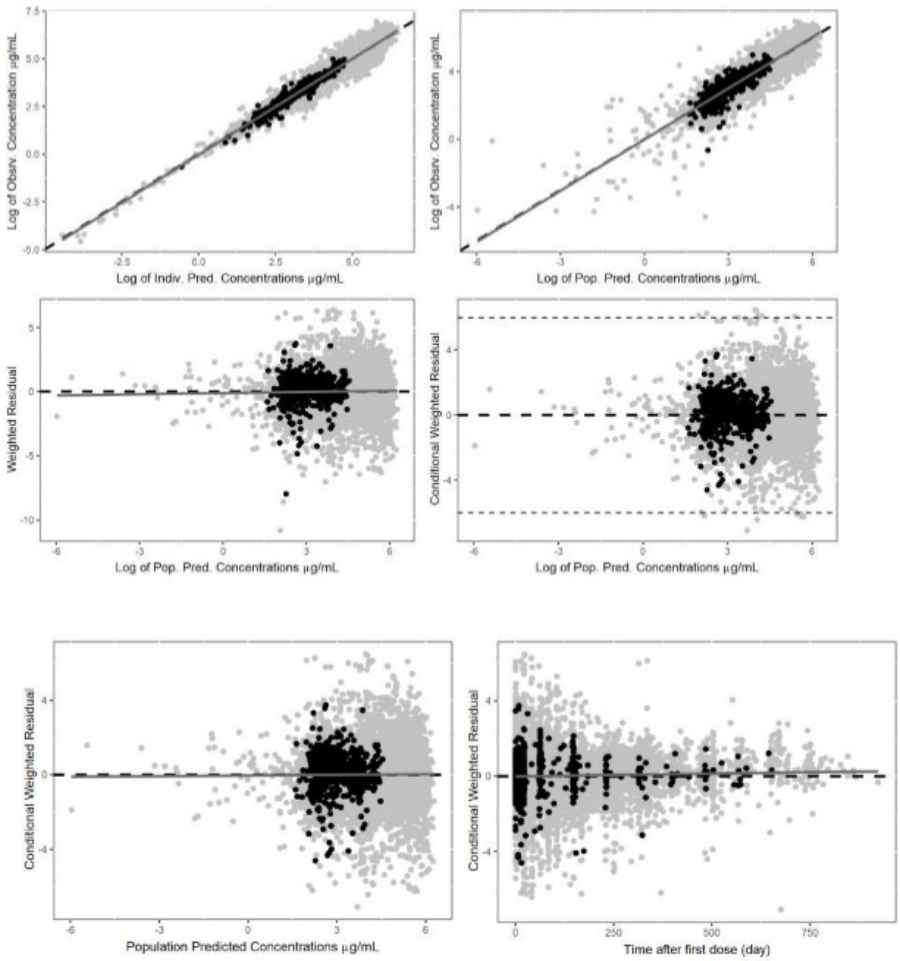
Comparison of Population Pharmacokinetic Parameters of Pembrolizumab (MK-3475) from the Existing Model vs. Updated Model Including Additional Pediatric Subjects with Solid Tumors and cHL and Adult cHL Subjects

	The Previous Model N=3104 [Ref. 5.3.5.3: 04LL90]			Update Model N=3293		
Parts and Studies included in the analysis	**Adult solid tumors;** A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from KN001, KN002, KN006, KN010 **Pediatrics solid tumors and cHL**: KN051 **Adult cHL:** KN013, KN087			**Adult solid tumors;** A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from KN001, KN002, KN006, KN010 **Pediatrics solid tumors and cHL**: KN051 **Adult cHL:** KN013, KN087, KN204		
Parameter	**Value**	**%RSE**	**%CV[a]**	**Value**	**%RSE**	**%CV[a]**
CL (L/day)	0.254	2.17	32.0	**0.252**	1.91	30.3
Vc (L)	3.45	0.694	19.7	**3.37**	0. 647	19
Q (L/day)	0.889	3.57	32.0	**0.888**	3.5	30.3
Vp (L)	2.82	4.17	19.7	**2.61**	3.14	19
IMAX	-0.207	8.19	17.8	**-0.25**	6.83	17.9
TI50 (day)	65.6	10.7		**61.6**	6.82	
Hill	3.06	5.19		**2.37**	11.6	
α for CL and Q	0.573	5.50		**0.604**	5	
α for Vc and Vpc	0.540	3.92		**0.59**	3.24	
Cancer type on CL (NSCLC)	0.0596	25.7		**0.0594**	26.4	
Cancer type on CL (HL)	-0.196	9.93		**-0.197**	7.9	
Age on CL[b]	0.602	24.9		**0.538**	11.7	
Albumin on CL	-0.718	12.0		**-0.86**	6.29	
Baseline ECOG on CL	0.0656	22.0		**0.065**	23.4	
Bilirubin on CL	-0.0446	28.3		**-0.0398**	35.8	
Baseline tumor size on CL[c]	0.103	8.92		**0.0985**	8.96	
eGFR on CL	0.118	16.7		**0.116**	17.1	
Gender on CL	-0.162	7.53		**-0.152**	7.8	
Age on Vc[b]	0.34	18.0		**0.292**	12.5	
Albumin on Vc	-0.204	19.4		**-0.258**	14.4	
Gender on Vc	-0.131	7.71		**-0.123**	7.41	
Residual error	0.241	1.84		**-0.221**	1.54	

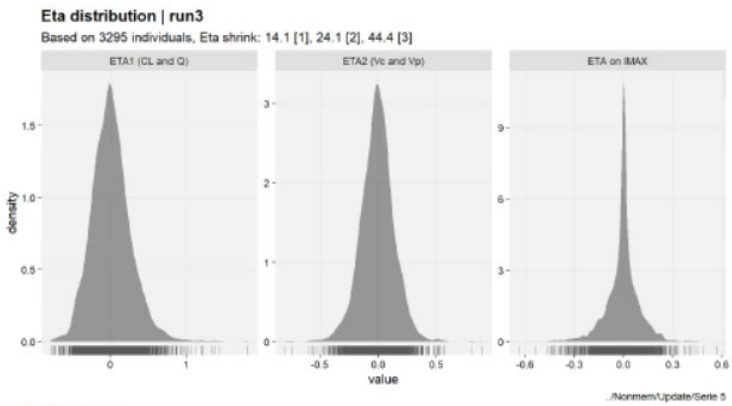
[a] %CV of residual error is related to estimate of between-subject variability on this parameter
[b] Age effect only for pediatric population (age < 18 years).
[c] Effect only applicable for solid tumor indications, not for HL.
Presented population parameter estimates exclude effects of covariates; therefore apply to a hypothetical typical patient with average characteristics. CL: clearance; Vc: central volume of distribution; Q: intercompartmental clearance; Vp: peripheral volume of distribution; Vd,ss: volume of distribution at steady state; t1/2: terminal half-life; %RSE: relative standard error (%); 95% CI: 95% confidence interval of parameter estimate based on bootstrap results; %CV: coefficient of variation of between-subject distributions of parameters; NA: not applicable.
Reviewed per SOP-QP2-005

Model diagnostics

Figure 7 Goodness of fit plots for the final model

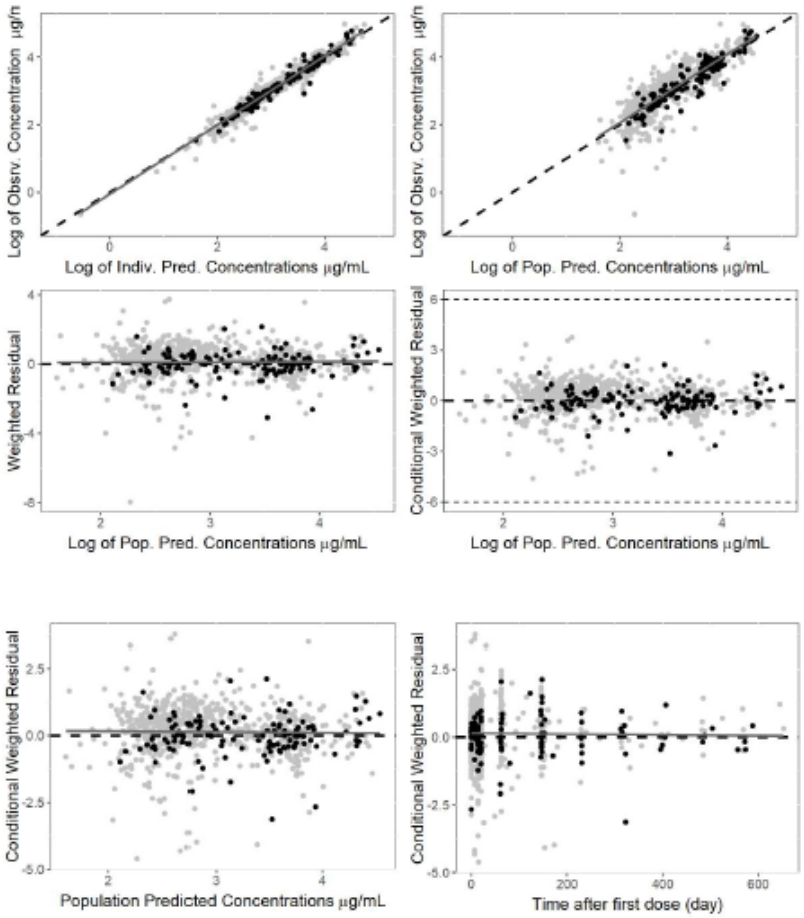


Black dots are pediatric individual data; Grey dots are individual data for adult subjects; dashed lines are zero line whilst solid lines are the smooth lines.
Reviewed per SOP-QP2-005



Note: black shaded area is the probability density.
Reviewed per SOP-QP2-005

Figure 8 GoF plots for the final model for the paediatric population



* Black dots represent pediatric cHL data and gray dots represent pediatric solid tumor data.

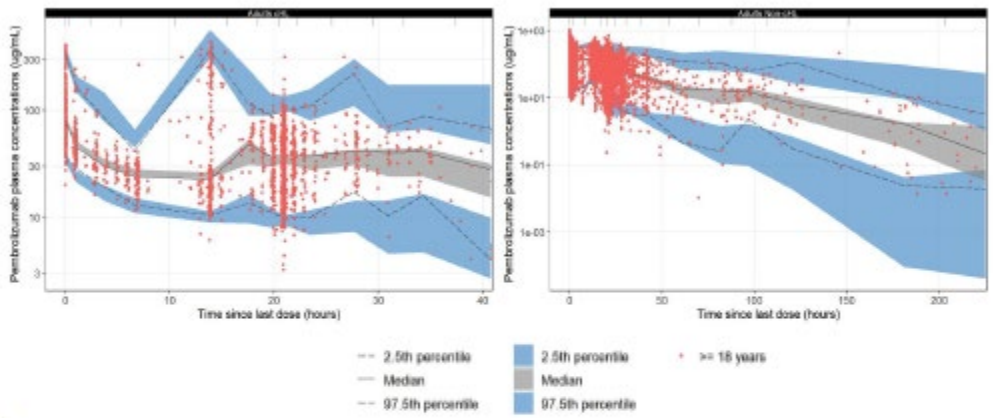
GoFs are provided for each age group (paediatric participants <3 years old, 3 to <6 years old, 6 to <12 years old, 12 to <18 years old, and adults >18 years old , with gray dots representing participants with solid tumors and black dots representing participants with cHL.

Overall, except for minor deviation, the observed data are aligned with the line of unity demonstrating that the model adequately described the data across the entire age range of the data.

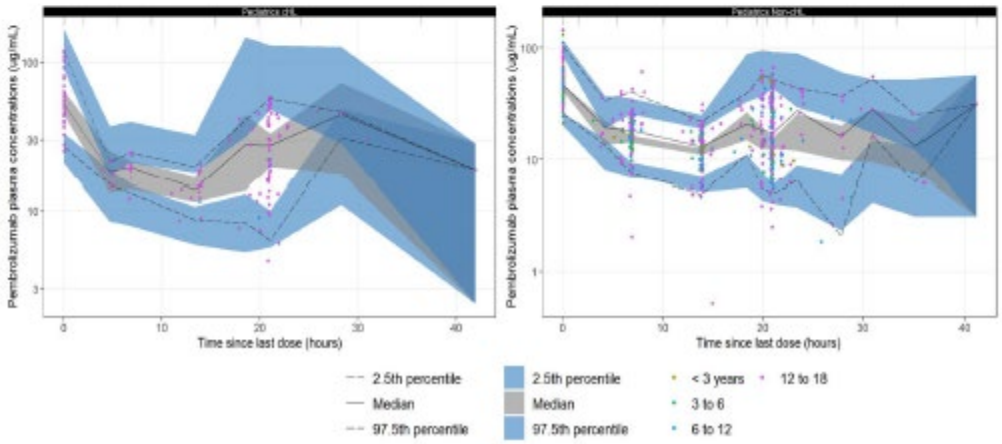
In addition, VPCs for adults and paediatric participants with solid tumors and cHL are provided in different panels showing that adults and paediatrics data with both solid or cHL tumor fall within those predicted by the Model.

Figure 12
Visual Predictive Check Figures for Adult (a) and Pediatric (b) Participants With cHL (Right Panels) and Solid Tumors (Left Panels)

a)



b)



PK results: Comparison of Pharmacokinetics in Paediatrics versus Adults

Post-hoc (Derived) PK Parameters

Distributions of individual post hoc parameter estimates for clearance and central volume of distribution in the paediatric and adult populations are presented in (Figure 1). Figure 2 presents distributions of derived pharmacokinetic parameters (based on the post hoc estimates) for the paediatric and adult subjects at the dose regimen of 2 mg/kg Q3W. Additionally, table 8 presents summaries of associated descriptive statistics for these post-hoc estimates of CL, Vc as well as the derived parameters at 2 mg/kg Q3W for paediatric and adult populations.

Figure 9 Comparison of CL and VL using the individual empirical Bayes parameters (paediatrics vs adults)

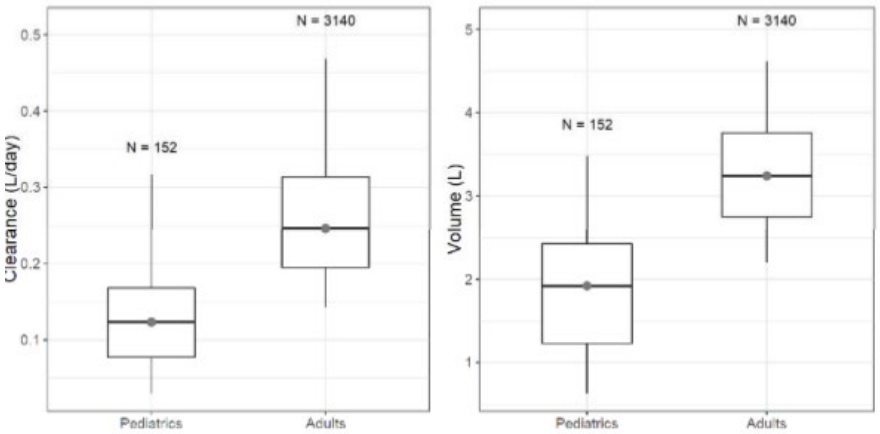
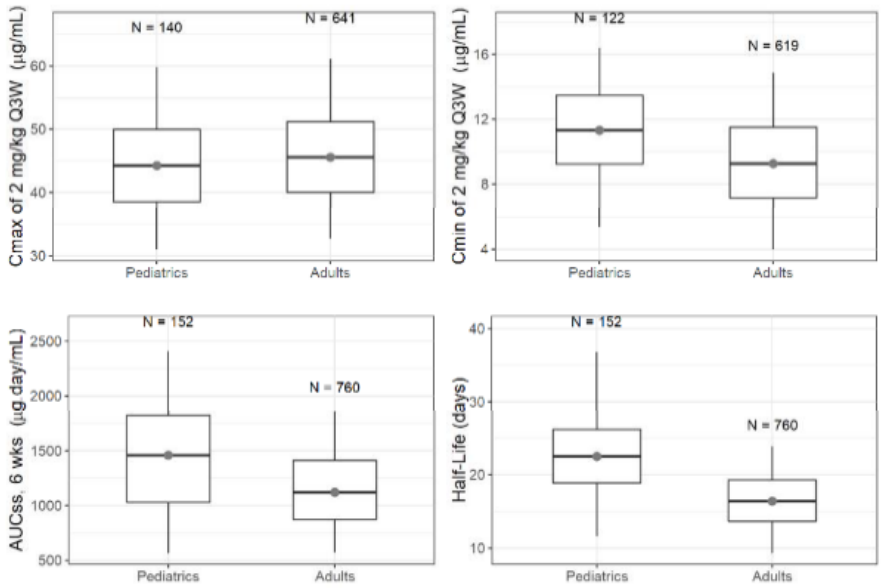


Figure 10 Derived individual PK parameters (C_{max}, AUC6wks, t1/2, C_{min}) at 2 mg/kg Q3W between paediatrics and adults



Note: Cmax is concentration at time of peak sample in Cycle 1 – Cmin is the observed trough concentration in Cycle 1
Reviewed per SOP-QP2-005

Overall, the pharmacokinetic model parameter estimates (CL and Vc) are lower for paediatric patients compared to adults. This was expected, since the parameters have been shown to be correlated to body weight. Exposure parameters following the weight-based regimen of 2 mg/kg Q3W are largely similar between the paediatric age groups and between paediatrics and adults.

Table 9 Comparison of descriptive statistics of derived individual PK parameters (CL, Vc) and Derived parameters (C_{max}, AUC6wks, t1/2, C_{min}) at 2 mg/kg Q3W between paediatrics and adults

Parameter	Population	Min	Q1	Median	Mean	Q3	Max	N*	Missing
CL (L/day)	2 to 6	0.021	0.032	0.045	0.047	0.057	0.088	22	0 (0.0%)
	6 to 12	0.036	0.068	0.092	0.099	0.109	0.262	35	0 (0.0%)
	12 to 18	0.031	0.127	0.152	0.196	0.209	1.616	92	0 (0.0%)
	>= 18 years	0.11	0.209	0.265	0.295	0.347	1.53	760	0 (0.0%)
Vc (L)	2 to 6	0.5	0.7	0.8	0.8	0.9	1.2	22	0 (0.0%)
	6 to 12	0.8	1.2	1.3	1.4	1.6	3.2	35	0 (0.0%)
	12 to 18	0.6	2.1	2.3	2.5	2.8	4.9	92	0 (0.0%)
	>= 18 years	1.2	2.7	3.3	3.4	3.8	8.6	760	0 (0.0%)
AUC6wks (mg.day/L)	2 to 6	762	1271	1478	1551	1926	2412	22	0 (0.0%)
	6 to 12	420	1013	1285	1376	1698	2412	35	0 (0.0%)
	12 to 18	145	1012	1483	1447	1806	3109	92	0 (0.0%)
	>= 18 years	238	873	1120	1161	1411	3015	760	0 (0.0%)
$Cmin_{,Cycle1}$ (µg/mL)	2 to 6	7	9.6	11.1	10.9	11.8	15.1	12	10 (45.5%)
	6 to 12	2.4	8	9.9	10.3	12.1	16.4	32	3 (8.6%)
	12 to 18	2.6	9.8	11.9	11.8	13.9	21.9	75	16 (18.5%)
	>= 18 years	1.4	7.1	9.3	9.3	11.5	24.3	619	141 (18.6%)
$Cmax_{,Cycle1}$ (µg/mL)	2 to 6	29.5	37.9	41.3	42.8	46.8	56.9	19	3 (13.6 %)
	6 to 12	30.6	37.7	40	42.8	46.9	59.9	33	2 (5.7%)
	12 to 18	26.1	40.7	45.2	46.4	53	79.5	85	7 (7.9%)
	>= 18 years	26.9	40	45.5	46.2	51.2	101.5	641	119 (15.6%)
Thalf (days)	2 to 6	16.9	24	30.3	30.5	35.8	46	22	0 (0.0%)
	6 to 12	10.2	20.2	22.7	23.1	27	33.7	35	0 (0.0%)
	12 to 18	3.2	16.2	21.3	20.4	24	33.6	92	0 (0.0%)
	>= 18 years	3	13.7	16.4	16.5	19.3	28.9	760	0 (0.0%)

Note: Cmax is concentration at time of peak sample in Cycle 1 – Cmin is the observed trough concentration in Cycle 1
*N = 3 pediatric subjects < 2 years old are not included in the table
Reviewed per SOP-QP2-005

CL and Vd are lower in children as expected, since they correlate directly with the BW.
The exposure parameters in the box plots are similar between children and adults. A total of 152 paediatric participants were included in the updated popPK model. The breakdown of participants by age group and tumor type is shown below

Table 10 Summary of number of subjects in each paediatric age group

Age Range	Solid Tumors	cHL
< 3	8	0
3 – <6	17	0
6 – <12	34	1
12 - <18	77	15

The majority of the paediatric participants is in older age groups 6 to <12 years old (n=35) and 12 to <18 years old (n=92); while in the younger age groups there are 8 patients <3 years old and 17 patients in the group 3 to <6 years old.
Box plots of post-hoc derived PK parameters for cHL paediatric patients in different group of age and adults shows a consistency in exposure parameters among groups except for the AUC values in age <3 years old (~50% higher compared to that in adults). This was already noted but however justified by the flat exposure-safety profile of Keytruda between 2 and 10 mg/kg.

The final model was subsequently used in simulations of pembrolizumab PK parameters and exposure parameters in different age groups of paediatric patients and compared to the estimates in adult patients to support pembrolizumab dose regimen selection in paediatric patients.

Simulations

Simulations of pembrolizumab pharmacokinetics and concentration-time profiles were performed for a dataset of 1000 paediatric subjects and 500 adult subjects, obtained through sampling subjects from the analysis dataset, augmented with additional paediatric oncology subject data down to 0.5 years of age. A summary of covariate information for the combined paediatric source dataset used for re-sampling is provided. The simulated dose regimens were the weight-based regimen of 2 mg/kg Q3W and the fixed dose regimen of 200 mg Q3W.

Table 11 Descriptive statistics of covariate information for paediatric subjects included in resampling dataset.

Covariate	Population	Min	Q1	Median	Mean	Q3	Max	N	Missing
Body weight (kg)	below 2 years	6.4	8.4	9.8	9.6	10.8	12.7	25	0 (0.0%)
	2 to 6 years	9.2	14	16	16.5	18	33.8	70	0 (0.0%)
	6 to 12 years	18.9	23.7	28.8	31.7	37.8	68.4	99	0 (0.0%)
	12 to 18 years	18.9	45.4	52.9	55.9	64.2	120	129	0 (0.0%)
Age (years)	below 2 years	0.3	0.9	1.1	1.1	1.4	1.9	25	0 (0.0%)
	2 to 6 years	2	3	4	3.9	4.9	5.9	70	0 (0.0%)
	6 to 12 years	6	7.9	9	9	10.4	11.9	99	0 (0.0%)
	12 to 18 years	12	13.1	15	14.7	16	17.5	129	0 (0.0%)
Albumin (g/L)	below 2 years	26	38	42	40.8	44	46.4	25	0 (0.0%)
	2 to 6 years	33	38.2	41.1	41.4	44	60.8	70	0 (0.0%)
	6 to 12 years	25	39	41	41.1	43.2	51	99	0 (0.0%)
	12 to 18 years	25	39	42	41.2	45	53	129	0 (0.0%)
Bilirubin (µmol/L)	below 2 years	1.7	3.4	5.1	5.7	6.8	17.1	25	0 (0.0%)
	2 to 6 years	0	3.4	5.1	5.2	6.8	11	69	1 (1.4%)
	6 to 12 years	1.7	3.4	5.1	6.1	7.4	22	99	0 (0.0%)
	12 to 18 years	1.7	5.1	7	8	10.3	27.9	129	0 (0.0%)
eGFR ($ml/min/1.73m^2$)	below 2 years	76.7	109.7	138.5	137.6	159.9	264.6	25	0 (0.0%)
	2 to 6 years	50	112.5	134.5	139.8	163.7	299.4	69	1 (1.4%)
	6 to 12 years	66.4	112.9	137	135.8	153.6	214.1	98	1 (1.0%)
	12 to 18 years	53	94.1	111.9	115.4	134.9	229.2	128	1 (0.77%)

Reviewed per SOP-QP2-005

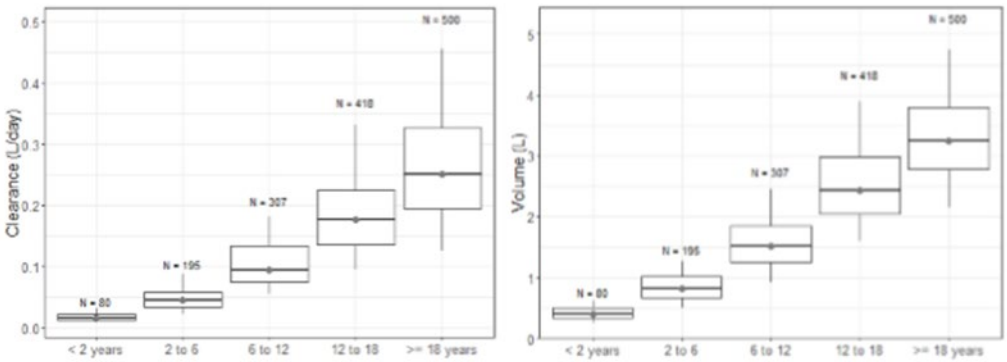
The resampling dataset was augmented with a paediatric oncology dataset from another program and comprised of 171 participants (aged 0.5 – 17 years), included 22 different tumor types.

Table 12 listing of tumour types and number of participants in augmented paediatric dataset

Tumor Type	N
Acute Lymphoblastic Leukemia	4
Acute Promyelocytic Leukemia	1
CNS	37
Endodermal Sinus Tumor	1
Ewing Sarcoma	5
Head and Neck	5
Hepatobiliary	7
Hepatoblastoma	2
Lymphoblastic Lymphoma T	1
Lymphoproliferative	5
Myeloproliferative	1
Nephroblastoma	2
Neuroblastoma	12
Neuroendocrine	3
Non-Hodgkin Lymphoma	1
Osteosarcoma	4
PNET	2
Retinoblastoma	3
Rhabdomyosarcoma	3
Sarcoma	62
Urogenital	8
Wilms Tumor	2

Predicted individual CL (at time=0) and Vc values are summarized in Figure 3 and Table 10. Figure 4 and Table 11 summarize predictions of AUC6wks (based on CL at time=0), Cmax,ss and Cmin,ss for different paediatric age groups and adults. In the weight-based regimen of 2 mg/kg Q3W, exposure values are similar across the age groups of 6-12 years, 12-18 years and adults. Predicted AUC6wks, Cmin,ss, Cmax,ss were respectively 20%, 57% and 10% higher for the group of 2-6 years compared to adults. Predicted exposures for the group below 2 years are more than double those of the adult reference group.

Figure 3 **Pembrolizumab (MK-3475) Predicted Clearance and Central Volume of Distribution for Pediatrics and Adults**



Reviewed per SOP-QP2-005

Figure 4 **Pembrolizumab (MK-3475) Predicted Exposure Parameters for Pediatrics and Adults**

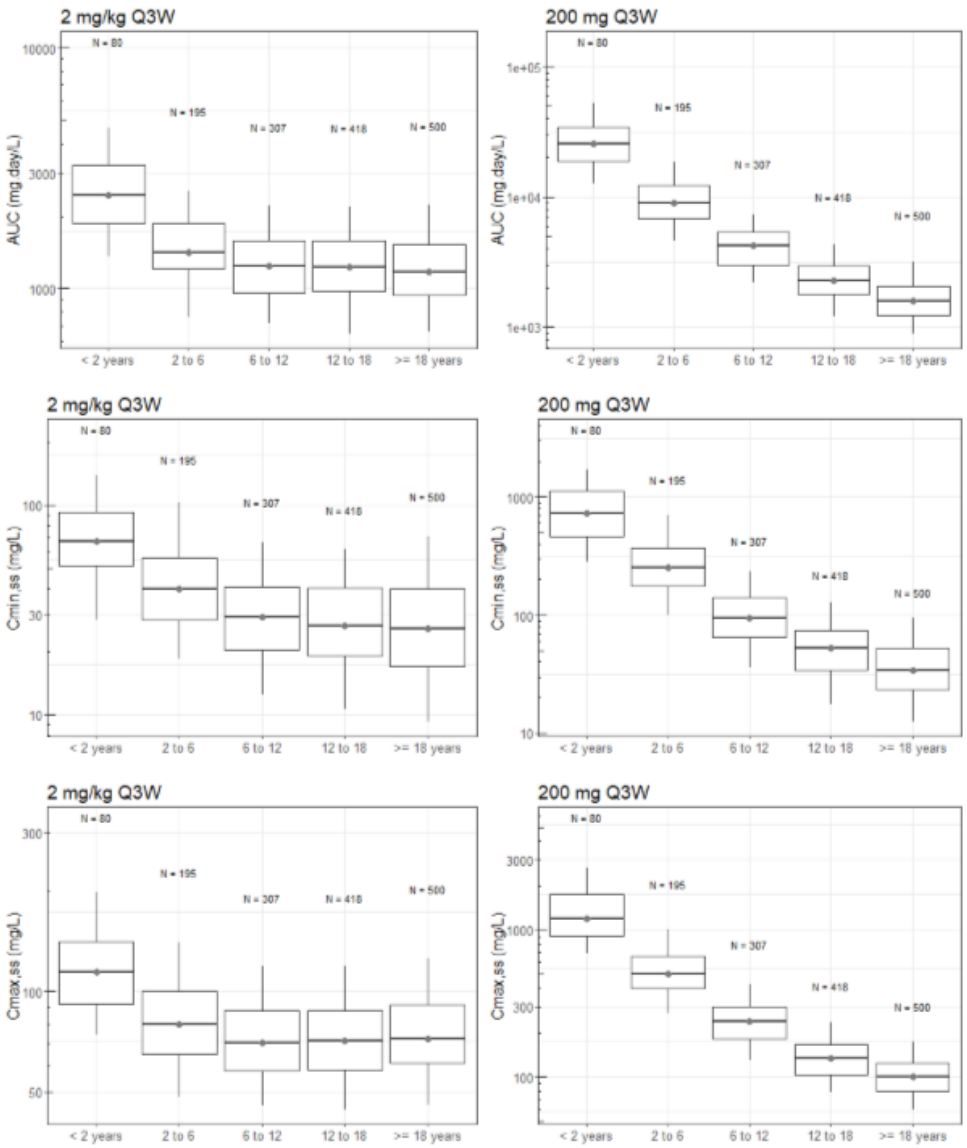


Table 13 Descriptive statistics of predicted individual PK parameters (CL, Vc) for paediatric and adult patients

	<2 years	2-6 years	6-12 years	12-18 years	>18 years
	N=80	N=195	N=307	N=418	N=500
CL (at time=0) (L/day)					
Median	0.0156	0.0442	0.0949	0.177	0.25
Q1	0.0116	0.0324	0.0745	0.1349	0.1941
Q3	0.0212	0.0586	0.1338	0.2239	0.3259
Vc (L)					
Median	0.407	0.813	1.513	2.435	3.251
Q1	0.335	0.672	1.244	2.046	2.787
Q3	0.502	1.017	1.858	2.985	3.798

Reviewed per SOP-QP2-005

Table 14 Descriptive statistics of predicted individual exposure PK parameters (AUC6wks, Cmin,ss, Cmax,ss) for paediatric and adult patients at 2mg/kg Q3W

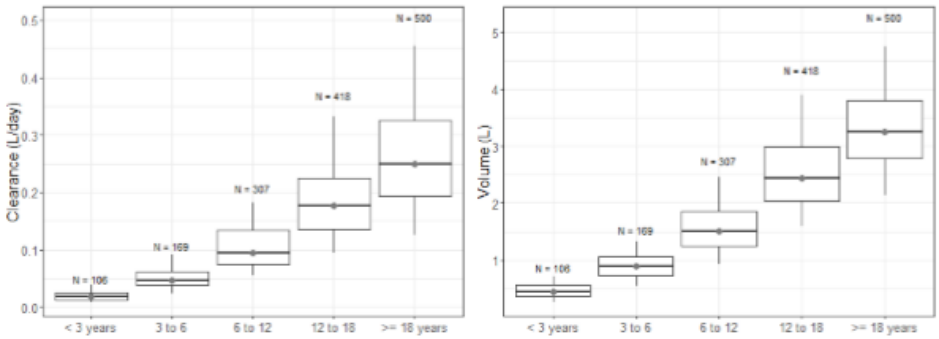
	<2 years	**2-6 years**	**6-12 years**	**12-18 years**	**>18 years**
	N=80	N=195	N=307	N=418	N=500
AUC6wks (mg.day/L)					
Median	2448.5	1413.8	1243.5	1232.6	1175.3
Q1	1864.1	1201	955	972.8	938
Q3	3261.7	1872.8	1583.4	1575.5	1525.8
Cmin,ss (mg/L)					
Median	67.6	40.1	29.3	26.7	25.6
Q1	51.6	28.5	20.4	19	17.1
Q3	92.5	56.1	40.8	40.3	39.9
Cmax,ss (mg/L)					
Median	114.5	79.9	70.2	71	72.3
Q1	92	64.8	57.9	58.4	61
Q3	141.2	100.5	87.4	87.8	91.2

Predicted individual CL (at time=0) and Vc values and predictions of AUC6wks (based on CL at time=0), Cmax,ss and Cmin,ss for another age categorization (<3 years / ≥3 -<6 years / ≥6 -<12 years / ≥12 -<18 years / ≥18 years) are presented below.

When an age of 3 years is used as cut-off for the first age group, predicted AUC6wks, Cmin,ss, Cmax,ss become respectively 17%, 52% and 9% higher for the group of 3-6 years compared to adults. For the group below 3 years old, AUC6wks, Cmin,ss, Cmax,ss are predicted to be 2, 2.4 and 1.5 fold higher compared to the values in adults, respectively.

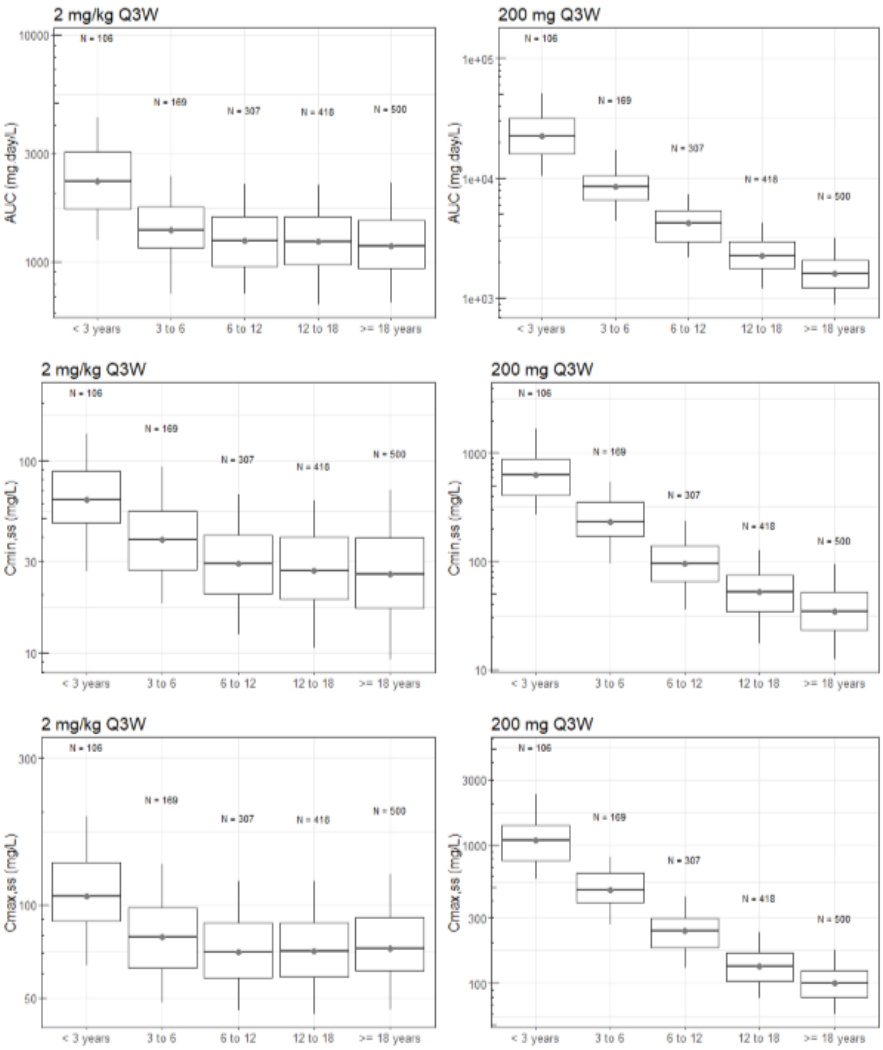
Figure 11 Predicted CL and Vc

Appendix 5 Pembrolizumab (MK-3475) Predicted Clearance and Central Volume of Distribution for Pediatrics and Adults using a 3 years old cut-off



Reviewed per SOP-QP2-005

Appendix 6 Pembrolizumab (MK-3475) Predicted Exposure Parameters for Pediatrics and Adults using a 3 years old cut-off



Reviewed per SOP-QP2-005

Appendix 7 Descriptive Statistics of Predicted Individual PK Parameters (CL, Vc) for Pediatric and Adult Patients using a 3 years old cut-off

	<3 years	3-6 years	6-12 years	12-18 years	>18 years
	N=106	N=169	N=307	N=418	N=500
CL (at time=0) (L/day)					
Median	0.0179	0.0472	0.0949	0.177	0.25
Q1	0.0126	0.038	0.0745	0.1349	0.1941
Q3	0.0249	0.0608	0.1338	0.2239	0.3259
Vc (L)					
Median	0.443	0.887	1.513	2.435	3.251
Q1	0.361	0.724	1.244	2.046	2.787
Q3	0.568	1.058	1.858	2.985	3.798

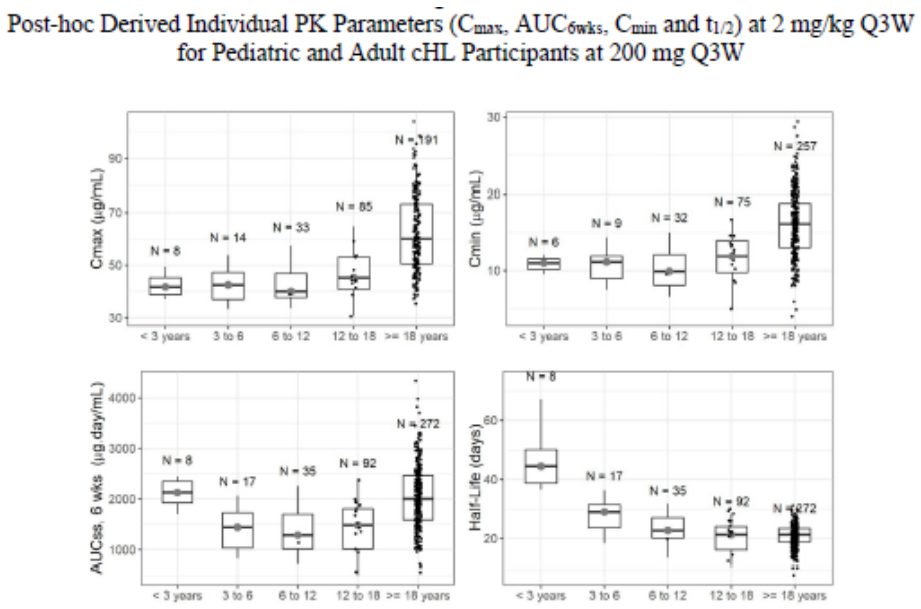
Reviewed per SOP-QP2-005

Appendix 8 Descriptive Statistics of Predicted Individual Exposure Parameters (AUC6wks, Cmin,ss, Cmax,ss) for Pediatric and Adult Patients at 2 mg/kg Q3W using a 3 years old cut-off

	<3 years	**3-6 years**	**6-12 years**	**12-18 years**	**>18 years**
	N=106	N=169	N=307	N=418	N=500
AUC6wks (mg.day/L)					
Median	2255.1	1375.7	1243.5	1232.6	1175.3
Q1	1713.5	1157.1	955	972.8	938
Q3	3049.2	1747.6	1583.4	1575.5	1525.8
Cmin,ss (mg/L)					
Median	62.7	38.8	29.3	26.7	25.6
Q1	47.8	27	20.4	19	17.1
Q3	88.1	54.5	40.8	40.3	39.9
Cmax,ss (mg/L)					
Median	107.1	78.6	70.2	71	72.3
Q1	88.6	62.5	57.9	58.4	61
Q3	137.2	97.7	87.4	87.8	91.2

Reviewed per SOP-QP2-005

Figure 12 Comparison of the model derived individual PK parameters for paediatric participants dosed at 2 mg/kg Q3W pembrolizumab with adult cHL participants dosed at 200 mg Q3W.



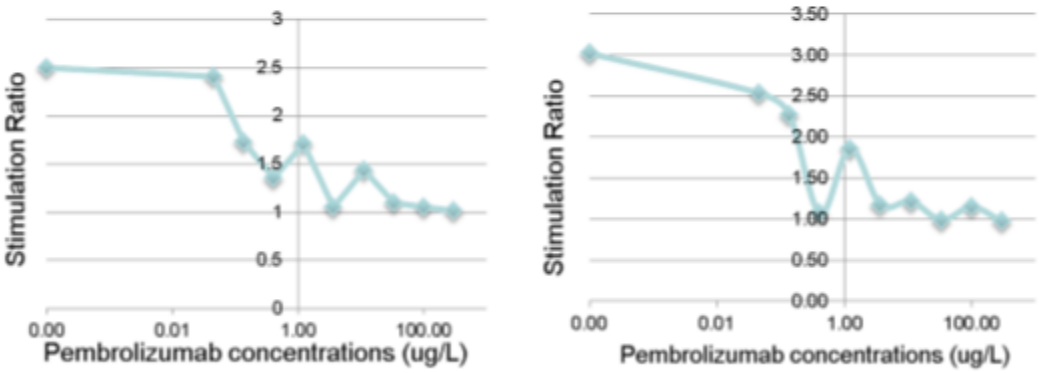
*Black dots highlight cHL participants

Moreover box plots of post-hoc derived PK parameters for cHL paediatric patients in different group of age and adults shows a consistency in exposure parameters among groups except for the AUC values in age <3 years old (~50% higher compared to that in adults), but this higher value is not of concern, considering the flat exposure-safety relationship for Keytruda. Of note, this does not relate to any conclusions regarding safety.

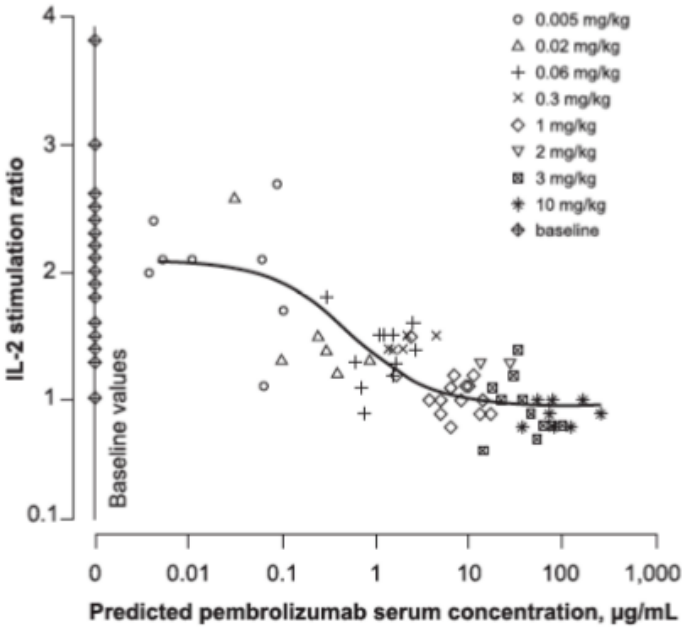
Interleukin 2 (IL-2) Stimulation

The interleukin 2 (IL-2) release biomarker reflects the functional blockade of the PD-1 pathway by pembrolizumab and is utilized as a measure of target engagement. An in-vitro IL-2 stimulation assay was performed to investigate if there is a shift in the IL-2 stimulation curve between adults and children to guide the determination of the recommended Phase 2 dose (RP2D) of pembrolizumab in paediatric patients. For the in-vitro IL-2 stimulation assay, two pre-dose baseline samples were collected in each of the first 12 subjects enrolled. At the end, 10 subjects provided 20 evaluable samples. Each evaluable sample was divided into two aliquots. One of the aliquot from these samples was spiked with pembrolizumab concentrations at 300 ug/mL, 100 ug/mL, 33.3 ug/mL, 11.1 ug/mL, 3.70 ug/mL, 1.23 ug/mL, 0.412 ug/mL, 0.137 ug/mL, 0.0457 ug/mL, and 0 ug/mL with 1 ug/mL staphylococcal enterotoxin B (SEB). The remaining aliquots from these samples were respectively spiked with an additional 25 ug/mLof pembrolizumab (i.e., respective concentrations in these samples were 325 ug/mL, 125 ug/mL, 58.3 ug/mL 36.1 ug/mL, 28.7 ug/mL, 26.23 ug/mL 25.412 ug/mL, 25.137 ug/mL, 25.0457 ug/mL and 25 ug/mL) along with the same amount of SEB. The stimulation ratios were calculated by measuring the IL-2 concentrations in the two aliquots respectively, i.e. 300 ug/mL with 325 ug/mL, 100 ug/mL with 125 ug/mL, etc. The IC50 of the concentration-stimulation ratio curves of in-vitro IL-2 assay in paediatric patients (figures below) were compared with that of adult patients using banked blood samples from adult cancer patients in KN001.

Interleukin 2 (IL-2) Stimulation Ratio as a Function of Plasma Concentration in 10 Pediatric Subjects from KN051



Interleukin 2 (IL-2) Stimulation Ratio as a Function of Plasma Concentration of Pembrolizumab in KN001



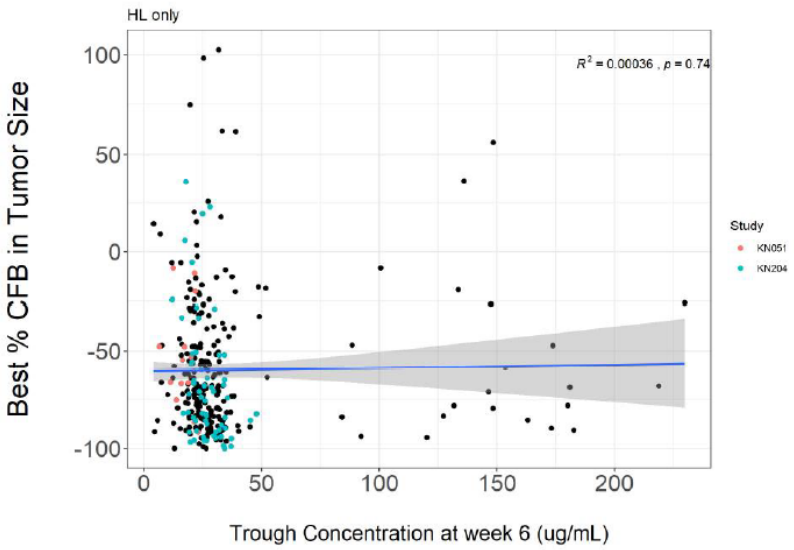
Data source: [Ref. 5.4: 0534YZ]

Exposure-response analysis

Exposure-response analysis for best percent change from baseline tumor size, demonstrating similar relationships between adult and paediatric participants with cHL is shown in Figure below.

Figure 13

Exposure (C_{min} at Week 6)-Response for Best Percent Change From Baseline Tumor Size Based on KEYNOTE-204 (Green Dots), KEYNOTE-051 (Red Dots) and KEYNOTE-013 and KEYNOTE-087 (Black Dots)



2.3.5. Discussion on clinical pharmacology

Overall, the PK and clinical pharmacology of pembrolizumab is well-known and described over a large exposure range and various indications.

Participants with rrcHL in KEYNOTE-204 and KEYNOTE-087 and paediatric participants with rrcHL in KEYNOTE-051 comprise the primary participant populations for this application.
KEYNOTE-051 is an ongoing Phase I/II Study of Pembrolizumab (MK-3475) in Children With Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumor or Lymphoma (KEYNOTE-051). As of the data cutoff date for the submitted report (10-JAN-2020), 162 participants (N=22 rrcHL patients) were enrolled out of a total of up to 310 participants that was planned to be enrolled.
In total, there were 151 participants in KEYNOTE-051 with evaluable PK samples.

Based on the existing robust characterization of pembrolizumab PK, a comparison was conducted between the observed PK of pembrolizumab in children from study KEYNOTE-051 and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024).

New "overlay" figures at Cycle 1 and steady state are generated for KEYNOTE-051 paediatric participants and KEYNOTE-204 adult cHL participants, based on the updated popPK model including adult cHL participants and paediatric participants with solid tumors and cHL described in Report 05G4NL. Observed data shown in blue refer to cHL participants and data shown in green refer to paediatric participants with solid tumors. The paediatric data in KEYNOTE-051 and adult data from KEYNOTE-204 remain well within the range of predicted concentration profiles using the updated popPK model.

The Applicant proposes to extrapolate the efficacy data in adult patients with rrcHL from KEYNOTE-087 and KEYNOTE-204 to paediatric patients with rrcHL using a model-based PK bridging analysis. In addition, KEYNOTE-051 will provide supportive efficacy and safety data in rrcHL paediatric patients.

The objectives of the population PK analysis described in this report were: 1) to update the existing population pharmacokinetic model from report 04LL90 with additional paediatric data from KN051 in solid tumors and cHL and adult cHL data from KN204 and 2) to compare pembrolizumab pharmacokinetics and exposures in different age groups of paediatric patients to those in adult patients
Specifically, data from adults with solid tumors (N = 2840) and data from 301 adult rrcHL participants in KEYNOTE-013, KEYNOTE-087, and KEYNOTE-204 were included in the analysis. In addition, 151 paediatric participants in KEYNOTE-051 receiving 2 mg/kg up to 200 mg Q3W were also included. From the study report P051V02MK3475 it is known that 22 paediatric participants with HL ranged in age from 10 to 17 years. Four participants were 10 to 13 years of age and 18 participants were 14 to 17 years of age.
Only 16 paediatric subjects are assumed to be involved the PK data analyses. In total only 122 PK samples have been included in the PK analysis (0.63%). Age of these subjects ranged from 11-17 years of age (median: 15 years). Weight ranged from 32.5 to 103.4 kg with a median weight of 50.8 kg.
Age cut-off is set to 3 years of age. This is not supported by clinical data so far. Exposure simulations have been conducted for the age groups of 2-6 years of age and 3-6 years of age. No clinical and no PK data have been measured so far in paediatric patients below the age of 11 with HL.
The existing population PK model for pembrolizumab was used as a basis for an update of the model with the addition of data from paediatric patients with solid tumors and cHL and adult cHL patients. Models parameters including covariate effect have been re-estimate for the refined model. The values of parameters estimates are very similar between the previous popPK model and the updated one.
Goodness-of-fit plots were utilized to assess the adequacy of the structural model to describe the pooled dataset.
As a general comment the goodness of fit evaluation demonstrated the absence of a structural bias as a function of drug concentration or time and showed that data from paediatric subjects is equally well described as the data from adult subjects.
However, no tornado plots (to demonstrate the single covariate effects) or (stratified) VPC have been provided. In general, weight and age is incorporated. The inclusion of age effect on both, volume of distribution and clearance seems to be necessary on top on weight to describe the paediatric data.
The MAH used the number of prior line of therapies as a stratification variable, to present the post-hoc model predictions of AUC6wks (Cmax,ss and Cmin,ss and half-life, similar for paediatric and adult participants. In both populations (adults and paediatrics), there is not a clear trend across different prior lines of therapy.
The reference population PK model has been re-run including weight, allometrically scaled with fixed exponents (0.75 for CL and 1.0 for V) in the model, instead of age as requested. The parameter estimates and OFV for the new model, Including Weight as Allometrically Scaled Fixed Exponents and Without Age), are compared (Run 8) with the final model with age and estimated exponents for weight (Run 6)
The difference in OFV between the new model (Run 8) and the Reference model (Run 6) is an increase of 503.861 points.
This significant increase in OFV together with the GOF plots for Run 8 and Run 6, suggests that the reference model with age and extimated exponents better describes the data respect to the new model with no age and fixed exponent.
Simulated exposures (C_{min}, $C_{max,}$ and AUC) for pediatric participants dosed at 2 mg/kg Q3W obtained using the newly requested model, Run 8 showed that PK parameters across the weight range of the pediatric participants are contained within the 5th and 95th percentile of adult values.

The MAH provided the GoF plots for the paediatric population only distinguishing cHL data (black dots) and solid tumors data (gray dots), as requested.
GoFs are provided for each age group (paediatric participants <3 years old, 3 to <6 years old, 6 to <12 years old, 12 to <18 years old, and adults >18 years old , with gray dots representing participants with solid tumors and black dots representing participants with cHL. Overall, except for minor deviation, the observed data are aligned with the line of unity demonstrating that the model adequately described the

data across the entire age range of the data. In addition, VPCs for adults and paediatric participants with solid tumors and cHL are provided in different panels showing that adults and paediatrics data with both solid or cHL tumor fall within those predicted by the Model.

CL and Vd are lower in children as expected, since they correlate directly with the BW.
The exposure parameters in the box plots are similar between children and adults. A total of 152 paediatric participants were included in the updated popPK model. The majority of the paediatric participants is in older age groups 6 to <12 years old (n=35) and 12 to <18 years old (n=92); while in the younger age groups there are 8 patients <3 years old and 17 patients in the group 3 to <6 years old.
Box plots of post-hoc derived PK parameters for cHL paediatric patients in different group of age and adults shows a consistency in exposure parameters among groups except for the AUC values in age <3 years old (~50% higher compared to that in adults). This was already noted but however justified by the flat exposure-safety profile of Keytruda between 2 and 10 mg/kg.
The final model was subsequently used in simulations of pembrolizumab PK parameters and exposure parameters in different age groups of paediatric patients and compared to the estimates in adult patients to support pembrolizumab dose regimen selection in paediatric patients.

The final population PK model was used to predict the pembrolizumab concentrations following single dose and at steady state for the patients in the simulation dataset (different age groups 2-6 (3-6), 6-12, 12-18, >18 years of age).

Simulations following 2 mg/kg Q3W and 200 mg Q3W support the per kg dosing as exposure at steady state is expected to be in the range of adult exposure (in terms of Cmin_ss, Cmax_ss and AUC) assuming paediatric patients of 6 years of age or older.

Below the age of 6, exposure reached at steady state is higher compared to adults.
Descriptive statistics of predicted individual exposure parameters for paediatric and adult patients shows that Cmin is about 50% higher in the 3-6 age group, although the median value is within the Q3 for adults. More explicitly, assuming a lower age limit of 3 years for the first age group, predicted AUC6wks, Cmin,ss, Cmax,ss are simulated to be respectively 17%, 52% and 9% higher for the group of 3-6 years compared to adults. There are not participants <11 years old with cHL in the analysis dataset and the results in the 3 to 6 years old age group are informed by participants with solid tumors.

Simulations from the final model were performed to assess the exposure to pembrolizumab in paediatric patients at the dose regimens of 2 mg/kg Q3W or 200 mg Q3W and compared to the exposures in adult patients.
The MAH recognized that there is a small number of paediatric subjects in the younger age group (from CSR P051V02MK3475 it seems that paediatric patients ranged from 10 to 17 years) and the resampling dataset was augmented with a paediatric oncology dataset from another program.
This dataset, comprised of 171 participants (aged 0.5 – 17 years), included 22 different tumor types.
Simulations following 2 mg/kg Q3W and 200 mg Q3W support the per kg dosing as exposure at steady state is expected to be in the range of adult exposure (in terms of Cmin_ss, Cmax_ss and AUC) assuming paediatric patients of 6 years of age or older.
Below the age of 6, exposure reached at steady state is higher compared to adults.
Descriptive statistics of predicted individual exposure parameters for paediatrics and adult patients shows that Cmin is about 50% higher in the 3-6 age group, although the median value is within the Q3 for adults. More explicitly, assuming a lower age limit of 3 years for the first age group, predicted AUC6wks, Cmin,ss, Cmax,ss are simulated to be respectively 17%, 52% and 9% higher for the group of 3-6 years compared to adults.
There are not participants <11 years old with cHL in the analysis dataset and the results in the 3 to 6 years old age group are informed by participants with solid tumors.

In Figure 16, the model derived individual PK parameters for paediatric participants dosed at 2 mg/kg Q3W pembrolizumab are compared with adult cHL participants dosed at 200 mg Q3W. The figure demonstrates that observed exposure parameters in the paediatric participants (cHL data are shown in black dots) are generally within the range of values for adult cHL participants dosed at 200 mg Q3W.
Moreover box plots of post-hoc derived PK parameters for cHL paediatric patients in different group of age and adults shows a consistency in exposure parameters among groups except for the AUC values in age <3 years old (~50% higher compared to that in adults), but this higher value is not of concern, considering the flat exposure-safety relationship for keytruda.
Of note, this does not relate to any conclusions regarding safety.

An in-vitro IL-2 stimulation assay was performed to investigate if there is a shift in the IL-2 stimulation curve between adults and children to guide the determination of the recommended Phase 2 dose (RP2D) of pembrolizumab in paediatric patients.
The relationship between IL-2 stimulation and pembrolizumab concentration was assessed based on 10 participants. The IC50 of the concentration-stimulation ratio curves of in-vitro IL-2 assay in paediatric patients were compared with that of adult patients using banked blood samples from adult cancer patients in KN001.
According to the MAH, the IC50 value of the IL-2 stimulation ratio curves in paediatric subjects are consistent with that found in adult subjects supporting the dose of pembrolizumab 2 mg/kg Q3W. This in indicated in Figures 4 and 5, however the IC50 values are hard to compare by eye.
The MAH presented results from an Imax model that was fitted to the available limited IL-2 data. The estimated IC50 value was found to be 0.14 ug/mL in paediatrics patients (no measure of variability provided), which is in the same range to the IC50 value of 0.535 ug/mL found in adults characterized with a wide 95% CI of 0.123 – 2.33, covering the paediatric estimate at the lower end. Paediatric patients might need less exposure to reach the same level of inhibition; however the data base in paediatrics with respect to IL-2 biomarker is limited.

E-R relationship for best percent change from baseline tumour size remains very flat, also after recalculation and including adult cHL data from KEYNOTE-204 with a dosing regimen of 200 mg Q3W and paediatric cHL data from KEYNOTE-051 with a dosing regimen of 2 mg/kg Q3W.

The incidence of ADA in paediatric participants was consistent with the adult population.

2.3.6. Conclusions on clinical pharmacology

The data package on clinical pharmacology to support the current variation is limited. There are so far no clinical and no PK data available below the age of 10.

Observed PK concentrations in paediatric patients administered with 2 mg/kg Q3W from study KEYNOTE-051 were within the range of predicted concentration (reference popPK model) for adults administered with the same dose of 2 mg/kg Q3W. However, some issues were identified about this comparison (VPC plots, pooling of subject with different tumors types, etc).

The MAH submitted a popPK analysis built on an existing population PK model for pembrolizumab in patients with various tumor types previously described in Report 04LL90 and proposed to extrapolate the efficacy and safety data in adult patients to paediatric patients with rrcHL using a model-based PK bridging analysis with supportive efficacy and safety data in rrcHL paediatric patients obtained from study KEYNOTE-051. The extrapolation is acceptable from the PK point of view.

Further follow up data from the final study report from KEYNOTE -051 will be received in the context of the PIP completion.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Pembrolizumab was initially approved for advanced melanoma at 2 mg/kg Q3W. Subsequent approvals for adult participants for multiple indications are at 200 mg Q3W dosing regimens. The 200 mg fixed dose is now the standard dose globally utilized and approved for numerous other pembrolizumab indications. This is also the recommended dose of pembrolizumab for all ongoing clinical studies except paediatric studies.

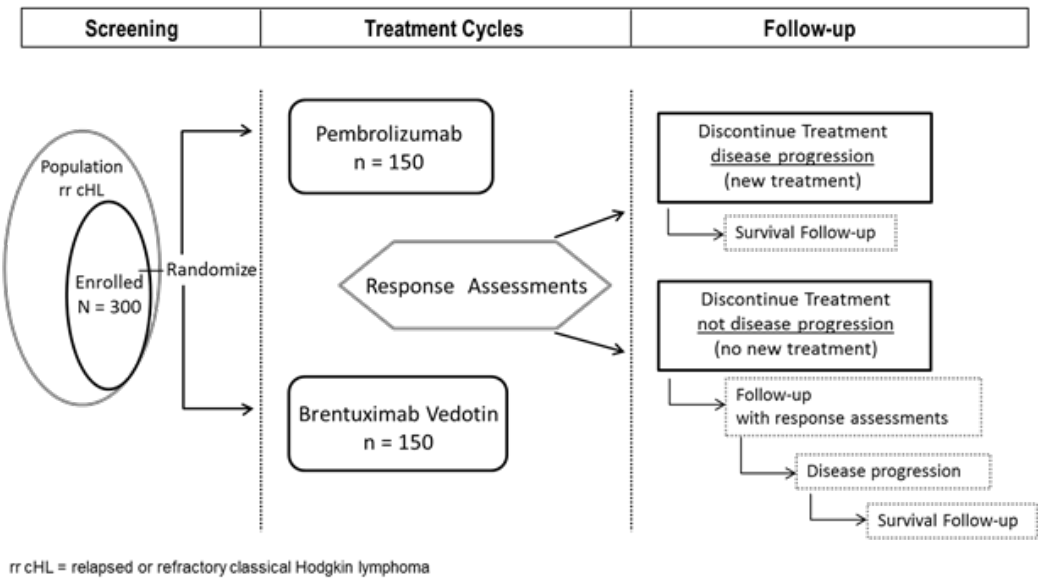
Pembrolizumab has been dosed at 200 mg Q3W in participants with cHL (KN-204 and KN-087). The clinical data in participants with cHL demonstrates efficacy at 200 mg Q3W, which in conjunction with an integrated body of evidence in previously approved indications, supports the recommendation of 200 mg Q3W as the appropriate dose for patients with cHL. An additional dosing regimen of 400 mg Q6W was approved in the EU on 28-MAR-2019 for all monotherapy indications approved at the time, including cHL.

PK exposures in paediatric patients at the 2 mg/kg (up to 200 mg) Q3W dose are expected to be similar to those in adults at 200 mg Q3W dose. The dose of 2 mg/kg (up to 200 mg) Q3W is proposed for use in paediatric patients with cHL. For additional details on paediatric PK, modeling, and extrapolation of adult data see above sections under Clinical Pharmacology.

2.4.2. Main study(ies)

Keynote (KN)-204 - A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma

Figure 14 Study design



rr cHL = relapsed or refractory classical Hodgkin lymphoma

Methods

Study participants

Main Inclusion Criteria

- Age ≥18 years
- Patients have relapsed (disease progression after most recent therapy) or refractory (failure to achieve CR or PR to most recent therapy) classical HL.
- Patients have achieved a CR or PR to BV or BV-containing regimens, if previously treated with BV.
- Measurable disease defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral computed tomography (CT) scan or combined CT/positron emission tomography (PET) scan. Minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis.
- Provide evaluable core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy.
- Performance status of 0 or 1 on ECOG Performance Scale.
- Demonstrate adequate organ function: ANC ≥1,000/mcL, platelets ≥75,000/mcL, haemoglobin (Hb) > 8.0 g/dl, creatinine≤1.5 X upper limit of normal (ULN) or measured or calculated creatinine clearance (CrCl) ≥60.0 mL/min for subjects with creatinine levels >1.5 X ULN, total bilirubin ≤1.5 X ULN, AST/ALT ≤2.5 X ULN O(≤5 X ULN for subjects with liver metastases), PT and PTT ≤1.5 X ULN. All screening were to be performed within 7 days of treatment initiation.

Main exclusion criteria

- Severe (≥ Grade 3) hypersensitivity to the active substance or to any of the excipients in BV or pembrolizumab.
- Diagnosis of immunosuppression or the subject was receiving systemic steroid therapy (exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Prior monoclonal antibody within 4 weeks prior to first dose of therapy in the study or the subjects did not recover (i.e., ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
- Prior chemotherapy, targeted small molecule therapy, or radiation therapy including investigational agents within 4 weeks prior to study Day 1 or the subjects did not recover (i.e., ≤Grade 1 or at baseline) from AEs due to a previously administered agent.
- Prior allogeneic SCT (alloHSCT) within the last 5 years. Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease (GVHD).
- Known progressing additional malignancy or malignancy that required active treatment in the last 3 years.
- Active central nervous system (CNS) involvement. Subjects with previously treated brain lesions could participate provided they are radiologically stable (i.e., without evidence of progression for at least 4 weeks by repeat imaging, clinically stable, and without requirement of steroid treatment for at least 14 days prior to the first dose of trial treatment).

- Active autoimmune disease that required systemic treatment in the past 2 years (i.e., with the use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
- History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
- Active infection requiring systemic therapy, history of HIV infection or history of active tuberculosis, active hepatitis B (e.g. HBsAg reactive) or hepatitis C (e.g. HCV RNA is detected).
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, CTLA-4 antibody (including ipilimumab), or OX-40, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
- Eligibility for allogeneic or autologous stem cell transplantation per investigator assessment.

Treatments

Table 15 Summary of Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	1 dose on Day 1 of every 3 weeks = 1 cycle	IV infusion	Up to 35 cycles per participant	Experimental
Brentuximab vedotin	1.8 mg/kg (maximum 180 mg per dose)	1 dose on Day 1 of every 3 weeks = 1 cycle	IV infusion	Up to 35 cycles per participant	Comparator

Treatments were continued for up to 35 cycles per participant or until documented PD as described in the IWG response criteria [Cheson, 2007] by BICR, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, or administrative reasons.

Objectives

Primary objectives:

- to compare PFS as assessed by blinded independent central review (BICR), according to the IWG response criteria [Cheson, 2007] between treatment arms, including clinical and imaging data following autologous stem-cell transplantation (ASCT) or allogeneic stem cell transplantation (alloHSCT).
- to compare OS between treatment arms.

The study was considered to have met its primary objective if pembrolizumab is superior to BV in either PFS or OS.

Secondary objectives:

- to compare PFS (PFS-secondary), as assessed by BICR, according to the IWG response criteria [Cheson, 2007] between treatment arms, excluding clinical and imaging data following ASCT or alloHSCT.
- to compare the objective response rate (ORR) as assessed by BICR according to the IWG response

criteria [Cheson, 2007] between treatment arms.

- to evaluate the complete remission rate (CRR) as assessed by BICR according to the IWG response criteria [Cheson, 2007] between treatment arms.
- to evaluate PFS, CRR, and ORR as assessed by the investigator according to the IWG response criteria [Cheson, 2007] by treatment arm.

Exploratory objectives:

- to determine the duration of response (DOR) as assessed by BICR and investigator assessment according to the IWG response criteria [Cheson, 2007] by treatment arm.
- to compare the changes from baseline between the treatment arms in health-related quality-of-life (HR-QoL) assessments using the EORTC QLQ-C30 and EuroQol EQ-5D.
- to evaluate second progression-free survival (PFS2) as assessed by the investigator according to the IWG response criteria [Cheson, 2007] by treatment arm.
- to evaluate PFS as assessed by the investigator, according to the IWG response criteria [Cheson, 2007] by treatment arm, including clinical and imaging data following ASCT or alloHSCT.
- To evaluate PFS, ORR, CRR, and DOR as assessed by BICR according to the Lugano criteria [Cheson, 2014] by treatment arm.

Outcomes/endpoints

The following efficacy endpoints were assessed by treatment arm:

Primary

Progression-free survival (PFS) – PFS is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first, as per IWG criteria assessed by BICR, including clinical and imaging data following auto-SCT or allo-SCT.

Overall Survival (OS) - OS is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary

Progression-free survival (PFS-secondary) – Progression-free-survival (PFS-secondary) is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first, as per IWG criteria assessed by BICR, excluding clinical and imaging data following auto-SCT or allo-SCT.

Objective Response Rate (ORR) – ORR is defined as the proportion of the subjects in the analysis population who achieved at least a partial response (CR+PR) as per IWG criteria assessed by BICR.

Complete Remission Rate (CRR) – CRR is defined as the proportion of the subjects in the analysis population who achieved a complete remission (CR) as per IWG criteria assessed by BICR.

PFS, ORR, and CRR as per IWG criteria assessed by investigator

Exploratory

Duration of Response (DOR) – DOR is defined as time from first response to disease progression or death due to any cause, whichever occurs first in subjects who achieve a PR or better, as per IWG criteria assessed by BICR and by investigator.

ORR by PD-L1 Status – as per IWG criteria assessed by BICR for subjects with prepembrolizumab PD-L1 positive versus PD-L1 negative.

ORR Post-progression – as per IWG criteria assessed by investigator in subjects who achieved at least a partial response (CR+PR) after initial progression of disease.

PFS, ORR, CRR, and DOR – as per Lugano criteria assessed by BICR

Second Progression-free Survival (PFS2) – defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first, by investigator assessment.

PFS including clinical and imaging data after auto-SCT or allo-SCT as per IWG criteria assessed by investigator.

Disease assessment

Following screening, lymphoma disease response assessments occurred at Week 12 (±7 days) and every 12 weeks (±7 days). CT scans were repeated every 12 weeks. PET was repeated at Week 12, Week 24, to confirm CR, and as clinically indicated. Response assessments and imaging continued to be performed until documented disease progression by BICR review, start of new anti-cancer treatment, withdrawal of consent, death or study end, whichever occurs first

For subjects receiving pembrolizumab, after the first documentation of progression, it was the discretion of the investigator to stop trial treatment or to keep a clinically stable subject on trial treatment until repeat imaging performed 4-6 weeks later confirmed progression. Clinical stability was defined as the absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values), no decline in ECOG performance status and absence of rapid progression of disease or progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent medical intervention. Subjects deemed clinically unstable were not required to have repeated imaging for confirmation. If progression was confirmed, then the subject had to be discontinued from trial treatment. If progression was not confirmed, then the subject could resume/continue trial treatment provided that the sponsor was consulted and provided approval to continue treatment, no other anti-tumour therapy (e.g., chemotherapy, radiation, etc.) had been administered.

Treatment with BV was stopped at any time a lymphoma disease response assessment, verified by blinded independent central review showed PD. Although pembrolizumab could be continued, if PD was verified by blinded independent central review, the subject was considered to have progressed (i.e., counted as an event) at the initial PD assessment for the primary PFS analysis.

PROs assessment

Patient-reported outcomes (PROs) were assessed using the eEuroQol-5D (eEQ-5D), version 1.0, as provided by the EuroQol Group, and the EORTC QLQ-C30, version 3.0, as provided by the EORTC Quality of Life Group. Patient-reported outcomes (PROs) were assessed pre-dose at Cycle 1 (baseline), Cycle 3 (Week 6), Cycle 5 (Week 12), Cycle 7 (Week 18), and Cycle 9 (Week 24) and every 12 weeks thereafter until PD or up to 1 year while the subject is receiving study treatment. Patient-reported outcomes were also obtained at discontinuation and at the 30-day Safety Follow-up Visit.

Sample size

The planned sample size was approximately 300 subjects. The study was event-driven. With 194 PFS events, the study had 85% power to detect a hazard ratio of 0.622 (pembrolizumab vs. BV) at alpha = 1.2% (one-sided). With 146 OS events, the study had 80% power to detect a hazard ratio of 0.600 at alpha = 1.25% (one-sided). It was assumed that OS and PFS followed an exponential distribution.

Power calculations assumed interim analyses (1 for PFS, 2 for OS), an enrolment period of 12 months and a cumulative dropout rate of 5% at the end of 3 years. The assumed median PFS and OS in the control arm of 5.6 and 22.4 months, respectively, were observed from a published study of subjects with relapsed/refractory HL treated with BV, all of whom had received prior SCT. The estimates of PFS and OS for BV in r/r HL subjects who have not received prior SCT were unknown at that time. However, based on limited data, the ORR and CRR for r/r HL subjects without prior SCT treated with BV were observed to be lower than those subjects with prior SCT. It was anticipated that the efficacy would be lower in the patient population not receiving SCT, so that control PFS estimate of 5.6 months and OS estimate of 22.4 months could be considered as over-estimates.

For the key secondary endpoint of ORR, which could only be tested if the PFS hypothesis was rejected, there was 90% power (1-sided 0.6% alpha) to detect an 18-20% improvement on the experimental arm assuming the true ORR for the control arm ranges between 60-70%, depending on the actual percentage of subjects without prior SCT enrolled.

Randomisation

Treatment allocation/randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects were randomly assigned in a 1:1 ratio to receive either 200-mg pembrolizumab or 1.8 mg/kg BV. Randomization was stratified by prior ASCT (Yes vs. No, with at least 100 subjects randomized within each level) and HL status after frontline therapy (primary refractory disease vs. relapsed disease less than 12 months after completion of frontline therapy vs. relapse 12 months or more after completion of frontline therapy).

Blinding (masking)

Not applicable. KN-204 was an open label study.

Statistical methods

The Intention-to-Treat (ITT) population served as the population for primary efficacy analysis. All randomized subjects were included in this population, and subjects were analysed in the treatment group to which they were randomized.

The non-parametric Kaplan-Meier (KM) method was used to estimate the PFS, PFS2 and OS curve in each treatment group. The treatment difference in PFS, PFS2 and OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard (PH) model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., HR) between treatment arms.

For the primary PFS analysis, for the subjects who have PD, the true date of disease progression was approximated by the date of the first assessment at which PD is objectively documented per IWG by BICR, including clinical and imaging data following auto-SCT or allo-SCT, regardless of discontinuation of study drug. Death was always considered as a confirmed PD event.

Table 16 Censoring rules for primary, secondary and Sensitivity analyses of PFS

Situation	Primary Analysis	Secondary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD and no death; subject receives SCT following study treatment in the absence of PD	Censored at last disease assessment	Censored at last disease assessment before SCT	Censored at last disease assessment	Censored at date of SCT
No PD and no death; subject receives SCT following study treatment in the absence of PD and new anticancer treatment is initiated after SCT	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before SCT	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥2 consecutive missed disease assessments	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessments	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death and lost to follow-up after ≥2 consecutive missed disease assessments	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment	Progressed at date of lost to follow-up

Adjustment for the effect of crossover on OS could be performed based on recognized methods, e.g., the Rank Preserving Structural Failure Time (RPSFT) model, two stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

Table 17 Censoring rules for PFS2

Outcome on initial study therapy	Receiving next line	Outcome of next line	Date of event or censoring	Outcome
Death; with or without PD	No	NA	Death date	Event
PD	Yes	No PD, but Death followed	Death date	Event
PD	Yes	PD	2nd PD	Event
PD	Yes	No PD and No death followed	Last assessment date without progression seen	Censored
No PD and no Death	No	NA	Last known alive date	Censored
No PD and no Death; but end of therapy due to toxicity or other reasons not for PD	Yes	PD or no PD	Event as the PD date (if "PD" from next line) or Death date (if "No PD" from next line, but Death followed); Censored as the last assessment date without progression seen (if "no PD" and "no Death" from next line)	Event/Censored

The analysis of ORR and CRR consisted of the point estimate and 95% 2-sided exact CI using the Clopper-Pearson method with at least 95% coverage of the true rate, by treatment group. The stratified Miettinen and Nurminen's method, weighted by stratum size, was used for comparison of the ORR between the treatment groups.

Response duration (DoR), an exploratory efficacy endpoint, was summarized descriptively by treatment arm using the KM method and was defined in the subset of subjects with a CR or PR, based on IWG criteria, as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause, whichever occurred first.

Table 18 Censoring rules for DOR.

Table 3: Censoring Rules for DOR

Situation	Primary Analysis		Sensitivity Analysis	
	Date of Progression or Censoring	Outcome	Date of Progression or Censoring	Outcome
No PD and no death; new anticancer	LDA	Censor (non-event)	LDA	Censor (non-event)

Situation	Primary Analysis		Sensitivity Analysis	
	Date of Progression or Censoring	Outcome	Date of Progression or Censoring	Outcome
treatment is not initiated				
No PD and no death; subject receives SCT following study treatment in the absence of PD	LDA	Censor (non-event)	Date of SCT	Censor (non-event)
No PD and no death; subject receives SCT following study treatment in the absence of PD and new anticancer treatment is initiated after SCT	LDA before new anticancer treatment	Censor (non-event)	Date of new anticancer treatment	End of response (event)
No PD and no death; new anticancer treatment is initiated	LDA before new anticancer treatment	Censor (non-event)	Date of new anticancer treatment	End of response (event)
PD or death documented after ≤1 missed disease assessment	Progression or death	End of response (event)	Progression or death	End of response (event)
PD or death documented after ≥2 consecutive missed disease assessments	LDA prior to the ≥2 consecutive missed disease assessments	Censor (non-event)	Progression or death	End of response (event)
No PD and no death and lost to follow-up after ≥2 consecutive missed disease assessments	LDA prior to the ≥2 consecutive missed disease assessments	Censor (non-event)	Date of lost to follow-up	End of response (event)
LDA = last disease assessment NOTE: Subjects are considered to have an ongoing response if censored, alive, have not progressed, and have not started a new anti-cancer therapy, have not been determined to be lost to follow-up, and the last non-NE imaging assessment is within two and half scheduled cycles (~30 weeks) of the data cutoff date.				

Interim Analysis:

Four interim analyses were planned for the study.

Table 19 Decision guidance at each efficacy analysis

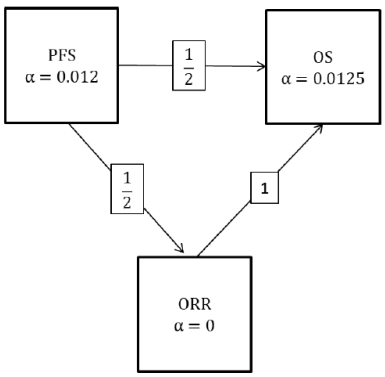
Analysis	Key Endpoints	Criteria for Conduct of Analysis	Value	Efficacy*
IA1	Final PFS-secondary	Three months after all subjects are enrolled and 110 PFS events are observed	HR at bound p-value (1-sided)	0.51 ≤0.0002
IA2	Interim PFS	Approximately 176 PFS events are observed	HR at bound p-value (1-sided)	0.68 ≤0.0057
IA3	Final PFS	Approximately 194 PFS events are observed**	HR at bound p-value (1-sided)	0.72 ≤0.0112
	Final ORR	Time of final PFS analysis‡‡	ORR Δ bound† p-value (1-sided)	~13-14% ≤0.00600
	First Interim OS	Time of final PFS analysis (approximately 91 OS events anticipated)	HR at bound p-value (1-sided)	0.51 ≤0.0006
IA4	Second Interim OS	Approximately 119 OS events are observed	HR at bound p-value (1-sided)	0.60 ≤0.0027
FA	Final OS	Approximately 146 OS events are observed	HR at bound p-value (1-sided)	0.69 ≤0.0120

Abbreviations: FA = final analysis; IA1 = interim analysis 1; IA2 = interim analysis 2; IA3 = interim analysis 3; IA4 = interim analysis 4; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS-secondary = progression-free survival secondary
*Actual value for OS depends on whether or not null hypotheses for PFS and ORR are rejected (see Section 3.8)
**If the PFS events accrue slower than expected, the Sponsor may conduct the final PFS analysis when all subjects have been followed up for 36 months, i.e. 36 months after last subject randomized
†Δ = ORR in pembrolizumab group – ORR in BV group, assuming expected ORR in BV group is between 60% and 70%
‡ORR analysis can be conducted at time of an Interim PFS if null hypothesis for PFS is rejected early

Multiplicity

For the superiority hypothesis, a Hwang-Shih-DeCani (HSD) alpha-spending function with gamma parameter was used to construct group sequential boundaries to control the type I error rate for both endpoints. With the selected gamma value of -8 selected, the HSD alpha-spending function was more conservative than the O'Brien-Fleming bound. The overall Type-I error across the testing of the OS, PFS and ORR hypotheses was controlled at 2.45% (one-sided).

Figure 15 Multiplicity control strategy



In addition (not shown in the Figure), α=0.05% (one-sided) was planned to be allocated to the PFS-secondary hypothesis, this endpoint will not be further analyzed, and the alpha level will not be re-allocated to other hypotheses. Group sequential methods were used to allocate alpha between the interim and final analyses (see above).

PROs

The following PRO endpoints were assessed for KN-204 at the time of the PFS IA:

• The mean score changes in EORTC QLQ-C30 global health status/quality of life scale from baseline to week 24

• The mean score change in QLQ-C30 functional scales from baseline to week 24.

• The mean score change in EQ-5D VAS and utility score from baseline to week 24.

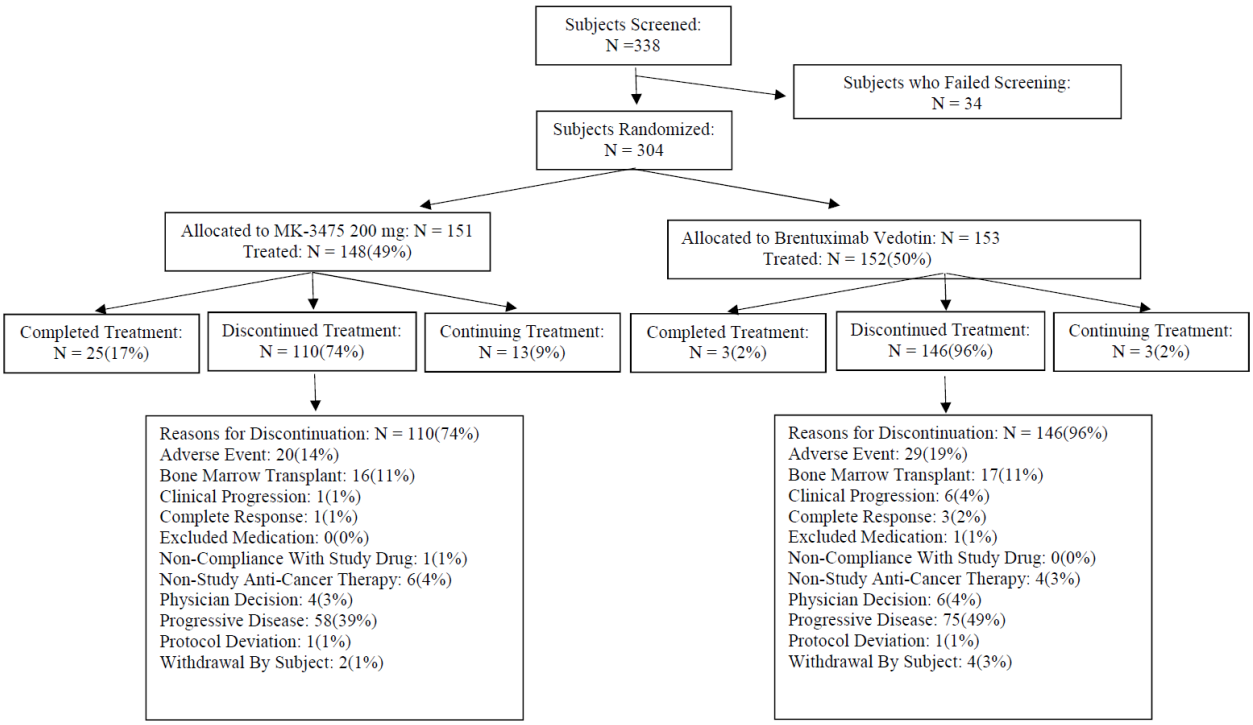
• The number and proportions of deterioration/stable/improvement from baseline to week 24, the time to deterioration (TTD), and the overall improvement rate during the study, i.e.: the QLQ-C30 global health status/quality of life scale (two items); the QLQ-C30 functional scales (five scales).

A change between -10 to 10 points was classified as "stable" and greater than 10 points as "improvement". The change of 10 points was chosen as this magnitude of change was perceived by patients as being clinically significant. Since missing data cannot be ignored, the number and proportion of patients who "improved", "stable", or "deteriorated", from baseline were summarized by treatment group at Week 24 based on MAR imputation of missing data.

Results

Participant flow

Figure 16 Participant flow



All 34 patients who were screened but not randomized did not meet inclusion or exclusion criteria.

Recruitment

Study KN-204 is conducted globally at 123 centres in 20 countries. The trial is currently ongoing, and the available data are based on the 2nd interim analysis (IA2). At the data cut-off date (17 Feb 2020), 304 participants were randomized (151 in the pembrolizumab arm and 153 in the BV arm). The date of the first patient first visit was 29 June 2016, the last patient last visit was 16 January 2020.

Conduct of the study

The original study protocol was dated 23 December 2015, and five protocol amendments were subsequently issued.

Table 20 Summary of Protocol amendments

Document	Date of Issue	Overall Rationale
Amendment 05	18-FEB-2020	To indicate that both clinical and imaging data following auto-SCT or allo-SCT will be collected and included in the evaluation of the primary PFS endpoint per IWG 2007 by BICR. For the primary analysis, participants who receive consolidative therapy following SCT and have not yet progressed will be censored at the date of their last assessment prior to initiation of the post-transplant consolidative therapy. Revision of the censoring rules of the primary analysis to censor participants at the last disease assessment prior to two or more consecutive missed disease assessments if 1) PD or death occurred after the two or more consecutive missed assessments, or 2) lost-to-follow-up occurred after two or more consecutive missed disease assessments if no PD and no death.
Amendment 04	22-NOV-2019	Due to the larger than expected number of participants who received an autologous-SCT or allogeneic-SCT in the context of the study, the Sponsor changed the exploratory endpoint of PFS based on IWG per BICR incorporating imaging data post-SC to the primary endpoint. To conduct the PFS analysis within a reasonable timeframe, the power of PFS is reduced to 85% and an interim for PFS has been added.
Amendment 03	16-NOV-2017	To modify the collection period for spontaneously reported pregnancy for participants receiving pembrolizumab to align with pembrolizumab template and US FDA request. Removal of PK and ADA objectives and associated blood collections as adequate data on pembrolizumab monotherapy in cHL are available. Modification of Exclusion Criteria #11 to delete the requirement for systemic

Document	Date of Issue	Overall Rationale
		therapy for an active infection to intravenously administered in order to make the criteria more stringent and align with pembrolizumab program standards. Addition of the exclusion of participants eligible for allogeneic or autologous SCT. Alignment of dose modification language with pembrolizumab label.
Amendment 02	01-AUG-2017	To allow prior treatment with brentuximab vedotin (BV) or BV-containing regimens provided participant responded (achieved a complete remission [CR] or partial remission [PR]) to prior BV or BV-containing regimens. To allow enrollment of participants who have relapsed or refractory classical Hodgkin Lymphoma and have received at least one prior chemotherapy regimen regardless of transplant eligibility. Additional follow-up included to allow for collection of ECI data post allo-SCT was included per US FDA request.
Amendment 01	20-JUN-2016	To exclude participants with a history of non-infectious pneumonitis requiring steroids due to a higher risk of developing pneumonitis with pembrolizumab, and to exclude participants with hypersensitivity to BV or any of its excipients.
Original Protocol	23-DEC-2015	Not Applicable

A total of 24 participants with 1 or more important protocol deviations were reported.

Table 21 ***Summary of Important Protocol Deviations (ITT Population)***

	MK-3475 200 mg		Brentuximab Vedotin	
	n	(%)	n	(%)
Subjects in population	151		153	
With one or more important protocol deviations	13	(8.6)	11	(7.2)
With no important protocol deviations	138	(91.4)	142	(92.8)
Discontinuation Criteria	**4**	**(2.6)**	**2**	**(1.3)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	1	(0.7)	0	(0.0)
Participant developed trial specific discontinuation criteria but was not discontinued from the trial.	3	(2.0)	2	(1.3)
Inclusion/ Exclusion Criteria	**2**	**(1.3)**	**1**	**(0.7)**
Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.Protocol Exceptions: The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.	0	(0.0)	1	(0.7)
Participants entered who do not have relapsed (disease progression after most recent therapy) or refractory (failure to achieve CR or PR to most recent therapy) classical Hodgkin lymphoma.	2	(1.3)	0	(0.0)
Prohibited Medications	**0**	**(0.0)**	**1**	**(0.7)**
Administration of potent/strong CYP3A4 inhibitors and inducers; or P-gp inhibitors in subjects receiving BV.	0	(0.0)	1	(0.7)
Safety Reporting	**7**	**(4.6)**	**4**	**(2.6)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	5	(3.3)	3	(2.0)
Post-allogenic-stem cell transplant events of clinical interest (ECIs) that occur after the normal safety follow up period must be assessed for seriousness and causality and reported to the sponsor as follows: within 24 hours if serious regardless of causality or if non-serious and considered to be drug-related; and 5 calendar days if non-serious and not considered to be drug-related.	3	(2.0)	1	(0.7)
Study Intervention	**0**	**(0.0)**	**1**	**(0.7)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	0	(0.0)	1	(0.7)
Trial Procedures	**0**	**(0.0)**	**2**	**(1.3)**
Baseline, week 12 or week 24 CT scans not performed during treatment phase to support study endpoints.	0	(0.0)	2	(1.3)
Every subject is counted a single time for each applicable row and column.				

Of these, 4 participants (3 in the pembrolizumab arm, 1 in the BV arm) had important protocol deviations that were considered to be clinically important. Clinically important deviation categories included:

- Inclusion/Exclusion criteria (n=2, pembrolizumab arm): participants entered who did not have relapsed or refractory cHL

- Safety reporting (n=1, pembrolizumab arm): post alloHSCT events of clinical interest that occur after the normal safety follow-up period must be assessed for seriousness and causality and reported to the Sponsor

- Study intervention (n=1, BV arm): participant was administered improperly stored study intervention that was deemed unacceptable

These 4 deviations did not compromise study data integrity so no per-protocol analyses were performed.

Baseline data

Baseline characteristics are summarised in Table below.

Table 22 ***Subject Characteristics (ITT Population)***

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	151		153		304	
Gender						
Male	84	(55.6)	90	(58.8)	174	(57.2)
Female	67	(44.4)	63	(41.2)	130	(42.8)
Age (Years)						
< 65	124	(82.1)	131	(85.6)	255	(83.9)
>= 65	27	(17.9)	22	(14.4)	49	(16.1)
Mean	41.9		40.8		41.4	
SD	17.5		17.1		17.3	
Median	36.0		35.0		35.0	
Range	18 to 84		18 to 83		18 to 84	
Race						
American Indian Or Alaska Native	1	(0.7)	0	(0.0)	1	(0.3)
Asian	13	(8.6)	13	(8.5)	26	(8.6)
Black Or African American	4	(2.6)	8	(5.2)	12	(3.9)
Multiple	4	(2.6)	5	(3.3)	9	(3.0)
Black Or African American White	3	(2.0)	5	(3.3)	8	(2.6)
White Asian	1	(0.7)	0	(0.0)	1	(0.3)
Native Hawaiian Or Other Pacific Islander	1	(0.7)	0	(0.0)	1	(0.3)
White	119	(78.8)	115	(75.2)	234	(77.0)
Missing	9	(6.0)	12	(7.8)	21	(6.9)
Race by Ethnicity						
Hispanic Or Latino	24	(15.9)	20	(13.1)	44	(14.5)
American Indian Or Alaska Native	1	(0.7)	0	(0.0)	1	(0.3)
Black Or African American	1	(0.7)	2	(1.3)	3	(1.0)
Multiple	3	(2.0)	4	(2.6)	7	(2.3)
White	19	(12.6)	14	(9.2)	33	(10.9)
Not Hispanic Or Latino	111	(73.5)	115	(75.2)	226	(74.3)
Asian	13	(8.6)	13	(8.5)	26	(8.6)
Black Or African American	2	(1.3)	5	(3.3)	7	(2.3)
Multiple	1	(0.7)	1	(0.7)	2	(0.7)
Native Hawaiian Or Other Pacific Islander	1	(0.7)	0	(0.0)	1	(0.3)
White	94	(62.3)	96	(62.7)	190	(62.5)
Not Reported	8	(5.3)	10	(6.5)	18	(5.9)
Black Or African American	0	(0.0)	1	(0.7)	1	(0.3)
White	4	(2.6)	4	(2.6)	8	(2.6)

Missing	4	(2.6)	5	(3.3)	9	(3.0)
Unknown	6	(4.0)	5	(3.3)	11	(3.6)
Black Or African American	1	(0.7)	0	(0.0)	1	(0.3)
White	2	(1.3)	1	(0.7)	3	(1.0)
Missing	3	(2.0)	4	(2.6)	7	(2.3)
Missing	2	(1.3)	3	(2.0)	5	(1.6)
Race Group						
White	119	(78.8)	115	(75.2)	234	(77.0)
All Others	23	(15.2)	26	(17.0)	49	(16.1)
Missing	9	(6.0)	12	(7.8)	21	(6.9)
Age Group (Years)						
< 65	124	(82.1)	131	(85.6)	255	(83.9)
>= 65 to < 75	18	(11.9)	16	(10.5)	34	(11.2)
>= 75 to < 85	9	(6.0)	6	(3.9)	15	(4.9)
US Region						
US	11	(7.3)	13	(8.5)	24	(7.9)
Ex-US	140	(92.7)	140	(91.5)	280	(92.1)
EU Region						
EU	49	(32.5)	46	(30.1)	95	(31.3)
Ex-EU	102	(67.5)	107	(69.9)	209	(68.8)
World Region						
North America	27	(17.9)	30	(19.6)	57	(18.8)
Europe	49	(32.5)	46	(30.1)	95	(31.3)
Japan	9	(6.0)	7	(4.6)	16	(5.3)
Rest of the World	66	(43.7)	70	(45.8)	136	(44.7)
Disease Subtype						
Classical Hodgkin Lymphoma Mixed Cellularity	23	(15.2)	17	(11.1)	40	(13.2)
Classical Hodgkin Lymphoma Nodular Sclerosis	119	(78.8)	127	(83.0)	246	(80.9)
Classical Hodgkin Lymphoma Lymphocyte Depleted	3	(2.0)	3	(2.0)	6	(2.0)
Classical Hodgkin Lymphoma Lymphocyte Rich	1	(0.7)	1	(0.7)	2	(0.7)
Missing	5	(3.3)	5	(3.3)	10	(3.3)
ECOG Performance Status						
0	86	(57.0)	100	(65.4)	186	(61.2)
1	64	(42.4)	53	(34.6)	117	(38.5)
2	1	(0.7)	0	(0.0)	1	(0.3)
Stratification: Prior Auto-SCT Status						
Yes	56	(37.1)	56	(36.6)	112	(36.8)
No	95	(62.9)	97	(63.4)	192	(63.2)
Stratification: Disease Status After Frontline Therapy						
Primary Refractory	61	(40.4)	62	(40.5)	123	(40.5)
Relapsed < 12 Months	42	(27.8)	42	(27.5)	84	(27.6)
Relapsed >= 12 Months	48	(31.8)	49	(32.0)	97	(31.9)
Refractory or Relapsed After Any Line of Prior Therapy						
Yes	149	(98.7)	153	(100.0)	302	(99.3)
No	2	(1.3)	0	(0.0)	2	(0.7)
Response to First Regimen Before Study Treatment						

Refractory	47	(31.1)	40	(26.1)	87	(28.6)
Relapse	97	(64.2)	102	(66.7)	199	(65.5)
Other	7	(4.6)	11	(7.2)	18	(5.9)
Response to Last Regimen Before Study Treatment						
Refractory	65	(43.0)	64	(41.8)	129	(42.4)
Untreated Relapse	50	(33.1)	61	(39.9)	111	(36.5)
Other	36	(23.8)	28	(18.3)	64	(21.1)
Number of Prior Lines of Therapy						
Subjects with data	151		153		304	
Mean	2.7		2.8		2.8	
SD	1.5		1.6		1.6	
Median	2.0		3.0		2.0	
Range	1 to 10		1 to 11		1 to 11	
Number of Prior Regimens						
Subjects with data	151		153		304	
Mean	2.8		2.9		2.8	
SD	1.5		1.6		1.6	
Median	2.0		3.0		3.0	
Range	1 to 10		1 to 11		1 to 11	
PD-L1 Status						
>=1%	142	(94.0)	133	(86.9)	275	(90.5)
<1%	0	(0.0)	3	(2.0)	3	(1.0)
Missing	9	(6.0)	17	(11.1)	26	(8.6)
Prior Use of Brentuximab Vedotin						
Y	5	(3.3)	10	(6.5)	15	(4.9)
N	146	(96.7)	143	(93.5)	289	(95.1)
Prior Radiation						
Yes	58	(38.4)	61	(39.9)	119	(39.1)
No	93	(61.6)	92	(60.1)	185	(60.9)
Bulky Disease						
Yes	35	(23.2)	25	(16.3)	60	(19.7)
No	116	(76.8)	128	(83.7)	244	(80.3)
Baseline B Symptoms						
Yes	43	(28.5)	36	(23.5)	79	(26.0)
No	108	(71.5)	116	(75.8)	224	(73.7)
Missing	0	(0.0)	1	(0.7)	1	(0.3)
Baseline Bone Marrow Involvement						
Yes	12	(7.9)	5	(3.3)	17	(5.6)
No	139	(92.1)	148	(96.7)	287	(94.4)
Database Cutoff Date: 16JAN2020						

In KEYNOTE-204, a total of 55 participants received 1 prior line of therapy and all were considered ineligible for auto-SCT at the time of enrolment

Table 23 Summary of reasons for transplant ineligibility at baseline (subjects with one prior therapy)-ITT

	MK-3475 200 mg (N=27)	Brentuximab Vedotin (N=28)	Total (N=55)
Chemorefractory and did not receive prior SCT	11 (40.7)	10 (35.7)	21 (38.2)
Not Chemorefractory* and did not receive prior SCT	16 (59.3)	18 (64.3)	34 (61.8)
*Reasons for transplant ineligibility include age and comorbidities. Database Cutoff Date: 16JAN2020			

The majority of participants (61.8%) receiving study treatment in second line were ineligible for auto-SCT due to age and/or comorbidities and a proportion of the participants (21.8%) were refractory to the primary therapy.

Table 24 Baseline characteristics of the participants with one prior line of therapy in the pembrolizumab and BV treatment arms (ITT).

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		28		55	
Gender						
Male	17	(63.0)	17	(60.7)	34	(61.8)
Female	10	(37.0)	11	(39.3)	21	(38.2)
Age (Years)						
< 65	15	(55.6)	18	(64.3)	33	(60.0)
>= 65	12	(44.4)	10	(35.7)	22	(40.0)
Mean	53.1		51.5		52.3	
SD	21.5		17.9		19.6	
Median	47.0		50.0		49.0	
Range	22 to 84		22 to 81		22 to 84	
Race						
Asian	5	(18.5)	3	(10.7)	8	(14.5)
Black Or African American	0	(0.0)	3	(10.7)	3	(5.5)
Multiple	1	(3.7)	0	(0.0)	1	(1.8)
White Asian	1	(3.7)	0	(0.0)	1	(1.8)
White	18	(66.7)	18	(64.3)	36	(65.5)
Missing	3	(11.1)	4	(14.3)	7	(12.7)
Race by Ethnicity						
Not Hispanic Or Latino	24	(88.9)	22	(78.6)	46	(83.6)
Asian	5	(18.5)	3	(10.7)	8	(14.5)
Black Or African American	0	(0.0)	2	(7.1)	2	(3.6)
Multiple	1	(3.7)	0	(0.0)	1	(1.8)
White	18	(66.7)	17	(60.7)	35	(63.6)
Not Reported	0	(0.0)	4	(14.3)	4	(7.3)
Black Or African American	0	(0.0)	1	(3.6)	1	(1.8)
White	0	(0.0)	1	(3.6)	1	(1.8)
Missing	0	(0.0)	2	(7.1)	2	(3.6)
Unknown	2	(7.4)	2	(7.1)	4	(7.3)
Missing	2	(7.4)	2	(7.1)	4	(7.3)
Missing	1	(3.7)	0	(0.0)	1	(1.8)

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Race Group						
White	18	(66.7)	18	(64.3)	36	(65.5)
All Others	6	(22.2)	6	(21.4)	12	(21.8)
Missing	3	(11.1)	4	(14.3)	7	(12.7)
Age Group (Years)						
< 65	15	(55.6)	18	(64.3)	33	(60.0)
>= 65 to < 75	6	(22.2)	9	(32.1)	15	(27.3)
>= 75 to < 85	6	(22.2)	1	(3.6)	7	(12.7)
US Region						
US	0	(0.0)	4	(14.3)	4	(7.3)
Ex-US	27	(100.0)	24	(85.7)	51	(92.7)
EU Region						
EU	9	(33.3)	11	(39.3)	20	(36.4)
Ex-EU	18	(66.7)	17	(60.7)	35	(63.6)
World Region						
North America	4	(14.8)	5	(17.9)	9	(16.4)
Europe	9	(33.3)	11	(39.3)	20	(36.4)
Japan	3	(11.1)	2	(7.1)	5	(9.1)
Rest of the World	11	(40.7)	10	(35.7)	21	(38.2)
Disease Subtype						
Classical Hodgkin Lymphoma Mixed Cellularity	3	(11.1)	3	(10.7)	6	(10.9)
Classical Hodgkin Lymphoma Nodular Sclerosis	22	(81.5)	23	(82.1)	45	(81.8)
Classical Hodgkin Lymphoma Lymphocyte Rich	1	(3.7)	0	(0.0)	1	(1.8)
Missing	1	(3.7)	2	(7.1)	3	(5.5)
ECOG Performance Status						
0	18	(66.7)	23	(82.1)	41	(74.5)
1	9	(33.3)	5	(17.9)	14	(25.5)

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Stratification: Prior Auto-SCT Status						
No	27	(100.0)	28	(100.0)	55	(100.0)
Stratification: Disease Status After Frontline Therapy						
Primary Refractory	11	(40.7)	7	(25.0)	18	(32.7)
Relapsed < 12 Months	10	(37.0)	8	(28.6)	18	(32.7)
Relapsed >= 12 Months	6	(22.2)	13	(46.4)	19	(34.5)
Refractory or Relapsed After Any Line of Prior Therapy						
Yes	26	(96.3)	28	(100.0)	54	(98.2)
No	1	(3.7)	0	(0.0)	1	(1.8)
Response to First Regimen Before Study Treatment						
Refractory	7	(25.9)	5	(17.9)	12	(21.8)
Relapse	19	(70.4)	22	(78.6)	41	(74.5)
Other	1	(3.7)	1	(3.6)	2	(3.6)
Response to Last Regimen Before Study Treatment						
Refractory	7	(25.9)	5	(17.9)	12	(21.8)
Untreated Relapse	20	(74.1)	23	(82.1)	43	(78.2)
Number of Prior Lines of Therapy						
Subjects with data	27		28		55	
Mean	1.0		1.0		1.0	
SD	0.0		0.0		0.0	
Median	1.0		1.0		1.0	
Range	1 to 1		1 to 1		1 to 1	
Number of Prior Regimens						
Subjects with data	27		28		55	
Mean	1.1		1.0		1.1	
SD	0.3		0.2		0.2	
Median	1.0		1.0		1.0	
Range	1 to 2		1 to 2		1 to 2	
PD-L1 Status						
>=1%	25	(92.6)	24	(85.7)	49	(89.1)
Missing	2	(7.4)	4	(14.3)	6	(10.9)
Prior Use of Brentuximab Vedotin						
N	27	(100.0)	28	(100.0)	55	(100.0)
Prior Radiation						
Yes	3	(11.1)	5	(17.9)	8	(14.5)
No	24	(88.9)	23	(82.1)	47	(85.5)
Bulky Disease						
Yes	6	(22.2)	2	(7.1)	8	(14.5)
No	21	(77.8)	26	(92.9)	47	(85.5)
Baseline B Symptoms						
Yes	5	(18.5)	4	(14.3)	9	(16.4)
No	22	(81.5)	23	(82.1)	45	(81.8)
Missing	0	(0.0)	1	(3.6)	1	(1.8)
Baseline Bone Marrow Involvement						
Yes	4	(14.8)	2	(7.1)	6	(10.9)
No	23	(85.2)	26	(92.9)	49	(89.1)
Database Cutoff Date: 16JAN2020						

Source: [P204V01MK3475: adam-adsl]

A total of 249 participants received 2 or more prior lines of therapy;

Table 25 Baseline characteristics for participants who received 2 or more lines of therapy in the pembrolizumab and BV treatment arms

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	124		125		249	
Gender						
Male	67	(54.0)	73	(58.4)	140	(56.2)
Female	57	(46.0)	52	(41.6)	109	(43.8)
Age (Years)						
< 65	109	(87.9)	113	(90.4)	222	(89.2)
≥ 65	15	(12.1)	12	(9.6)	27	(10.8)
Mean	39.5		38.4		38.9	
SD	15.6		16.1		15.8	
Median	34.5		34.0		34.0	
Range	18 to 79		18 to 83		18 to 83	
Race						
American Indian Or Alaska Native	1	(0.8)	0	(0.0)	1	(0.4)
Asian	8	(6.5)	10	(8.0)	18	(7.2)
Black Or African American	4	(3.2)	5	(4.0)	9	(3.6)
Multiple	3	(2.4)	5	(4.0)	8	(3.2)
Black Or African American White	3	(2.4)	5	(4.0)	8	(3.2)
Native Hawaiian Or Other Pacific Islander	1	(0.8)	0	(0.0)	1	(0.4)
White	101	(81.5)	97	(77.6)	198	(79.5)
Missing	6	(4.8)	8	(6.4)	14	(5.6)
Race by Ethnicity						
Hispanic Or Latino	24	(19.4)	20	(16.0)	44	(17.7)
American Indian Or Alaska Native	1	(0.8)	0	(0.0)	1	(0.4)
Black Or African American	1	(0.8)	2	(1.6)	3	(1.2)
Multiple	3	(2.4)	4	(3.2)	7	(2.8)
White	19	(15.3)	14	(11.2)	33	(13.3)
Not Hispanic Or Latino	87	(70.2)	93	(74.4)	180	(72.3)
Asian	8	(6.5)	10	(8.0)	18	(7.2)
Black Or African American	2	(1.6)	3	(2.4)	5	(2.0)
Multiple	0	(0.0)	1	(0.8)	1	(0.4)
Native Hawaiian Or Other Pacific Islander	1	(0.8)	0	(0.0)	1	(0.4)

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
White	76	(61.3)	79	(63.2)	155	(62.2)
Not Reported	8	(6.5)	6	(4.8)	14	(5.6)
White	4	(3.2)	3	(2.4)	7	(2.8)
Missing	4	(3.2)	3	(2.4)	7	(2.8)
Unknown	4	(3.2)	3	(2.4)	7	(2.8)
Black Or African American	1	(0.8)	0	(0.0)	1	(0.4)
White	2	(1.6)	1	(0.8)	3	(1.2)
Missing	1	(0.8)	2	(1.6)	3	(1.2)
Missing	1	(0.8)	3	(2.4)	4	(1.6)
Race Group						
White	101	(81.5)	97	(77.6)	198	(79.5)
All Others	17	(13.7)	20	(16.0)	37	(14.9)
Missing	6	(4.8)	8	(6.4)	14	(5.6)
Age Group (Years)						
< 65	109	(87.9)	113	(90.4)	222	(89.2)
≥ 65 to < 75	12	(9.7)	7	(5.6)	19	(7.6)
≥ 75 to < 85	3	(2.4)	5	(4.0)	8	(3.2)
US Region						
US	11	(8.9)	9	(7.2)	20	(8.0)
Ex-US	113	(91.1)	116	(92.8)	229	(92.0)
EU Region						
EU	40	(32.3)	35	(28.0)	75	(30.1)
Ex-EU	84	(67.7)	90	(72.0)	174	(69.9)
World Region						
North America	23	(18.5)	25	(20.0)	48	(19.3)
Europe	40	(32.3)	35	(28.0)	75	(30.1)
Japan	6	(4.8)	5	(4.0)	11	(4.4)
Rest of the World	55	(44.4)	60	(48.0)	115	(46.2)
Disease Subtype						
Classical Hodgkin Lymphoma Mixed Cellularity	20	(16.1)	14	(11.2)	34	(13.7)

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Classical Hodgkin Lymphoma Nodular Sclerosis	97	(78.2)	104	(83.2)	201	(80.7)
Classical Hodgkin Lymphoma Lymphocyte Depleted	3	(2.4)	3	(2.4)	6	(2.4)
Classical Hodgkin Lymphoma Lymphocyte Rich	0	(0.0)	1	(0.8)	1	(0.4)
Missing	4	(3.2)	3	(2.4)	7	(2.8)
ECOG Performance Status						
0	68	(54.8)	77	(61.6)	145	(58.2)
1	55	(44.4)	48	(38.4)	103	(41.4)
2	1	(0.8)	0	(0.0)	1	(0.4)
Stratification: Prior Auto-SCT Status						
Yes	56	(45.2)	56	(44.8)	112	(45.0)
No	68	(54.8)	69	(55.2)	137	(55.0)
Stratification: Disease Status After Frontline Therapy						
Primary Refractory	50	(40.3)	55	(44.0)	105	(42.2)
Relapsed < 12 Months	32	(25.8)	34	(27.2)	66	(26.5)
Relapsed ≥ 12 Months	42	(33.9)	36	(28.8)	78	(31.3)
Refractory or Relapsed After Any Line of Prior Therapy						
Yes	123	(99.2)	125	(100.0)	248	(99.6)
No	1	(0.8)	0	(0.0)	1	(0.4)
Response to First Regimen Before Study Treatment						
Refractory	40	(32.3)	35	(28.0)	75	(30.1)
Relapse	78	(62.9)	80	(64.0)	158	(63.5)
Other	6	(4.8)	10	(8.0)	16	(6.4)
Response to Last Regimen Before Study Treatment						
Refractory	58	(46.8)	59	(47.2)	117	(47.0)
Untreated Relapse	30	(24.2)	38	(30.4)	68	(27.3)
Other	36	(29.0)	28	(22.4)	64	(25.7)
Number of Prior Lines of Therapy						

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Subjects with data	124		125		249	
Mean	3.1		3.2		3.1	
SD	1.4		1.5		1.5	
Median	3.0		3.0		3.0	
Range	2 to 10		2 to 11		2 to 11	
Number of Prior Regimens						
Subjects with data	124		125		249	
Mean	3.1		3.3		3.2	
SD	1.4		1.5		1.5	
Median	3.0		3.0		3.0	
Range	2 to 10		2 to 11		2 to 11	
PD-L1 Status						
≥1%	117	(94.4)	109	(87.2)	226	(90.8)
<1%	0	(0.0)	3	(2.4)	3	(1.2)
Missing	7	(5.6)	13	(10.4)	20	(8.0)
Prior Use of Brentuximab Vedotin						
Y	5	(4.0)	10	(8.0)	15	(6.0)
N	119	(96.0)	115	(92.0)	234	(94.0)
Prior Radiation						
Yes	55	(44.4)	56	(44.8)	111	(44.6)
No	69	(55.6)	69	(55.2)	138	(55.4)
Bulky Disease						
Yes	29	(23.4)	23	(18.4)	52	(20.9)
No	95	(76.6)	102	(81.6)	197	(79.1)
Baseline B Symptoms						
Yes	38	(30.6)	32	(25.6)	70	(28.1)
No	86	(69.4)	93	(74.4)	179	(71.9)
Baseline Bone Marrow Involvement						
Yes	8	(6.5)	3	(2.4)	11	(4.4)

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
No	116	(93.5)	122	(97.6)	238	(95.6)
Database Cutoff Date: 16JAN2020						

Source: [P204V01MK3475: adam-adsl]

Numbers analysed

A total of 304 participants were included in the ITT population, 151 in the pembrolizumab arm and 153 in the BV arm. Safety analyses were based on the ASaT population, which included all 300 randomized participants who received at least one dose of study treatment. A total of 148 received pembrolizumab and 152 received BV.

Outcomes and estimation

At the data cut-off date, the median duration of follow-up was 24.9 (range: 1.8 to 42.0) and 24.3 (range: 0.6 to 42.3) months in the pembrolizumab and BV arms, respectively. Data cut-off date was 16 Jan 2020.

Table 26 ***Summary of Efficacy Results for KEYNOTE-204***

	Pembrolizumab (N=151)	**Brentuximab Vedotin (N=153)**

Primary outcome: PFS (ITT analysis population)		
Median PFS, months (95% CI) [a]	13.2 (10.9, 19.4)	8.3 (5.7, 8.8)
Hazard Ratio (95% CI), p-value	0.65 (0.48, 0.88),p= 0.00271	
Secondary efficacy outcomes		
Median PFS – secondary, months (95% CI) [a] (no alpha spent at IA2)	12.6 (8.7, 19.2)	8.2 (5.6, 8.6)
Hazard Ratio (95% CI)	0.62 (95% CI: 0.46, 0.85)	
ORR % (95% CI)	65.6 (57.4, 73.1)	54.2 (46.0, 62.3)
Difference estimate (95% CI),p-value	11.3 (0.2,22.1), *p*=0.022534	
CRR % (95% CI)	24.5 (17.9, 32.2)	24.2 (17.6, 31.8)
Exploratory efficacy outcomes		
Median DOR, months (Range) [a]	20.7 (0.0+ - 33.2+)	13.8 (0.0+ - 33.9+)
Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL at Week 24, LS Mean (95% CI)	7.29 (3.94, 10.64)	-1.31 (-5.17, 2.55)
Difference in LS Mean (95% CI)	8.60 (3.89, 13.31)	

Response was assessed based on Central Assessment (BICR = Blinded Independent Central Review) per IWG response criteria [Cheson, 2007]. The 95% CIs for response rates were calculated based on the binomial exact method.

"+" indicates there is no progressive disease by the time of last disease assessment.

[a] Estimated from product-limit (Kaplan-Meier) method for censored data.

CRR=complete remission rate; DOR = duration of response; LS = least squares; NR = not reached; ORR=objective response rate; PFS=progression-free survival.

Database Cutoff Date: 16-JAN-2020.

Primary endpoints:

- **Progression-free Survival –primary (including clinical and imaging data post-SCT)**

PFS was longer in the pembrolizumab arm compared with the BV arm. The HR for PFS was 0.65 (95% CI: 0.48, 0.88): the one-sided log-rank test was p=0.00271 which crossed the pre-specified boundary for statistical significance at IA2 [≤0.0043].

An improvement in PFS was observed for participants in the pembrolizumab arm, with a median PFS of 13.2 months (95% CI: 10.9, 19.4), compared with 8.3 months (95% CI: 5.7, 8.8) for participants in the BV arm (see Table below).

Table 27 ***Analysis of PFS based on central review per IWG 2007 (primary analysis)***

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)	PFS Rate at Months 24 in % [†] (95% CI)
MK-3475 200 mg	151	81 (53.6)	1861.2	4.4	13.2 (10.9, 19.4)	53.9 (45.0, 61.9)	35.4 (26.2, 44.6)
Brentuximab Vedotin	153	88 (57.5)	1269.3	6.9	8.3 (5.7, 8.8)	35.6 (26.9, 44.4)	25.4 (17.1, 34.5)

Pairwise Comparison	Hazard Ratio[‡] (95% CI)[‡]	p-value[§]
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.65 (0.48, 0.88)	0.00271

[†] From product-limit (Kaplan-Meier) method for censored data.

[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

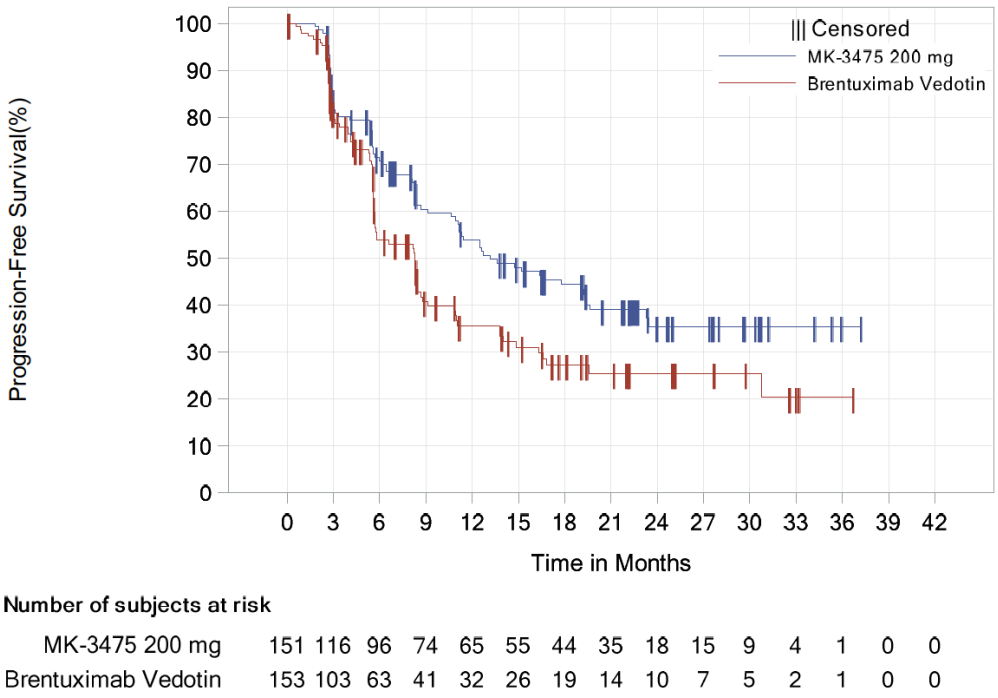
[§] One-sided p-value based on log-rank test stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

NR= Not Reached

Database Cutoff Date: 16JAN2020

The PFS rates at 12 and 24 months by KM estimation were 53.9% and 35.4%, respectively, in the pembrolizumab arm compared with 35.6% and 25.4% in the BV arm (see Figure below).

Figure 17 ***KM Estimates of PFS Based on Central Review per IWG 2007 (ITT)***



Sensitivity analyses ignoring censoring for events occurring after ≥2 missed visits (Sensitivity analysis 1) and treating discontinuation of treatment as an event (Sensitivity analysis 2) were consistent with the primary PFS

- Sensitivity analysis 1: PFS HR 0.66 (95% CI 0.49, 0.88), p-value 0.00265
- Sensitivity analysis 2: PFS HR 0.62 (95% CI 0.48, 0.82)

PFS assessed by the investigator (secondary endpoint) using IWG 2007 criteria showed a more marked PFS benefit than PFS assessed by BICR (HR 0.49, 95% CI: 0.36, 0.67, p<0.00001). Sensitivity analyses for PFS assessed by the investigator showed consistent results (Sensitivity analysis 1 by Inv. HR 0.50,

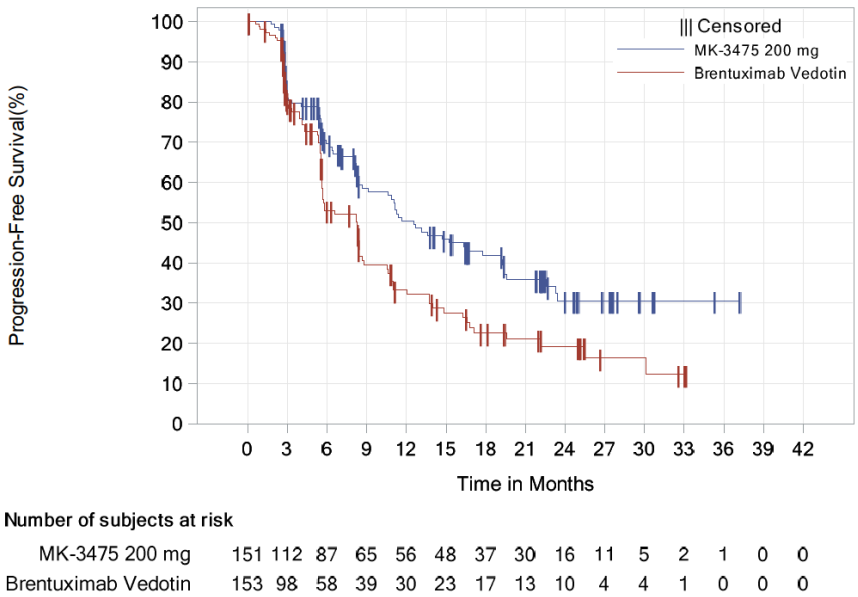
95% CI 0.37 - 0.68, p<0.00001; Sensitivity analysis 2 by Inv. HR 0.52, 95% CI 0.39 - 0.68, p<0.00001).

Secondary endpoints

- **Progression-free Survival-Secondary (excluding clinical and imaging data post-SCT)**

PFS-secondary, excluding clinical and imaging data post-ASCT, indicated a clinically improvement in the pembrolizumab arm compared with the BV arm: HR 0.62 (95% CI: 0.46, 0.85), although no alpha was spent for this endpoint. Median PFS was 12.6 months (95% CI:8.7, 19.2) in the pembrolizumab arm, compared with 8.2 months (95% CI: 5.6, 8.6) for participants in the BV arm. The PFS-secondary rates at 12 and 24 months by KM estimation were 50.4% (95% CI: 41.3, 58.9) and 30.6% (95% CI: 21.5, 40.2), respectively, in the pembrolizumab arm compared with 33.3% (95% CI: 24.6, 42.2) and 19.1% (95% CI: 11.6, 28.1) in the BV arm (see Figure below).

Figure 188 ***KM estimates of PFS based on central review per IWG 2007 (secondary analysis)***



Results of PFS-secondary assessed by investigator remained consistent with PFS-secondary based on BICR.

The HR for PFS secondary was 0.47 (95% CI: 0.35, 0.64). The PFS secondary rates at 12 and 24 months by KM estimation were 59.4% and 38.9%, respectively, in the pembrolizumab arm compared with 32.1% and 17.0% in the BV arm.

Stem Cell Transplant Pre and Post-Study Therapy

Nearly equal percentages of participants in both the pembrolizumab and BV arms underwent auto-SCT or allo-SCT following study treatment.

Table 28 ***Summary of Subsequent Stem Cell Transplant***

	MK-3475 200 mg (N=148)	Brentuximab Vedotin (N=152)
Autologous Transplant (%)	30 (20.3)	34 (22.4)
Allogeneic Transplant (%)	14 (9.5)	13 (8.6)
† The following subjects had one autologous transplant and one allogeneic transplant, and is counted in both rows: PPD		
Database Cutoff Date: 16JAN2020		

Sensitivity analyses with consideration of SCT indicate that the results are consistent with the primary analysis, regardless of baseline SCT and chemorefractory status or whether participants received SCT post study treatment.

Table 29: PFS by BCIR per IWG 2007 (Sensitivity Analyses with Consideration of SCT)

PFS Analysis	Description	HR† (95% CI)†
1	Baseline SCT and chemorefractory status‡ as a subgroup	
	Received prior SCT	0.72 (0.42, 1.23)
	Chemorefractory and did not receive prior SCT	0.65 (0.42, 1.03)
	Not chemorefractory and did not receive prior SCT	0.53 (0.26, 1.06)
2	Baseline SCT and chemorefractory status‡ as a covariate	0.65 (0.48, 0.88)
3	Post study treatment SCT* as a time-dependent covariate	0.61 (0.45, 0.83)
4	Post study treatment SCT* as a time-dependent covariate with treatment interaction	0.62 (0.45, 0.86)

SCT: stem cell transplant
HR: hazard ratio
† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
‡ Baseline SCT and chemorefractory status has three levels: received prior SCT versus chemorefractory and did not receive prior SCT versus not chemorefractory and did not receive prior SCT.
*Based on the first autologous or allogeneic stem cell transplant received after study treatment.

- Objective Response Rate (ORR) and complete response rate (CRR)

The ORR (BICR per IWG response criteria) was 65.6% (95% CI: 57.4, 73.1) for pembrolizumab and 54.2% (95% CI: 46.0, 62.3) for BV. The 11.3% (95% CI: 0.2, 22.1) difference in response rates was not statistically significant (stratified Miettinen and Nurminen's method p-value: 0.022534).

Results of ORR assessed by the investigator were consistent with ORR based on BICR. The CRR (BICR per IWG response criteria) was 24.5% (95% CI: 17.9%, 32.2%) for pembrolizumab and 24.2% (95% CI: 17.6%, 31.8%) for BV. CRR assessed by the investigator was consistent with the primary analysis of CRR.

ORR based on investigator review per IWG 2007 including responses post-PD (exploratory endpoint) demonstrated a similar ORR of 68.9% [95% CI 60.8, 76.2] in the pembrolizumab arm.

Table 29: Summary of Best Overall Response Based on Central Review per IWG 2007 (ITT)

	MK-3475 200 mg			Brentuximab Vedotin		
	n	(%)	(95% CI)[†]	n	(%)	(95% CI)[†]
Number of Subjects in Population	151			153		
Complete Response (CR)	37	(24.5)	(17.9, 32.2)	37	(24.2)	(17.6, 31.8)
Partial Response (PR)	62	(41.1)	(33.1, 49.3)	46	(30.1)	(22.9, 38.0)
Objective Response (CR+PR)	**99**	**(65.6)**	**(57.4, 73.1)**	**83**	**(54.2)**	**(46.0, 62.3)**
Stable Disease (SD)	21	(13.9)	(8.8, 20.5)	36	(23.5)	(17.1, 31.1)
Progressive Disease (PD)	26	(17.2)	(11.6, 24.2)	28	(18.3)	(12.5, 25.4)
Not Evaluable (NE)	1	(0.7)	(0.0, 3.6)	1	(0.7)	(0.0, 3.6)
No Assessment (NA)	4	(2.6)	(0.7, 6.6)	5	(3.3)	(1.1, 7.5)

[†] Based on binomial exact confidence interval method.
Excludes data after autologous SCT or allogeneic SCT.
Database Cutoff Date: 16JAN2020

Exploratory endpoints

Progression-free Survival Exploratory - per Lugano Criteria

The HR for PFS was 0.61 (95% CI: 0.45, 0.83). The median PFS was 13.8 months in the pembrolizumab arm (95% CI: 8.8, 17.9) and 8.3 months in the BV arm (95% CI: 5.7, 8.4).

Table 32 Analysis of PFS per Lugano 2014 (primary analysis) and IWG - ITT

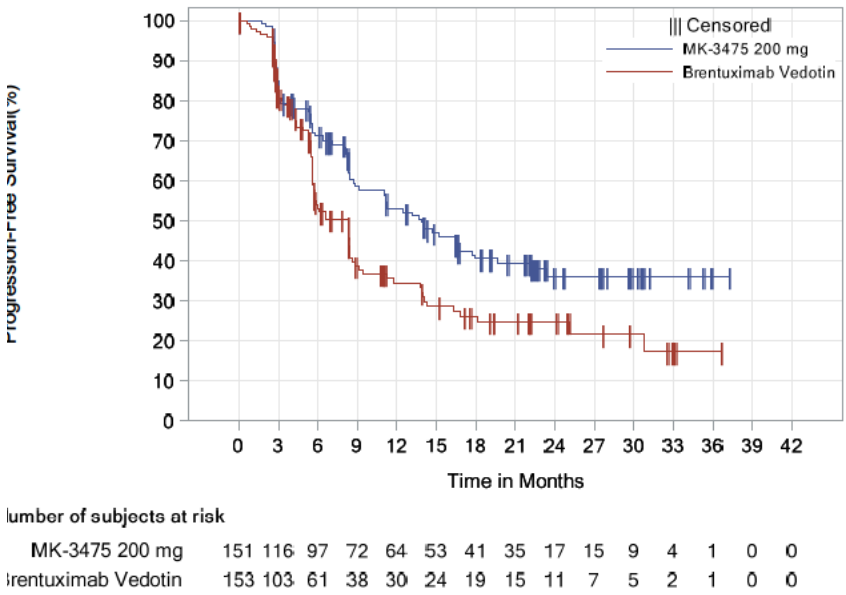
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)	PFS Rate at Months 24 in % [†] (95% CI)
MK-3475 200 mg	151	81 (53.6)	1843.6	4.4	13.8 (8.8, 17.9)	53.0 (44.1, 61.1)	36.1 (27.1, 45.2)
Brentuximab Vedotin	153	89 (58.2)	1243.5	7.2	8.3 (5.7, 8.4)	34.5 (25.8, 43.4)	24.8 (16.7, 33.7)

Pairwise Comparison	Hazard Ratio[‡] (95% CI)[‡]	p-value[§]
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.61 (0.45, 0.83)	0.00075

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
[§] One-sided p-value based on log-rank test stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
NR= Not Reached
Database Cutoff Date: 16JAN2020

The PFS rates at 12 and 24 months by KM estimation were 53.0% and 36.1%, respectively, in the pembrolizumab arm compared with 34.5% and 24.8% in the BV arm.

Figure 21 Kaplan- Meier Estimates of PFS per Lugano 2014 (primary analysis), ITT



Sensitivity analyses per Lugano, considering PD or death after ≥2 missed visits as an event (Sensitivity Analysis 1) and treating the initiation of new anticancer therapy (other than SCT) as an event for participants without PD or death (Sensitivity Analysis 2), were consistent with the primary PFS result.

Objective Response Rate per Lugano Criteria – Exploratory endpoint

Table 30 Analysis of ORR based on BICR per Lugano criteria.

Treatment	N	Number of Objective Response	Objective Response Rate (%) (95% CI)	Difference in Percentage MK-3475 200 mg vs. Brentuximab Vedotin	
				Estimate (95% CI)†	p-Value††
MK-3475 200 mg	151	110	72.8 (65.0,79.8)	5.5 (-4.7,15.7)	0.145516
Brentuximab Vedotin	153	103	67.3 (59.3,74.7)		

† Based on Miettinen & Nurminen method stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Excludes data after autologous SCT or allogeneic SCT.

Database Cutoff Date: 16JAN2020

Complete Remission Rate per Lugano Criteria

Table 31 Summary of Best Overall response per Lugano Criteria

	MK-3475 200 mg			Brentuximab Vedotin		
	n	(%)	(95% CI)[†]	n	(%)	(95% CI)[†]
Number of Subjects in Population	151			153		
Complete Response (CR)	42	(27.8)	(20.8, 35.7)	47	(30.7)	(23.5, 38.7)
Partial Response (PR)	68	(45.0)	(36.9, 53.3)	56	(36.6)	(29.0, 44.8)
Objective Response (CR+PR)	**110**	**(72.8)**	**(65.0, 79.8)**	**103**	**(67.3)**	**(59.3, 74.7)**
Stable Disease (SD)	10	(6.6)	(3.2, 11.8)	18	(11.8)	(7.1, 18.0)
Progressive Disease (PD)	27	(17.9)	(12.1, 24.9)	25	(16.3)	(10.9, 23.2)
Not Evaluable (NE)	0	(0.0)	(0.0, 2.4)	2	(1.3)	(0.2, 4.6)
No Assessment (NA)	4	(2.6)	(0.7, 6.6)	5	(3.3)	(1.1, 7.5)

Excludes data after autologous SCT or allogeneic SCT.
[†] Based on binomial exact confidence interval method.
Database Cutoff Date: 16JAN2020

- Time to response (TTR) and Duration of response (DoR)

The median time to response was 2.8 months in both treatment arms. Median DOR was longer in the pembrolizumab arm compared with BV, 20.7 months (range: 0.0+ to 33.2+ months) and 13.8 months (range: 0.0+ to 33.9+), respectively.

*Table 325****: Time to Response and DOR based on Central Review in Subjects with Response***

	MK-3475 200 mg (N=151)	Brentuximab Vedotin (N=153)
Number of subjects with response[†]	100	83
Time to Response (months)		
Mean (SD)	3.7 (3.9)	2.9 (0.6)
Median (Range)	2.8 (1.0-31.2)	2.8 (1.3-7.3)
Response Duration[‡] (months)		
Median (Range)	20.7 (0.0+ - 33.2+)	13.8 (0.0+ - 33.9+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	66 (79.9)	34 (59.6)
≥12 months	48 (62.4)	23 (50.0)
≥18 months	31 (53.7)	13 (42.8)
≥24 months	11 (47.4)	7 (42.8)

[†] Includes subjects with best overall response as complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 16JAN2020

In the pembrolizumab arm, a higher percentage of participants had extended responses for ≥12 months (62.4% for pembrolizumab, 50.0% for BV) and ≥24 months (47.4% for pembrolizumab, 42.8% for BV) by KM estimation, compared with the BV arm (see Figure below).

Figure 19 ***KM Estimates of DOR; Central Review per IWG 2007 in Subjects with Response***

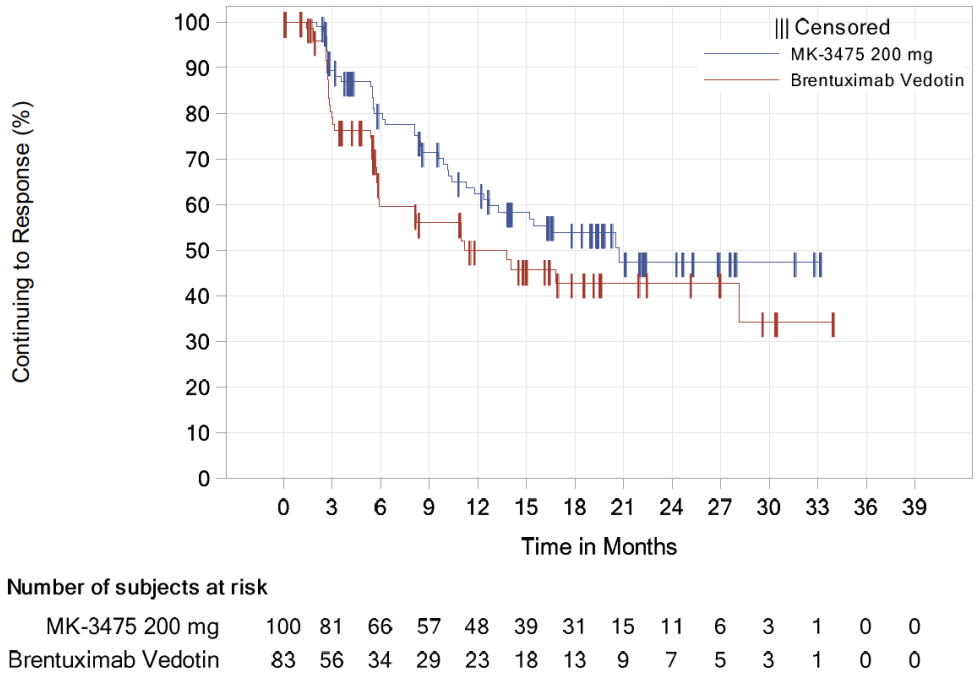


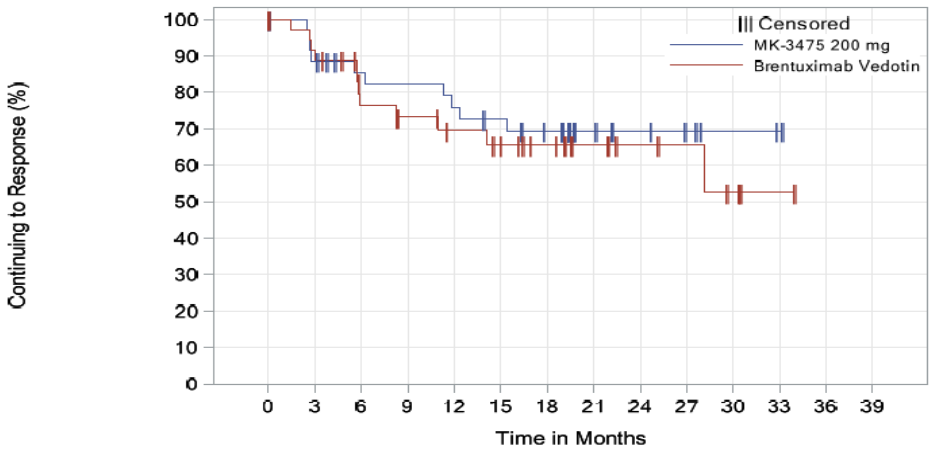
Table 331 Time to response and Duration of response for participants who achieved CR per BICR

	MK-3475 200 mg (N=151)	Brentuximab Vedotin (N=153)
Number of subjects with response[†]	37	37
Time to Response (months)		
Mean (SD)	3.1 (1.3)	2.8 (0.3)
Median (Range)	2.8 (1.0-8.4)	2.8 (1.3-3.3)
Response Duration[‡] (months)		
Median (Range)	NR (0.0+ - 33.2+)	NR (0.0+ - 33.9+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	27 (85.4)	24 (76.4)
≥12 months	24 (75.9)	18 (69.5)
≥18 months	18 (69.4)	12 (65.7)
≥24 months	6 (69.4)	6 (65.7)

[†] Includes subjects with best overall response as complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adrs; adtte]

Figure 190 Kaplan – Meier estimates of Duration of response for participants who achieved CR per BICR



Number of subjects at risk

MK-3475 200 mg	37	31	27	26	24	22	18	8	6	4	2	1	0	0
Brentuximab Vedotin	37	33	24	21	18	15	12	8	6	5	3	1	0	0

Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adrs; adtte]

Time to Response and Duration of Response per Lugano Criteria

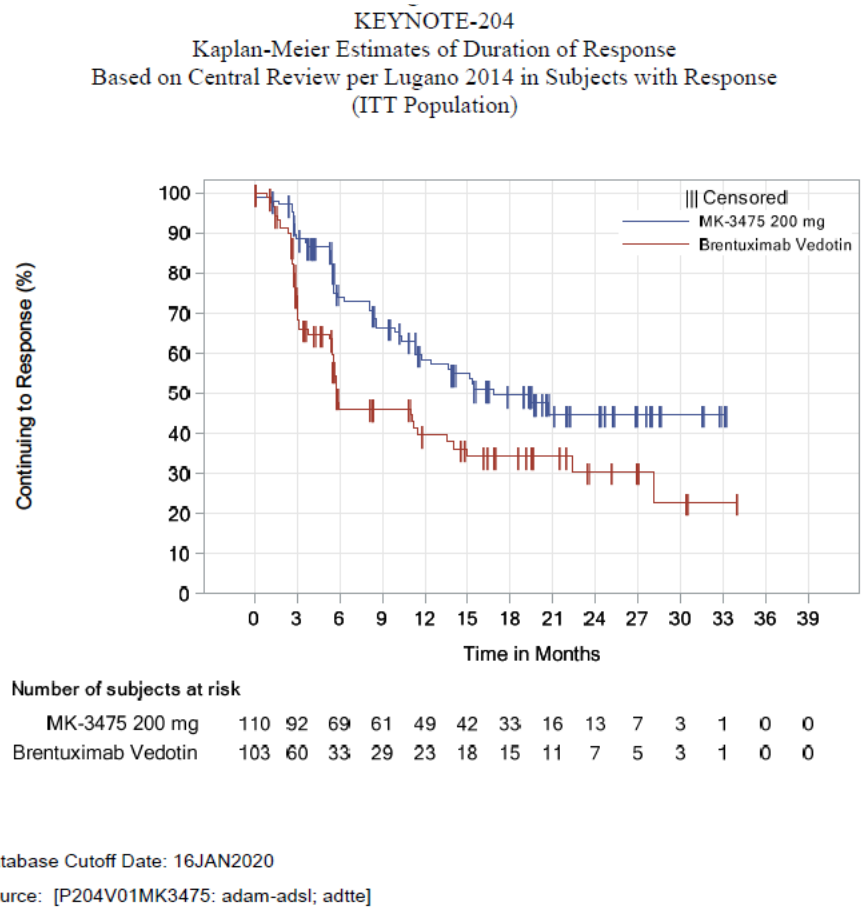
Median time to response was 2.8 months in both the pembrolizumab arm and the BV arm. Median response duration was notably longer for pembrolizumab (16.8 months; range: 0.0+ to 33.2+ months) compared with BV (5.8 months; range: 0.0+ to 33.9+ months). A larger proportion of participants in the pembrolizumab arm experienced extended response duration: 44.8% of participants in the pembrolizumab arm had response duration ≥24 months, compared with 30.5% in the BV arm.

Table 36 Summary of Time to Response and Duration of Response per Lugano Criteria

	MK-3475 200 mg (N=151)	Brentuximab Vedotin (N=153)
Number of subjects with response[†]	110	103
Time to Response (months)		
Mean (SD)	2.9 (0.6)	2.9 (0.5)
Median (Range)	2.8 (1.0-6.7)	2.8 (1.3-5.8)
Response Duration[‡] (months)		
Median (Range)	16.8 (0.0+ - 33.2+)	5.8 (0.0+ - 33.9+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	69 (74.0)	33 (46.2)
≥12 months	49 (58.5)	23 (39.6)
≥18 months	33 (49.5)	15 (34.3)
≥24 months	13 (44.8)	7 (30.5)

[†] Includes subjects with best overall response as complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 16JAN2020

Figure 20 Kaplan – Meier Estimates of Duration of response based on central review per Lugano 2014 in subjects with response



Second progression-free survival (PFS2)

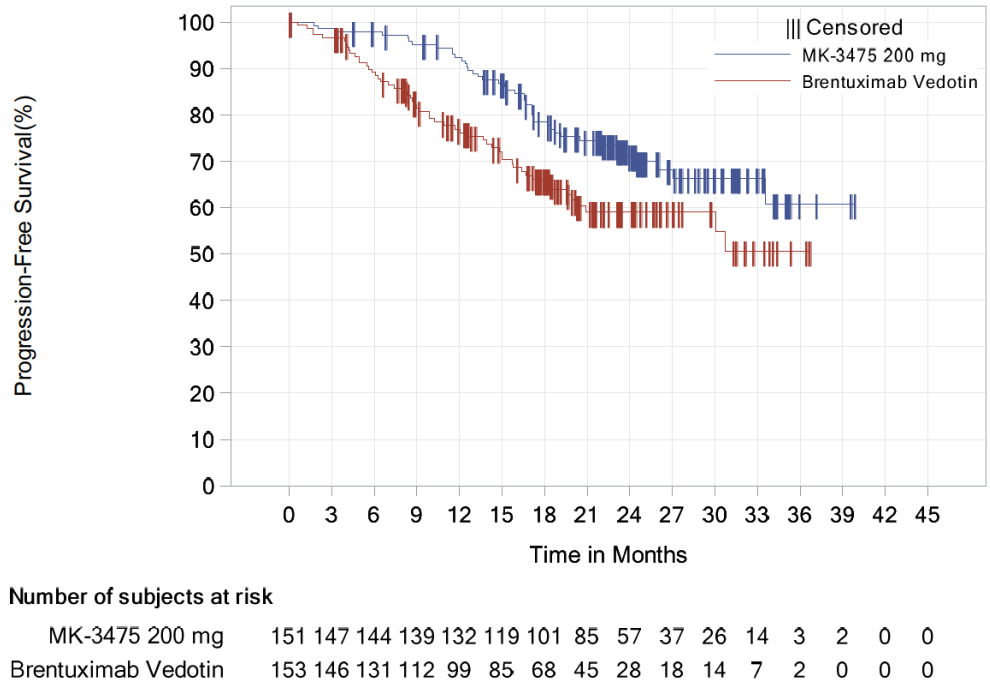
Median PFS2 was not reached in either arm (pembrolizumab 95% CI: 33.5, not reached; BV 95% CI: 20.9, not reached). The PFS2 rates at 12 and 24 months by KM estimation were 92.4% (95% CI: 86.8, 95.7) and 71.3% (95% CI: 62.6, 78.3), respectively, in the pembrolizumab arm compared with 77.0% (95% CI: 69.2, 83.1) and 59.1% (95% CI: 49.5, 67.4) in the BV arm (see Table and Figure below).

Table 37 ***Analysis of Second PFS Based on Investigator Review per IWG 2007***

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg	151	42 (27.8)	3242.5	1.3	NR (33.5, NR)	92.4 (86.8, 95.7)	71.3 (62.6, 78.3)
Brentuximab Vedotin	153	54 (35.3)	2477.7	2.2	NR (20.9, NR)	77.0 (69.2, 83.1)	59.1 (49.5, 67.4)

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡	p-value§
Primary		
MK-3475 200 mg vs. Brentuximab Vedotin	0.58 (0.38, 0.87)	0.00374

Figure 21 ***KM Estimates of Second PFS Based on Investigator Review per IWG 2007***



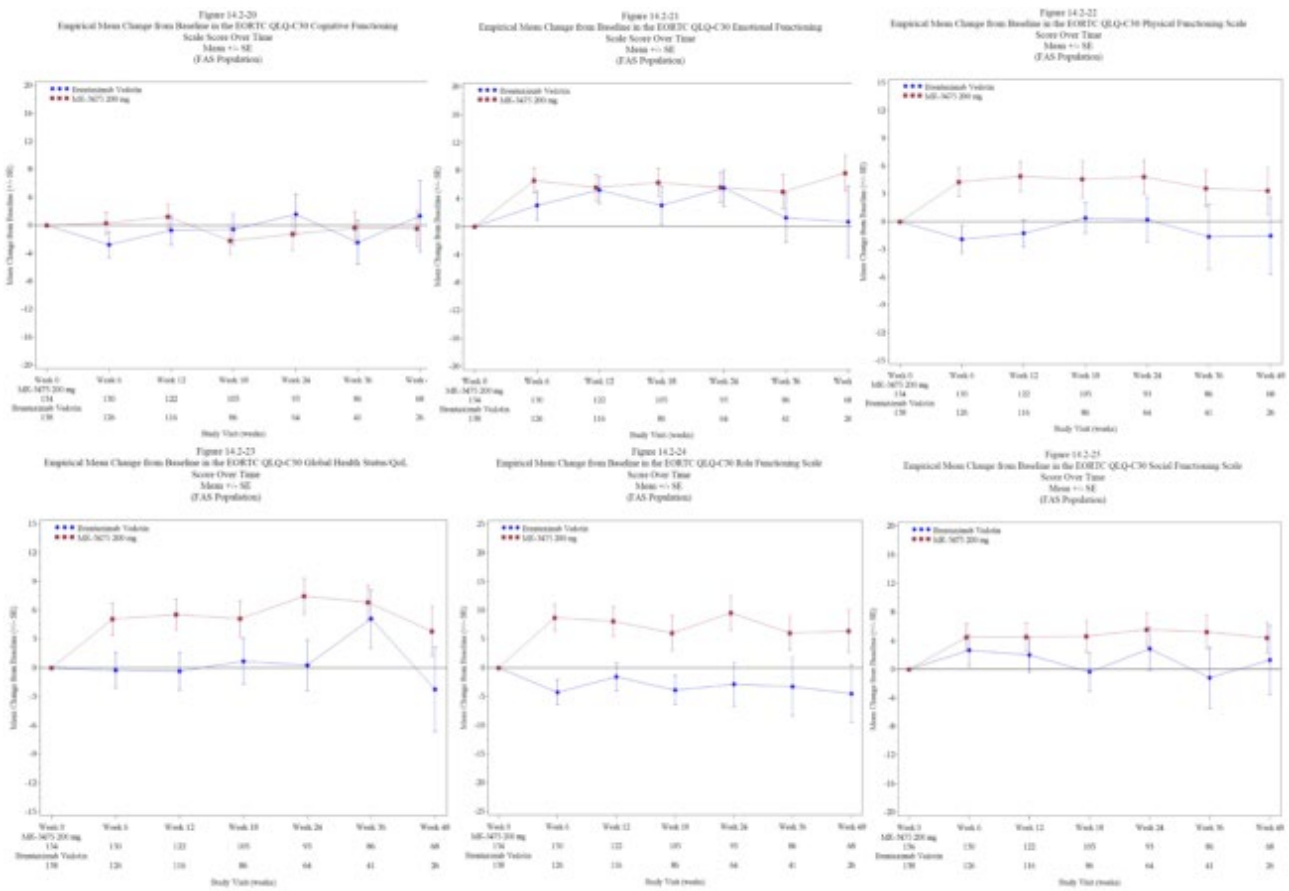
Patient Reported Outcomes (PROs)

EORTC QLQ-C30

Compliance rates for the EORTC QLQ-C30 remained high from baseline (~92%) to Week 48 (87 to 77%, per protocol). At baseline EORTC QLQ-C30 mean scores were similar across treatment arms, but by Week 24 they had improved in the pembrolizumab arm and deteriorated in the BV arm.

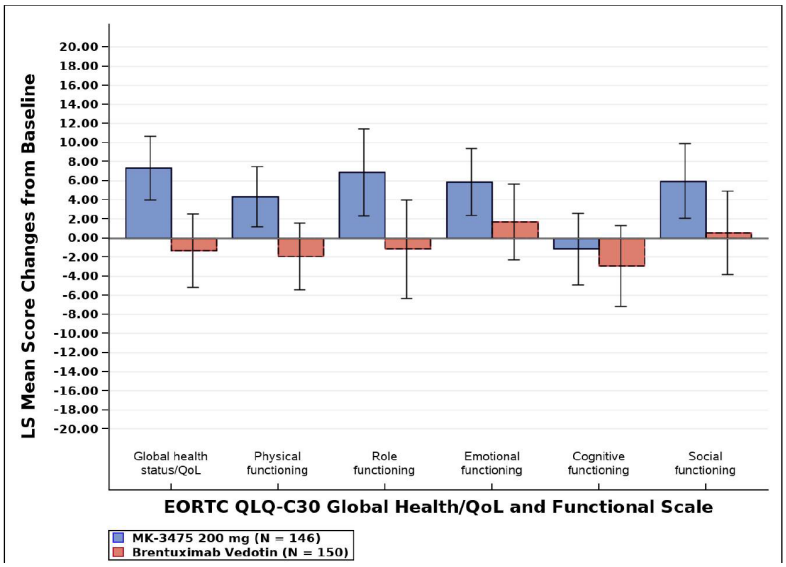
For GHS/QOL, a difference in LS means between the pembrolizumab arm and the BV arm at Week 24 was observed; the difference was 8.60 points, favouring pembrolizumab (95% CI: 3.89, 13.31; two-sided p=0.0004, not controlled for multiplicity). For physical functioning, a difference in LS means between the pembrolizumab arm and the BV arm at Week 24 was also observed; the difference was 6.24 points, favouring pembrolizumab (95% CI: 1.87, 10.62; two-sided p=0.0054, not controlled for multiplicity).

Figure 22 EORTC QLQ-C30 GHS/QOL and 5 functional scales based on mean score over time



The HR for the time to true deterioration for Pembrolizumab when compared with BV for the EORTC QLQ-C30 GHS/QOL scores was HR = 0.40; 95% CI: 0.22, 0.74; two-sided p=0.003, not controlled for multiplicity and for the physical functioning scores HR = 0.56; 95% CI: 0.32, 0.97; two-sided p=0.034, not controlled for multiplicity.

Figure 23 ***Change from Baseline for EORTC QLQ-C30 Functional Scale/Global Health Status/QoL at Week 24* LS Mean Change and 95% CI***



EQ-5D

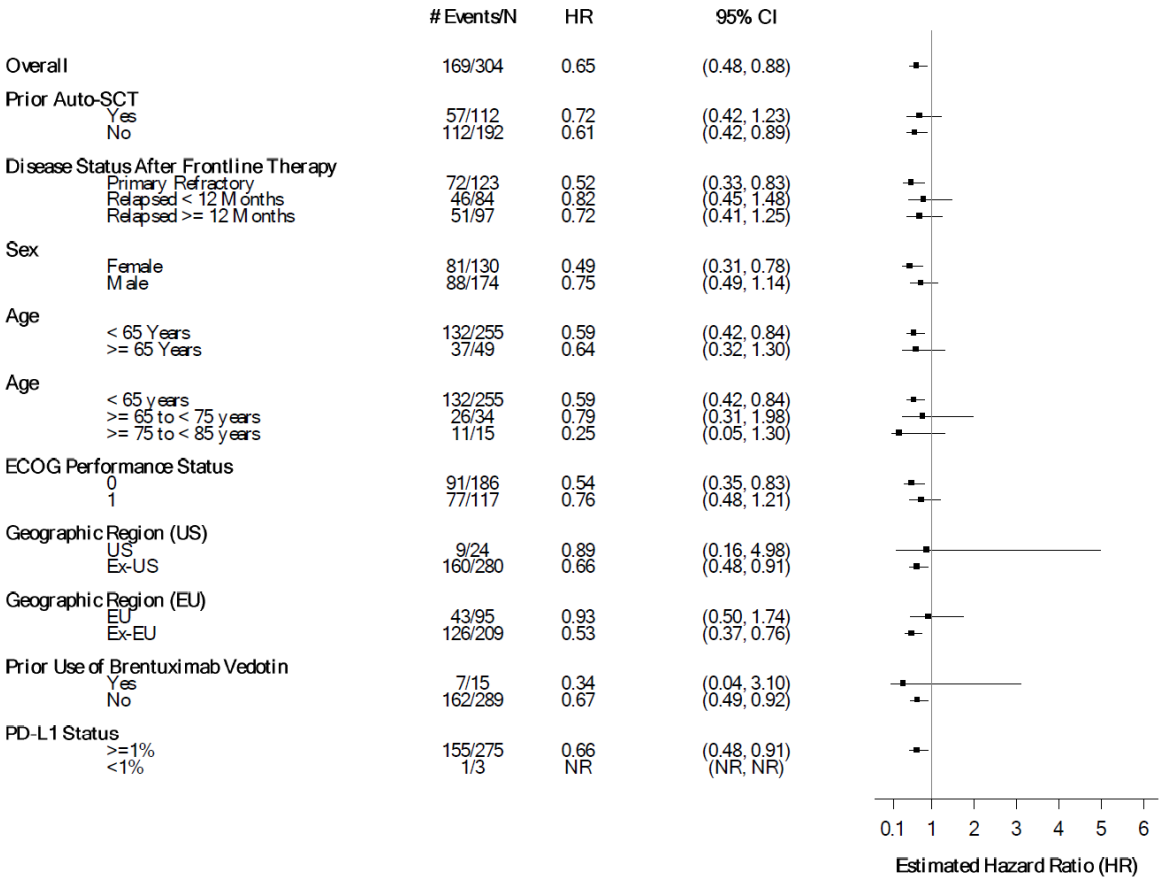
Results from EQ-5D analyses were consistent with the results of EORTC QLQ-C30 analyses. For EQ-5D utility scores, a difference in LS means between the pembrolizumab arm and the BV arm at Week 24 was observed; the difference was 0.09 points (95% CI: 0.04, 0.14; two-sided p=0.0004, not controlled for multiplicity). For EQ-5D visual analog scores, a difference in LS means between pembrolizumab and the BV arm at Week 24 was observed; the difference was 6.12 points, favouring pembrolizumab (95% CI: 1.91, 10.34; two-sided p=0.0046, not controlled for multiplicity).

Ancillary analyses

Subgroup analyses for PFS

PFS for pre-specified subgroups, including participants with and without prior ASCT, participants with primary refractory disease, and participants who are BV-naïve are consistent with the primary analysis:

Figure 24 ***Forest Plot of PFS Based on Central Review per IWG 2007 by Subgroup Factors***

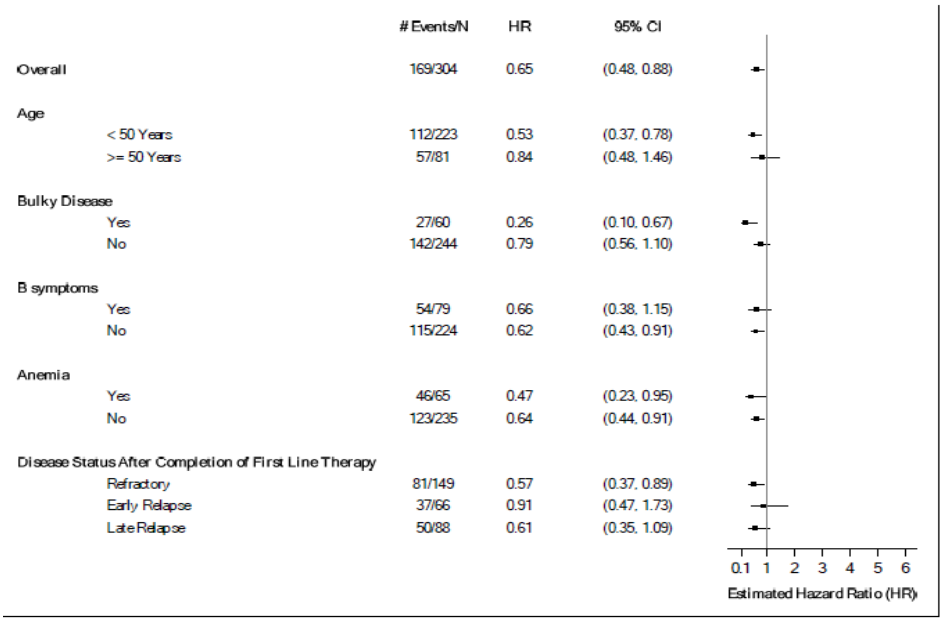


NR = Not Reached
Hazard ratio and 95% CI are based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy)
Database Cutoff Date: 16JAN2020

Post-hoc subgroup analyses stratified by prognostic factors

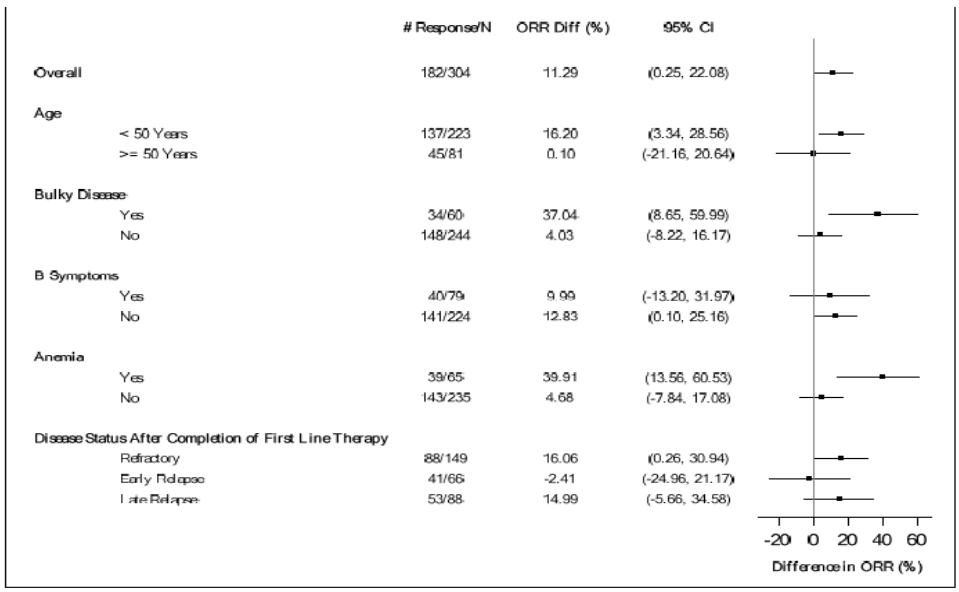
Post-hoc exploratory analyses for PFS and ORR according to recognised prognostic factors in cHL are summarised in Figures and Tables below:

Figure 25 Forest plot of PFS based on IWG 2007 by subgroup factors



R = Not Reached
azard ratio and 95% CI are based on Cox regression model with Efron's method of tie handling with treatment
: a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy
rimary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse
2 months or more after completion of frontline therapy)
atabase Cutoff Date: 16JAN2020

Figure 26 Forest plot of ORR based on IWG 2007 by subgroup factors



CI=confidence interval; IWG=International Working Group; NR=Not Reached; ORR=objective response rate; ITT=intention to treat.
Based on Miettinen & Nurminen method stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
Excludes data after autologous SCT or allogeneic SCT.
Database Cutoff Date: 16JAN2020

Table 348 Subject characteristics for select risk factors subgroups

	MK-3475 200 mg		Brentuximab Vedotin		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	151		153		304	
Age Group (Years)						
< 50	109	(72.2)	114	(74.5)	223	(73.4)
>= 50	42	(27.8)	39	(25.5)	81	(26.6)
Bulky Disease						
Yes	35	(23.2)	25	(16.3)	60	(19.7)
No	116	(76.8)	128	(83.7)	244	(80.3)
B Symptoms						
Yes	43	(28.5)	36	(23.5)	79	(26.0)
No	108	(71.5)	116	(75.8)	224	(73.7)
Missing	0	(0.0)	1	(0.7)	1	(0.3)
Anemia						
Yes	40	(26.5)	25	(16.3)	65	(21.4)
No	108	(71.5)	127	(83.0)	235	(77.3)
Missing	3	(2.0)	1	(0.7)	4	(1.3)
Disease Status After Completion of First Line Therapy						
refractory	68	(45.0)	81	(52.9)	149	(49.0)
early relapse	36	(23.8)	30	(19.6)	66	(21.7)
late relapse	46	(30.5)	42	(27.5)	88	(28.9)
Missing	1	(0.7)	0	(0.0)	1	(0.3)
Database Cutoff Date: 16JAN2020						

Source: [P204V01MK3475: adam-adsl]

These subgroup analyses are intended to provide additional context for the primary results and should be interpreted with caution as the study was not powered for a definitive demonstration of efficacy in these subgroups.

Age group

The <50 years group had better PFS and ORR results than the ≥50 years group (HR: 0.53 vs 0.84, ORR % difference: 16.20 vs 0.10).

Bulky disease

The PFS and ORR results were better in the group with bulky disease at baseline than the group without bulky disease (HR: 0.26 vs 0.79, ORR % difference: 37.04 vs 4.03).

B symptoms

The PFS and ORR results were similar between groups with and without B symptoms at baseline (HR: 0.66 vs 0.62, ORR % difference: 9.99 vs 12.83).

Anaemia

The PFS and ORR results were better in the group with anaemia at baseline than the group without anaemia (HR: 0.47 vs 0.64, ORR % difference: 39.91 vs 4.68). Baseline anaemia was defined as haemoglobin <12 g/dl (Male) or haemoglobin <10.5 g/dl (Female).

Disease status after completion of first-line therapy

In this analysis, participants with best response of PR to first-line therapy, in addition to CR, were considered as remission, and remission of less than 3 months, in addition to any response less than PR to first-line therapy, was considered as refractory. Based on this categorization, the refractory, early relapse and late relapse groups have 149, 66 and 88 participants, respectively; 1 participant with missing information was excluded. Results were as follows: refractory (PFS HR: 0.57, ORR % difference: 16.06), early relapse (PFS HR: 0.91, ORR % difference: -2.41), and late relapse (PFS HR: 0.61, ORR % difference: 14.99).

Efficacy by region (EU vs. Ex-EU subgroup)

Subgroup Analysis of PFS in EU vs. EX-EU subgroup (primary analysis)

The PFS HR for participants enrolled in the EU was 0.93 (95% CI: 0.50, 1.74), compared with 0.53 (95% CI: 0.37, 0.76) in Ex-EU participants.

Table 35 ***Analysis of PFS Based on Central Review per IWG 2007 (primary analysis) (EU)***

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg	49	24 (49.0)	577.2	4.2	16.4 (6.4, NR)	54.7 (38.7, 68.2)	40.9 (24.7, 56.5)
Brentuximab Vedotin	46	19 (41.3)	396.1	4.8	8.3 (5.6, NR)	40.3 (23.0, 57.0)	40.3 (23.0, 57.0)

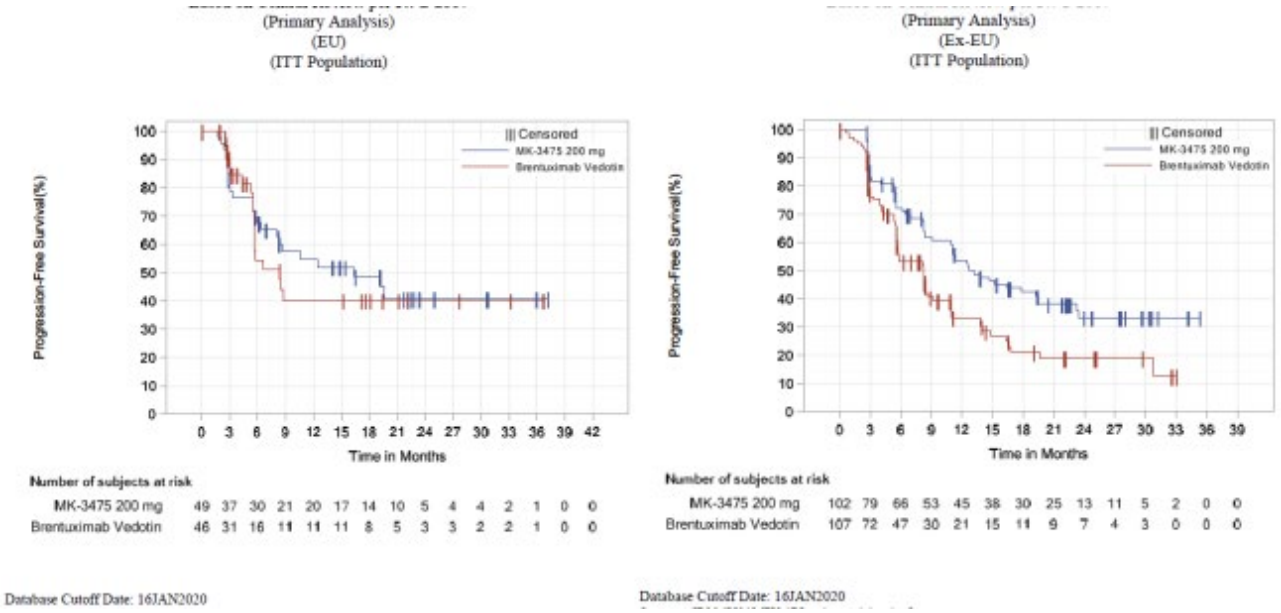
Pairwise Comparison	Hazard Ratio‡ (95% CI)‡
Primary	
MK-3475 200 mg vs. Brentuximab Vedotin	0.93 (0.50, 1.74)

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).

Database Cutoff Date: 16JAN2020

Figure 27 K-M estimates of PFS based on central review per IWG 2007 in EU vs ex-EU study sites



Most baseline characteristics in EU versus Ex-EU participants were well-balanced (data not shown). The magnitude and nature of noted differences in baseline characteristics in EU versus Ex-EU participants do not present a clear pattern to account for the higher HR in the EU population: more participants in the EU subgroup had prior use of BV (13.7% vs. 1.0%), fewer participants in the EU subgroup had baseline B symptoms (17.9% vs. 29.7%), and the median number of prior lines of therapy was lower in the EU subgroup (median 2.0 vs. 3.0, in the EU vs. EX-EU, respectively).

Subgroup Analysis of PFS-secondary in EU vs. EX-EU subgroup

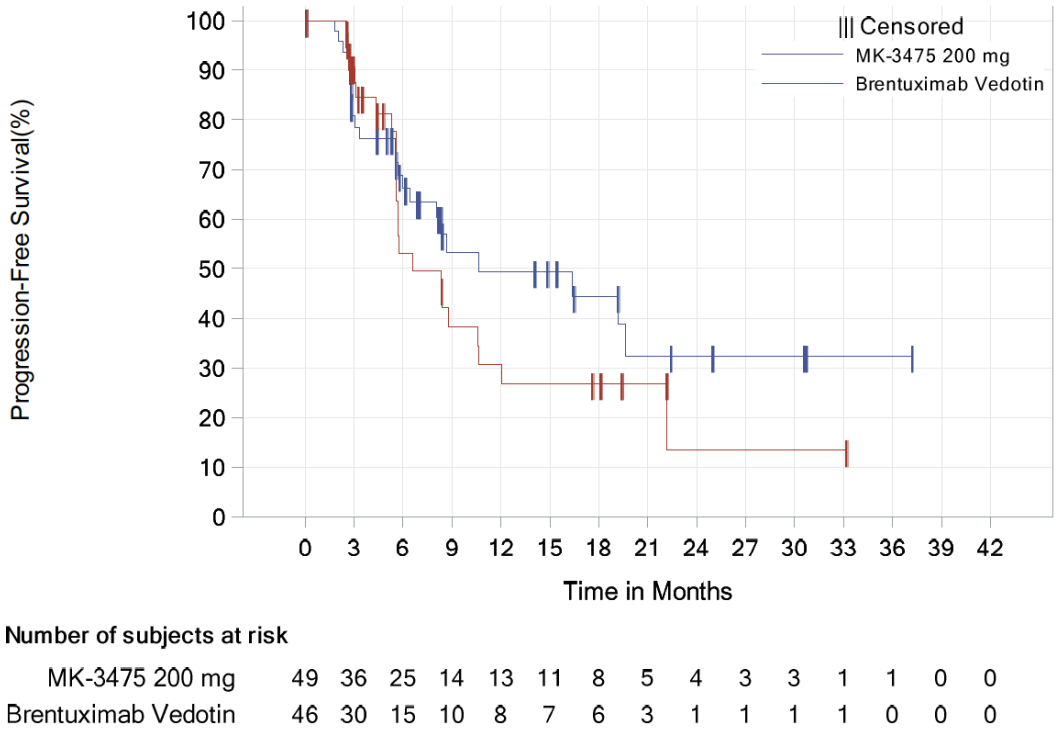
The observed HR for PFS-secondary, excluding clinical and imaging data post-SCT, favoured pembrolizumab monotherapy over BV in both EU and Ex-EU subgroups. The HR for PFS secondary was 0.75 (95% CI: 0.41, 1.39) in the EU subgroup and 0.57 (95% CI: 0.40, 0.81) in the Ex-EU subgroup.

Table 36 ***Analysis of PFS Based on Central Review per IWG 2007 (secondary analysis) (EU)***

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg	49	23 (46.9)	459.4	5.0	10.6 (6.4, NR)	49.4 (32.1, 64.6)	32.4 (14.8, 51.4)
Brentuximab Vedotin	46	23 (50.0)	336.9	6.8	6.6 (5.6, 10.6)	30.6 (15.0, 47.8)	13.4 (1.4, 38.9)

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡
Primary	
MK-3475 200 mg vs. Brentuximab Vedotin	0.75 (0.41, 1.39)

Figure 28 ***KM Estimates of PFS; Central Review per IWG 2007 (secondary analysis) (EU)***



Efficacy in transplant-ineligible patients by line of therapy

With Amendment 2, participants ineligible for auto-SCT were allowed to enrol in the study after failing just 1 prior line of treatment. It was further clarified in protocol Amendment 3 that participants who were eligible for auto SCT were excluded from enrolment. Of the 304 participants in KEYNOTE-204, 192 were ineligible for a transplant at the time of enrolment, and 112 had failed a transplant before enrolling; of the 192 ineligible participants, 55 had failed 1 prior therapy and 137 failed 2 or more prior therapies. Many treating physicians considered primary refractory disease patients as chemorefractory and rather than performing an auto-SCT that is unlikely to be of benefit, opted to enrol these participants into the study with the goal of achieving a better response and minimizing treatment-related toxicity.

In an exploratory post-hoc analysis of the 55 participants, 27 were in the pembrolizumab arm and achieved an ORR of 66.7% (95% CI: 46.0, 83.5) with a CR rate of 14.8% and 28 were in the BV arm and achieved an ORR of 53.6% (95% CI: 33.9, 72.5) with a CR rate of 35.7%. The PFS HR was 0.70 (95% CI: 0.31, 1.59); median PFS was 16.4 months (95% CI: 8.3, NR) and 8.4 months (95% CI: 5.4, NR) and PFS rates at 12 months were 58.9% (95% CI: 36.8, 75.5) and 37.4% (95% CI: 16.1, 58.9) in the pembrolizumab and BV arms, respectively (see Tables and Figure below)

Table 37 Summary of Best Overall Response Based on Central Review per IWG 2007 (subjects with one prior line of therapy)

	MK-3475 200 mg			Brentuximab Vedotin		
	n	(%)	(95% CI)[†]	n	(%)	(95% CI)[†]
Number of Subjects in Population	27			28		
Complete Response (CR)	4	(14.8)	(4.2, 33.7)	10	(35.7)	(18.6, 55.9)
Partial Response (PR)	14	(51.9)	(31.9, 71.3)	5	(17.9)	(6.1, 36.9)
Objective Response (CR+PR)	**18**	**(66.7)**	**(46.0, 83.5)**	**15**	**(53.6)**	**(33.9, 72.5)**
Stable Disease (SD)	6	(22.2)	(8.6, 42.3)	7	(25.0)	(10.7, 44.9)
Progressive Disease (PD)	3	(11.1)	(2.4, 29.2)	4	(14.3)	(4.0, 32.7)
Not Evaluable (NE)	0	(0.0)	(0.0, 12.8)	0	(0.0)	(0.0, 12.3)
No Assessment (NA)	0	(0.0)	(0.0, 12.8)	2	(7.1)	(0.9, 23.5)

[†] Based on binomial exact confidence interval method.
Excludes data after autologous SCT or allogeneic SCT.
Database Cutoff Date: 16JAN2020

Table 38 Analysis of PFS based on central review per IWG 2007

(Primary Analysis)
(Subjects With One Prior Line of Therapy)
(ITT Population)

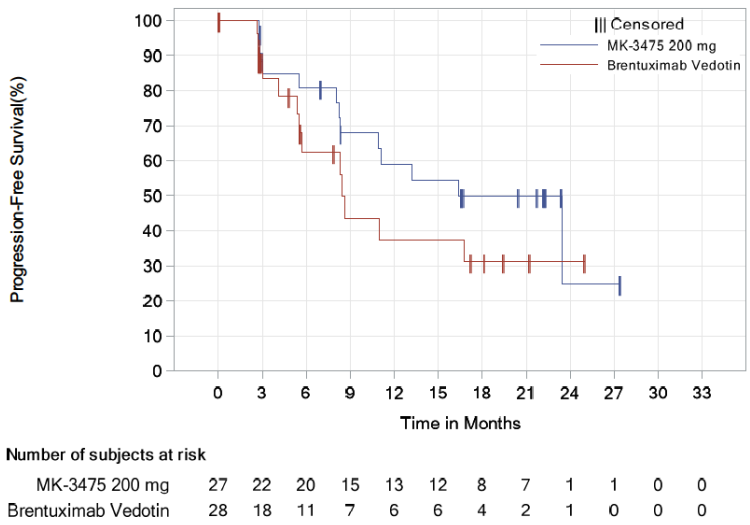
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)	PFS Rate at Months 24 in % [†] (95% CI)
MK-3475 200 mg	27	13 (48.1)	346.7	3.7	16.4 (8.3, NR)	58.9 (36.8, 75.5)	24.9 (2.0, 61.2)
Brentuximab Vedotin	28	13 (46.4)	217.9	6.0	8.4 (5.4, NR)	37.4 (16.1, 58.9)	31.2 (11.8, 53.0)

Pairwise Comparison	Hazard Ratio[‡] (95% CI)[‡]
Primary	
MK-3475 200 mg vs. Brentuximab Vedotin	0.70 (0.31, 1.59)

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
NR= Not Reached
Database Cutoff Date: 16JAN2020

Figure 29 K-M estimates of PFS based on central review per IWG 2007

(Primary Analysis)
(Subjects With One Prior Line of Therapy)
(ITT Population)



Number of subjects at risk

MK-3475 200 mg	27	22	20	15	13	12	8	7	1	1	0	0
Brentuximab Vedotin	28	18	11	7	6	6	4	2	1	0	0	0

Efficacy results in subjects with 2 or more prior lines of therapy in study KN-204 were summarised in Tables and Figure below.

Table 39 Summary of best Overall Response based on central review per IWG 2007

(Subjects With Two or More Prior Lines of Therapy)
(ITT Population)

	MK-3475 200 mg			Brentuximab Vedotin		
	n	(%)	(95% CI)[†]	n	(%)	(95% CI)[†]
Number of Subjects in Population	124			125		
Complete Response (CR)	33	(26.6)	(19.1, 35.3)	27	(21.6)	(14.7, 29.8)
Partial Response (PR)	48	(38.7)	(30.1, 47.9)	41	(32.8)	(24.7, 41.8)
Objective Response (CR+PR)	**81**	**(65.3)**	**(56.3, 73.6)**	**68**	**(54.4)**	**(45.3, 63.3)**
Stable Disease (SD)	15	(12.1)	(6.9, 19.2)	29	(23.2)	(16.1, 31.6)
Progressive Disease (PD)	23	(18.5)	(12.1, 26.5)	24	(19.2)	(12.7, 27.2)
Not Evaluable (NE)	1	(0.8)	(0.0, 4.4)	1	(0.8)	(0.0, 4.4)
No Assessment (NA)	4	(3.2)	(0.9, 8.1)	3	(2.4)	(0.5, 6.9)

[†] Based on binomial exact confidence interval method.
Excludes data after autologous SCT or allogeneic SCT.
Database Cutoff Date: 16JAN2020

Table 40 Analysis of PFS based on central review per IWG 2007

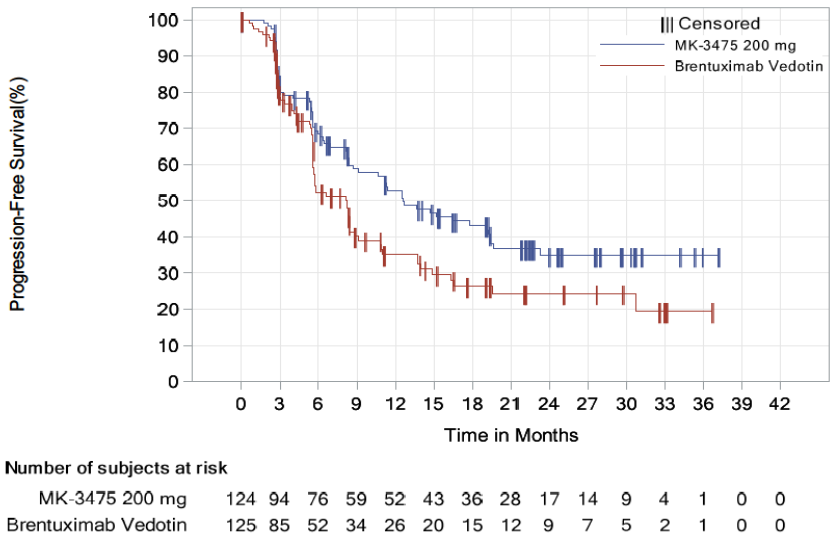
(Primary Analysis)
(Subjects With Two or More Prior Lines of Therapy)
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)	PFS Rate at Months 24 in % [†] (95% CI)
MK-3475 200 mg	124	68 (54.8)	1514.5	4.5	12.6 (8.7, 19.4)	52.8 (43.0, 61.7)	34.9 (25.2, 44.7)
Brentuximab Vedotin	125	75 (60.0)	1051.4	7.1	8.2 (5.6, 8.8)	35.3 (25.9, 44.8)	24.4 (15.6, 34.4)

Pairwise Comparison	Hazard Ratio[‡] (95% CI)[‡]
Primary	
MK-3475 200 mg vs. Brentuximab Vedotin	0.66 (0.47, 0.92)

From product-limit (Kaplan-Meier) method for censored data.
Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
NR= Not Reached
Database Cutoff Date: 16JAN2020

Figure 30 K-M estimates of PFS based on central review per IWG 2007, primary analysis, subjects with 2 or more prior lines of therapy



Of the 249 subjects with 2 or more prior lines of therapy, 137 were considered ineligible for auto-SCT at the time of enrolment [see Table below].

Table 41 Summary of reasons for transplant inegibility at baseline

(Subjects With Two or More Prior Lines of Therapy)
(ITT Population)

	MK-3475 200 mg (N=124)	Brentuximab Vedotin (N=125)	Total (N=249)
Chemorefractory and did not receive prior SCT	56 (45.2)	56 (44.8)	112 (45.0)
Not Chemorefractory* and did not receive prior SCT	12 (9.7)	13 (10.4)	25 (10.0)
*Reasons for transplant ineligibility include age and comorbidities. Database Cutoff Date: 16JAN2020			

Source: [P204V01MK3475: adam-adsl]

In an exploratory post-hoc analysis for the 137 transplant-ineligible participants with 2 or more prior lines of therapy, 68 were in the pembrolizumab arm and achieved an ORR of 61.8% (95% CI: 49.2, 73.3) with a CR rate of 26.5% and 69 were in the BV arm and achieved an ORR of 46.4% (95% CI: 34.3, 58.8) with a CR rate of 18.8% [see Table below].

Table 42 Summary of best overall response based on central review per IWG 2007

(Subjects with Two or More Prior Lines of Therapy and Not Received Prior Stem Cell Transplant)
(ITT Population)

	MK-3475 200 mg			Brentuximab Vedotin		
	n	(%)	(95% CI)†	n	(%)	(95% CI)†
Number of Subjects in Population	68			69		
Complete Response (CR)	18	(26.5)	(16.5, 38.6)	13	(18.8)	(10.4, 30.1)
Partial Response (PR)	24	(35.3)	(24.1, 47.8)	19	(27.5)	(17.5, 39.6)
Objective Response (CR+PR)	**42**	**(61.8)**	**(49.2, 73.3)**	**32**	**(46.4)**	**(34.3, 58.8)**
Stable Disease (SD)	8	(11.8)	(5.2, 21.9)	17	(24.6)	(15.1, 36.5)
Progressive Disease (PD)	15	(22.1)	(12.9, 33.8)	18	(26.1)	(16.3, 38.1)
Not Evaluable (NE)	1	(1.5)	(0.0, 7.9)	1	(1.4)	(0.0, 7.8)
No Assessment (NA)	2	(2.9)	(0.4, 10.2)	1	(1.4)	(0.0, 7.8)

† Based on binomial exact confidence interval method.
Excludes data after autologous SCT or allogeneic SCT.
Database Cutoff Date: 16JAN2020

The PFS HR was 0.62; median PFS was 11.1 months (95% CI: 7.0, 19.2) and 5.7 months (95% CI: 5.3, 8.2) in the pembrolizumab and BV arms, respectively [see Table and Figure below].

Table 43 Analysis of PFS based on central review per IWG 2007

(Primary Analysis)
(Subjects with Two or More Prior Lines of Therapy and Not Received Prior Stem Cell Transplant)
(ITT Population)

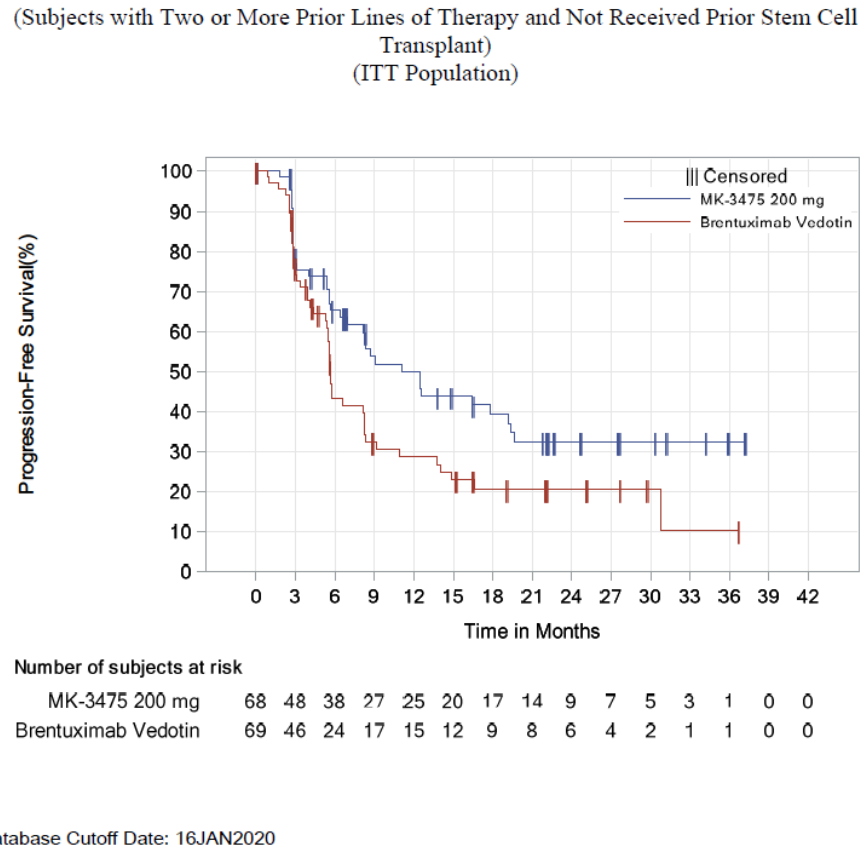
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg	68	38 (55.9)	759.9	5.0	11.1 (7.0, 19.2)	49.8 (36.3, 61.9)	32.4 (20.0, 45.3)
Brentuximab Vedotin	69	48 (69.6)	568.4	8.4	5.7 (5.3, 8.2)	28.6 (17.6, 40.6)	20.6 (11.0, 32.2)

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.62 (0.40, 0.95)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
NR= Not Reached
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adtte]

Figure 31 K-M estimates of PFS based on central review per IWG 2007



While these are unplanned analyses with limited numbers of participants in each subgroup of prior therapy, the PFS and response rates in participants who received 1 or 2 or more prior lines of therapy and in subjects who were ineligible for auto-SCT were consistent with those observed in the overall study results.

Summary of main study(ies)

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: Summary of Efficacy for trial KEYNOTE-204

Title: A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin (BV) in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (r/r cHL)		
Study identifier	P204V01MK3475	
Design	KEYNOTE-204 is an ongoing, randomized, open-label, Phase 3 study of pembrolizumab vs. BV. To be eligible, participants were to have relapsed or refractory cHL and received at least 1 prior multi-agent chemotherapy regimen. Prior treatment with BV or a BV-containing regimen was allowed, provided the participants had responded (partial or complete response) to the BV or BV-containing regimen.	
	Duration of main phase:	Up to three years 29-JUN-2016 (first patient first visit) 16-JAN-2020 (last patient, last visit)

	Duration of Run-in phase: Duration of Extension phase:		NA NA
Hypothesis	Superiority		
Treatments groups	Pembrolizumab		N=151, pembrolizumab 200 IV mg Q3W up to 35 cycles
	BV		N=153, brentuximab vedotin 1.8 mg/kg (max 180 mg) IV Q3W up to 35 cycles
Endpoints and definitions	Dual Primary endpoint	PFS primary	PFS as assessed by BICR defined as the time from randomization to the first documentation of lymphoma progression or death as a result of any cause [Cheson, 2007] and including clinical and imaging data following ASCT or allogeneic HSCT
	Dual Primary endpoint	OS	OS is defined as the time from randomization to death due to any cause.
	Secondary endpoint	ORR	ORR is defined as the proportion of the participants in the analysis population who have a complete response (CR) or partial response (PR) according to the IWG criteria.
	Secondary endpoint	CRR	CRR is defined as the proportion of subjects in the analysis population who achieved a complete remission according to the IWG criteria.
	Secondary endpoint	PFS secondary	PFS as assessed by BICR defined as the time from randomization to the first documentation of lymphoma progression or death as a result of any cause [Cheson, 2007] not including clinical and imaging data following ASCT or allogeneic HSCT
	Exploratory endpoint	DoR	DOR is defined as time from first response to disease progression or death due to any cause, whichever occurs first, in subjects who achieve a PR or better according to the IWG criteria.
	Exploratory endpoint	PFS2	PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first, by investigator assessment
Database lock	16-JAN-2020 (median survival follow-up about 25 months)		

Results and Analysis

Analysis description	**Primary Analysis** time point: **IA2**, primary PFS analysis, OS analysis only descriptive		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	BV
	Number of subjects	N=151	N=153
	mPFS Primary (months)	13.2	8.3
	(95%CI)	(10.9, 19.4)	(5.7, 8.8)
	ORR %	65.6%	54.2%
	(95%CI)	(57.4, 73.1)	(46.0, 62.3)
	CRR %	24.5%	24.2%
	95%CI	(17.9, 32.2)	(17.6, 31.8)
	mPFS Secondary (months)	12.6	8.2

	(95%CI)	(8.7, 19.2)	(5.6, 8.6)
	DoR (months)	20.7	13.8
	(range)	(0.0+, 33.2+)	(0.0+, 33.9+)
	PFS2 (months)	NR	NR
	(95%CI)	(33.5, NR)	(20.9, NR)
Effect estimate per comparison	Dual Primary endpoint PFS primary	Comparison groups	Pembrolizumab vs. BV
		HR	0.65
		95%CI	0.48, 0.88
		P-value	0.00271
	Secondary endpoint ORR	Comparison groups	Pembrolizumab vs. BV
		Difference in Percentage	11.3
		95%CI	0.2, 22.1
		P-value	0.022534
	Secondary endpoint ORR Secondary endpoint PFS secondary	Comparison groups	Pembrolizumab vs. BV
		HR	0.62
		95%CI	0.46, 0.85
		P-value	0.00110
	Secondary endpoint PFS secondary Secondary endpoint PFS2	Comparison groups	Pembrolizumab vs. BV
		HR	0.58
		95%CI	0.38, 0.87
		P-value	0.00374
Analysis description			

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

Efficacy analyses by cHL histology

Efficacy analyses by disease subtype at baseline are provided in Tables below in the HL population of studies KEYNOTE-204 (pembrolizumab arm) and KEYNOTE-087, both individually and pooled. Data on HL disease subtype were not collected in KEYNOTE-051 and therefore KEYNOTE-051 is not included in the integrated analysis.

Table 44

KEYNOTE-204
Integrated Analysis of PFS Based on BICR per IWG 2007 by Disease Subtype at Baseline

Study	Mixed Cellularity		Nodular Sclerosis		Lymphocyte Depleted		Lymphocyte Rich	
	N	PFS Median† (months) (95% CI)	N	PFS Median† (months) (95% CI)	N	PFS Median† (months) (95% CI)	N	PFS Median† (months) (95% CI)
KN-204	23	8.1 (5.4, 13.2)	119	12.7 (10.6, 22.6)	3	16.4*	1	16.4*
KN-087	24	10.9 (3.1, 22.1)	169	13.7 (11.2, 19.4)	5	8.4 (5.7, 11.1)	8	13.8 (2.5, NR)
Total	47	8.3 (5.5, 13.2)	288	13.7 (11.3, 19.3)	8	11.1 (5.7, 16.4)	9	13.8 (2.5, NR)

BICR=blinded independent central review; CI=confidence interval; IWG=international working group; KN=KEYNOTE; N=number of subjects; NR=Not Reached; PFS=progression-free survival.
† From product-limit (Kaplan-Meier) method for censored data.
Based on PFS secondary analysis of KN-204 and PFS primary analysis of KN-087.
*CIs for subgroups where N<5 were not calculated.
N: ITT population in KN-204 (pembrolizumab arm) and ASaT population in KN-087 with non-missing histology data.
Database Cutoff Dates: 16JAN2020 (KN-204), 21MAR2019 (KN-087).

Table 45

KEYNOTE-204
Integrated Analysis of ORR Based on BICR per IWG 2007 by Disease Subtype at Baseline

Study	Mixed Cellularity		Nodular Sclerosis		Lymphocyte Depleted		Lymphocyte Rich	
	N	ORR (%) (95% CI)†	N	ORR (%) (95% CI)†	N	ORR (%) (95% CI)†	N	ORR (%) (95% CI)†
KN-204	23	56.5 (34.5, 76.8)	119	67.2 (58.0, 75.6)	3	100.0*	1	100.0*
KN-087	24	62.5 (40.6, 81.2)	169	71.0 (63.5, 77.7)	5	80.0 (28.4, 99.5)	8	75.0 (34.9, 96.8)
Total	47	59.6 (44.3, 73.6)	288	69.4 (63.8, 74.7)	8	87.5 (47.3, 99.7)	9	77.8 (40.0, 97.2)

BICR=blinded independent central review; CI=confidence interval; IWG=international working group; KN=KEYNOTE; N=number of subjects; NR=Not Reached; ORR=objective response rate.
† Based on binomial exact confidence interval method.
*CIs for subgroups where N<5 were not calculated
N: ITT population in KN-204 (pembrolizumab arm) and ASaT population in KN-087 with non-missing histology data.
Database Cutoff Dates: 16JAN2020 (KN-204), 21MAR2019 (KN-087).

Four participants in KEYNOTE-087 and 5 in KEYNOTE-204 are missing disease subtype and not included in the analyses. Participants from the 2 studies were pooled without adjustments. Since a randomized study (KEYNOTE-204) is pooled with a single arm study (KEYNOTE-087), there are limits to the interpretability of time to event endpoints given potential differences in the patient populations.

Efficacy by EU vs. Ex-EU participants

Efficacy analyses of PFS and ORR are provided in Tables below in the cHL population pooled across studies KEYNOTE-204 (pembrolizumab arm), KEYNOTE-087 and KEYNOTE-051 by region (EU vs ex-EU).

The analysis common to all 3 studies was used in the integrated analysis, ie, "PFS secondary analysis" in KEYNOTE-204, which censors at last disease assessment before SCT or new anti-cancer therapy in the absence of PD, and considers PD or death after 2 or more missed assessments as an event. This was the primary PFS analysis in KEYNOTE-087 and KEYNOTE-051 and selected since both studies did not collect scans beyond SCT. Assessment by BICR per IWG 2007 was used for all 3 studies. The trend is generally

consistent across all 3 studies and in the pooled population and although the PFS median is lower in EU, the 95% CI is wide and overlaps that of the overall population and the medians observed in KEYNOTE-051 are based on small numbers compared to the other 2 studies. In the analyses, participants were pooled without adjustment for the individual study. Since a randomized study (KEYNOTE-204) is pooled with two single-arm studies (KEYNOTE-087 and KEYNOTE-051), there are limits to the interpretability of time-to-event endpoints given potential differences in the participant populations.

Table 46

KEYNOTE-204, KEYNOTE-087, and KEYNOTE-051
Integrated Analysis of PFS Based on BICR per IWG 2007 by Region

Study	All		EU		Ex-EU	
	N	PFS Median† (months) (95% CI)	N	PFS Median† (months) (95% CI)	N	PFS Median† (months) (95% CI)
KN-204	151	12.6 (8.7, 19.2)	49	10.6 (6.4, NR)	102	12.6 (8.3, 19.4)
KN-087	210	13.6 (11.1, 16.7)	108	11.3 (8.2, 16.3)	102	15.6 (11.1, 22.1)
KN-051	22	8.3 (4.0, 19.2)	7	4.0 (1.8, 19.2)	15	13.9 (4.4, 30.5)
Total	383	13.3 (11.1, 15.6)	164	11.3 (8.3, 16.3)	219	13.8 (11.1, 19.3)

† From product-limit (Kaplan-Meier) method for censored data.

Based on PFS secondary analysis of KN-204, and PFS primary analysis of KN-087 and KN-051. The "All" column corresponds to [Ref. 5.3.5.1: P204V01MK3475: Table 11-3] for KN-204, [Ref. 5.3.5.2: P087V02MK3475: Table 11-5] for KN-087, and [Table 51] for KN-051.

N: ITT population in KN-204 (pembrolizumab arm) and ASaT population in KN-087, KN-051(cHL)

Database Cutoff Dates: 16JAN2020 (KN-204), 21MAR2019 (KN-087), 10JAN2020 (KN-051)

Table 47

KEYNOTE-204, KEYNOTE-087, and KEYNOTE-051
Integrated Analysis of ORR Based on BICR per IWG 2007 by Region

Study	All		EU		Ex-EU	
	N	ORR (%) (95% CI)†	N	ORR (%) (95% CI)†	N	ORR (%) (95% CI)†
KN-204	151	65.6 (57.4, 73.1)	49	59.2 (44.2, 73.0)	102	68.6 (58.7, 77.5)
KN-087	210	71.0 (64.3, 77.0)	108	67.6 (57.9, 76.3)	102	74.5 (64.9, 82.6)
KN-051	22	54.5 (32.2, 75.6)	7	42.9 (9.9, 81.6)	15	60.0 (32.3, 83.7)
Total	383	67.9 (63.0, 72.5)	164	64.0 (56.2, 71.4)	219	70.8 (64.3, 76.7)

† Based on binomial exact confidence interval method.

N: ITT population in KN-204 (pembrolizumab arm) and ASaT population in KN-087, KN-051(cHL).

"All" column corresponds to [Ref. 5.3.5.1: P204V01MK3475: Table 11-5] for KN-204, [Ref. 5.3.5.2: P087V02MK3475: Table 11-1] for KN-087, and [Table 45] for KN-051.

Database Cutoff Dates: 16JAN2020 (KN-204), 21MAR2019 (KN-087), 10JAN2020 (KN-051)

For KEYNOTE-204, PFS Sensitivity Analysis 1 is provided by region in Tables below. This analysis considers PD or death after 2 or more missed assessments as an event and is otherwise the same as the primary analysis. The KM plots for these 2 analyses appear below. Results are generally consistent with the primary analysis by region in KEYNOTE-204.

Table 48

KEYNOTE-204
Analysis of Progression-Free Survival
Based on Central Review per IWG 2007
(Sensitivity Analysis 1)
(EU)
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg	49	24 (49.0)	577.2	4.2	16.4 (6.4, NR)	54.7 (38.7, 68.2)	40.9 (24.7, 56.5)
Brentuximab Vedotin	46	23 (50.0)	440.6	5.2	8.8 (5.7, 22.2)	40.7 (24.3, 56.4)	28.2 (10.8, 48.6)

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.87 (0.49, 1.57)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
NR= Not Reached
Database Cutoff Date: 16JAN2020

Table 49

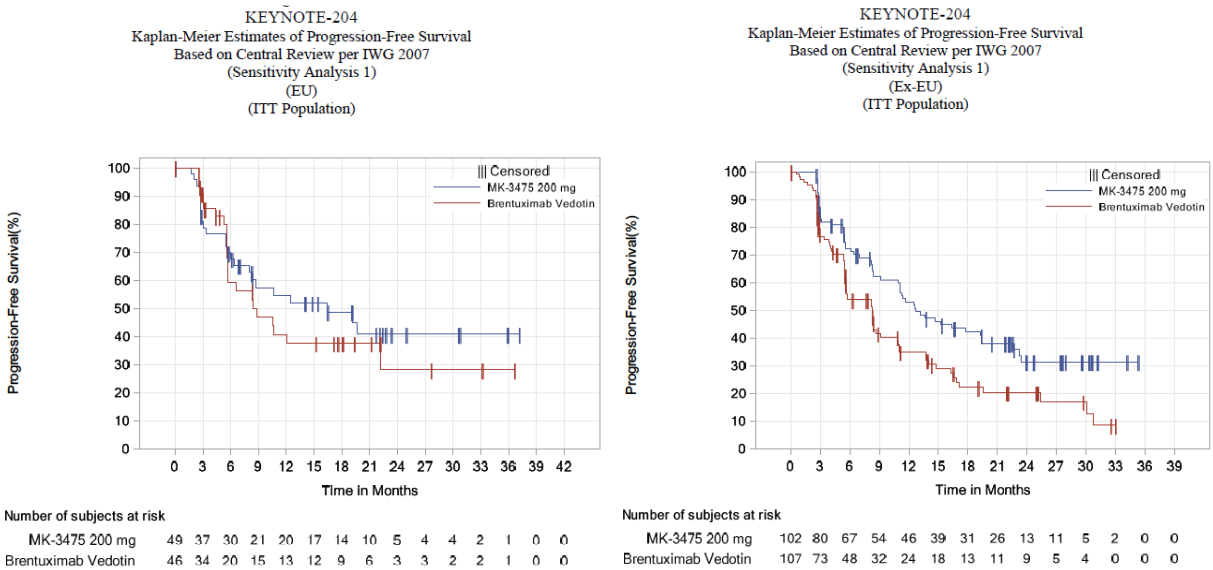
KEYNOTE-204
Analysis of Progression-Free Survival
Based on Central Review per IWG 2007
(Sensitivity Analysis 1)
(Ex-EU)
(ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)	PFS Rate at Months 24 in % † (95% CI)
MK-3475 200 mg	102	59 (57.8)	1304.1	4.5	12.7 (10.9, 19.4)	52.9 (42.2, 62.5)	31.4 (21.0, 42.4)
Brentuximab Vedotin	107	72 (67.3)	929.2	7.7	8.3 (5.6, 10.8)	34.9 (25.0, 45.0)	20.3 (11.9, 30.4)

Pairwise Comparison	Hazard Ratio‡ (95% CI)‡
Primary MK-3475 200 mg vs. Brentuximab Vedotin	0.57 (0.40, 0.81)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior auto-SCT (yes, no) and Hodgkin lymphoma status after frontline therapy (primary refractory versus relapsed less than 12 months after completion of frontline therapy versus relapse 12 months or more after completion of frontline therapy).
NR= Not Reached
Database Cutoff Date: 16JAN2020

Figure 32 K-M of PFS in EU vs ex-EU



The impact of SCT on PFS in KEYNOTE-204 is complex because a participant could have progressed prior to receiving SCT or not progressed but received anti-cancer therapy resulting in being censored prior to SCT. Furthermore, there is an analytical complication because the investigator decides whether to go to SCT whereas the primary assessment of PFS is by central review. Because the main difference between the PFS primary and secondary definition involves SCT, the MAH has looked more into their relationship and SCT.

Using the PFS secondary definition, there were 26 censored observations in the pembrolizumab arm and 23 in the BV arm in the EU subgroup of 95 participants, based on central review. Among those censored, the number receiving a subsequent SCT was similar across the 2 arms, 26 in total (14 in pembrolizumab arm, 12 in BV arm).

Looking into the possible magnitude of SCT on PFS, "additional" PFS time beyond the censoring date was considered based on the primary PFS definition, which does not censor at the time of SCT. For these 26 participants, approximately half (7 pembrolizumab, 5 BV) had additional PFS time ignoring the censoring due to SCT, slightly favoring the pembrolizumab arm. Of note, the arithmetic median "additional" PFS time was similar, 16.6 months (including 1 death) in the pembrolizumab arm compared with 18.5 months in the BV arm [Table 44]. For the remaining 14 participants, their PFS time is the same, either by the primary or secondary definition; 11 of these 14 participants had received other new anticancer therapy before receiving the SCT and were censored at the last assessment before the new anticancer therapy in both analyses.

Although the treatment effect in the EU subgroup using PFS secondary compared with PFS primary definition was stronger, it is unlikely this is explained by subsequent SCT.

Table 44
KEYNOTE-204
Additional PFS time in EU censored subjects receiving SCT

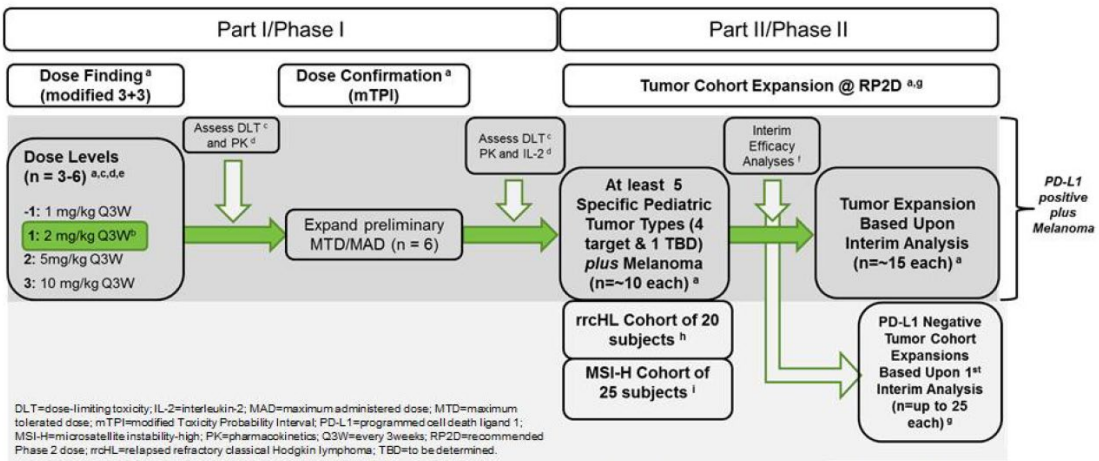
Treatment	Participant	Additional [a] PFS time after SCT
Pembrolizumab	[redacted]	33.1 months
		18.4 months
		17.4 months
		16.6 months
		14.7 months
		13.3 months
		4.4 months*
BV		33.9 months
		25.1 months
		18.5 months
		14.5 months
		11.7 months

[a] PFS primary minus PFS secondary
* death

Clinical studies in special populations (paediatrics)

Keynote (KN)-051 - A Phase I/II Study of Pembrolizumab (MK-3475) in Children With Advanced Melanoma or a PD-L1 Positive Advanced, Relapsed or Refractory Solid Tumour or Lymphoma

Figure 33 Study design



Methods

Study design and population

Study KN-051 is an ongoing, combined Phase 1 and Phase 2 (Part I and Part II), non-randomized, open-label, single-arm, multi-centre study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), toxicity, safety, and antitumor activity of pembrolizumab in in **paediatric** participants aged 6 months to <18 years of age with multiple tumour types.

Part I (dose finding and dose confirmation) has been completed. It used a modified 3+3 design (dose finding) and dose confirmation design according to a modified Toxicity Probability Interval approach. Part I also evaluated the safety, PK, PD, toxicity, and preliminary efficacy in paediatric participants with advanced melanoma or programmed cell death ligand 1-positive (PD-L1-positive) advanced, relapsed or refractory solid tumour or other lymphoma.

Part II (tumour cohort expansion at the RP2D) is ongoing. It further evaluates the safety and efficacy at the established RP2D in paediatric participants. In Part 2 participants were enrolled into one of the following tumour expansion Cohorts:

- PD-L1 positive advanced, relapsed or refractory solid tumors or other lymphoma;
- Advanced melanoma;
- rrcHL
- Advanced, relapsed or refractory MSI-H solid tumors.

Participants with melanoma, rrcHL, and MSI-H solid tumors were enrolled irrespective of PD-L1 status.

Participants with HL were initially enrolled in the Cohort of PD-L1-positive solid tumors and other lymphoma (n=15). After implementation of protocol Amendment 7, participants with HL were enrolled in the new, dedicated rrcHL Cohort (n=7).

Male and female participants aged 6 months to less than 18 years of age were eligible for this study.

Participants were required to have histologically or cytologically documented, locally advanced, or metastatic solid malignancy that was incurable and for which (a) participants failed prior standard therapy, (b) no standard therapy exists, or (c) standard therapy was not considered appropriate by the participant and treating physician. The Inclusion Criteria for the rrcHL Cohort were:

- Refractory to front-line therapy;
- High-risk and relapsed from front-line therapy; or
- Relapsed or refractory to second-line therapy.

As of protocol Amendment 08, enrolment was stopped for most solid tumours because signals of efficacy were not met in solid tumour target cohorts. However, enrolment continued for adolescent participants with melanoma (aged 12 to less than 18 years) and paediatric participants with rrcHL (aged 3 to less than 18 years) or MSI-H solid tumours (aged 6 months to less than 18 years), irrespective of PD-L1 status.

Treatments

The initial dose in Part I was pembrolizumab 2 mg/kg every 3 weeks (Q3W), the equivalent of the clinical adult dose. No dose escalation or de-escalation occurred. Therefore, Part I established 2 mg/kg Q3W as the paediatric recommended Phase 2 dose (RP2D) for Part II of the study.

Efficacy objectives and endpoints

ORR based on RECIST 1.1 per site assessment was the primary efficacy endpoint for solid tumors or lymphoma. Secondary efficacy endpoints included DOR, DCR, PFS by RECIST 1.1 and irRECIST, OS, and biomarkers.

For the dedicated rrcHL Cohort (post Amendment 7), primary efficacy endpoints was ORR per BICR assessment according to the IWG response criteria (*Note*: For the current interim analysis only results per investigator assessment were provided).

Secondary efficacy objectives were: to evaluate duration of response (DOR, defined as the time from first RECIST 1.1 response to documented progressive disease or death due to any cause, whichever occurs first, in participants who achieve a PR or better), disease control rate (DCR, defined as the proportion of participants with a response of CR, PR, or SD) and progression-free survival (PFS) by RECIST 1.1; to evaluate ORR, DOR, DCR, and PFS by irRECIST (i.e. immune-related RECIST) and overall survival (OS).

The primary efficacy objective in Part II was to evaluate antitumor activity of pembrolizumab in the rrcHL Cohort based on the ORR per blinded independent central radiology review (BICR) assessment according to the International Working Group (IWG) response criteria, based on assessments every 12 weeks. Secondary objectives in part II were to evaluate antitumor activity of pembrolizumab in the rrcHL Cohort according to the IWG response criteria based on assessments every 12 weeks by the following endpoints: ORR, DOR, and PFS per site assessment; ORR, DOR, and PFS per BICR; OS. Assessing the ORR of pembrolizumab by BICR using the Lugano Classification was an additional exploratory objective.

Disease response in paediatric participants in the PD-L1-positive solid tumours and other lymphoma cohort was retrospectively re-assessed using IWG 2007 criteria. In addition, Lugano criteria was also used for disease response re-assessment for both "PD-L1-positive solid tumors and other lymphoma" and "dedicated rrcHL" cohorts.

Sample size and statistical methods

A total of up to 310 participants was planned to be enrolled. The primary efficacy and safety population was the All Subjects as Treated population, which included all allocated participants who received ≥1 dose of pembrolizumab. ORR as assessed by the investigator was evaluated separately for each tumour type, and participants without response data were counted as non-responders. For DOR, PFS, and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves were provided. Participants without efficacy evaluation data or without survival data were censored at Day 1 in the PFS and OS analyses. Participants who did not achieve a response were excluded from the DOR analyses.

Results

Disposition, Demographics, and Baseline Characteristics

Median age was 13 years (range 1 to 17 years). Participants were enrolled across approximately 29 tumour types by primary diagnosis. The most common primary diagnoses (in ≥5% of participants) were solid tumour NOS (18.0%), HL NOS (9.3%), glioblastoma multiforme (9.3%), soft tissue neoplasm NOS (7.5%), neuroblastoma (6.2%), osteosarcoma (6.2%), melanoma (5.6%), and CNS primary tumour NOS (5.0%). The 22 participants with HL ranged in age from 10 to 17 years. Four participants were 10 to 13 years of age and 18 participants were 14 to 17 years of age. 3 participants were between 6 months and 2 years.

Table 50 Baseline characteristics of the 22 participants in KEYNOTE-051 with cHL

All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

	All Subjects as Treated	
	n	(%)
Subjects in population	22	
Gender		
Male	14	(63.6)
Female	8	(36.4)
Age (Years)		
10 - 13 years	4	(18.2)
14 - 17 years	18	(81.8)
Mean	14.9	
SD	1.7	
Median	15.0	
Range	11 to 17	
Race		
Asian	1	(4.5)
Multi-Racial	6	(27.3)
Black, White	6	(27.3)
White	15	(68.2)
Ethnicity		
Hispanic Or Latino	9	(40.9)
Not Hispanic Or Latino	10	(45.5)
Not Reported	3	(13.6)
Primary Diagnosis		
Hodgkin Lymphoma Nos	15	(68.2)
Relapsed Refractory Classical Hodgkin Lymphoma (Post-Amendment 7)	7	(31.8)
Lansky / Karnofsky Play Score		
100	14	(63.6)
90	3	(13.6)
80	5	(22.7)
Overall Staging#		
IA	2	(9.1)
II	1	(4.5)

	All Subjects as Treated	
	n	(%)
IIA	3	(13.6)
IIB	1	(4.5)
IIE	1	(4.5)
III	1	(4.5)
IIIA	3	(13.6)
IIIB	4	(18.2)
IV	4	(18.2)
IVB	2	(9.1)
Brain Metastases Present		
No	22	(100.0)
Prior Adjuvant/Neoadjuvant therapy		
Yes	1	(4.5)
No	21	(95.5)
Treatment Naive		
No	22	(100.0)
Number of Prior Therapies for recurrent/Metastatic Disease		
1	3	(13.6)
2	10	(45.5)
3	2	(9.1)
4	3	(13.6)
5 or more	4	(18.2)
# Overall Staging not required for diagnoses lacking standard staging systems. (Data Cutoff Date: 10JAN2020).		

Source: [P051V02MK3475: adam-adsl]

Study recruitment

The study is ongoing; first participant first visit was on 23-MAR-2015; at the data cut-off 10-JAN-2020 (IA9) 162 participants were enrolled, 161 were treated, 8 (5.0%) completed the protocol-specified maximum treatment duration of 35 administrations (approximately 2 years), 4 (2.5%) were continuing study treatment, and 157 (97.5%) discontinued study treatment. Fifty-one (31.7%) participants were ongoing in the study.

The median duration of follow-up was approximately 3-fold longer for participants with HL (23.7 months) than for participants with all other tumour types (8.3 months), primarily due to the large number of early deaths among the other tumour types.

Subsequent Oncologic Treatments - Relapsed/Refractory Hodgkin Lymphoma: 14 of the 22 participants with HL received subsequent oncologic therapies after discontinuing treatment with pembrolizumab (including chemotherapy, BV, pembrolizumab and nivolumab).

Efficacy outcomes

ORR (INV-assessed)

- rrcHL (n=22)

The ORR by Investigator Review was 42.9% (per IWG 2007 criteria) for the 7 participants in the dedicated rrcHL Cohort and 66.7% (confirmed responses per RECIST 1.1) for 15 participants with HL in the PD-L1-positive solid tumours and other lymphoma Cohort (see Tables below).

Table 51 ***Summary of BOR based on IWG 2007 per Investigator assessment – R/RHL (post-amendment 7) - all subjects as treated population part II***

Response Evaluation	All Subjects as Treated (N=7)		
	n	%	95% CI†
Complete Response (CR)	2	28.6	(3.7, 71.0)
Partial Response (PR)	1	14.3	(0.4, 57.9)
Best Overall Response (CR+PR)	**3**	**42.9**	**(9.9, 81.6)**
Stable Disease (SD)	3	42.9	(9.9, 81.6)
Disease Control Rate (SD+CR+PR)	**6**	**85.7**	**(42.1, 99.6)**
Progressive Disease (PD)	1	14.3	(0.4, 57.9)

†Based on binomial exact confidence interval method.
(Database Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adrs]

Table 52 ***Summary of BOR based on IWG 2007 per Investigator assessment – R/RHL (post-amendment 7) - all subjects as treated population – parts I and II***

Response Evaluation	All Subjects as Treated (N=15)		
	n	%	95% CI†
Complete Response (CR)	1	6.7	(0.2, 31.9)
Partial Response (PR)	9	60.0	(32.3, 83.7)
Best Overall Response (CR+PR)	**10**	**66.7**	**(38.4, 88.2)**
Stable Disease (SD)	2	13.3	(1.7, 40.5)
Disease Control Rate (SD+CR+PR)	**12**	**80.0**	**(51.9, 95.7)**
Progressive Disease (PD)	3	20.0	(4.3, 48.1)

Confirmed responses by RECIST 1.1 are included.
†Based on binomial exact confidence interval method.
(Database Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adrs]

Among the 22 cHL participants, the ORR was 54.5% based on IWG 2007 criteria and 63.6% based on Lugano criteria.

Table 53

KEYNOTE-051
Summary of Best Overall Response Based on IWG 2007 per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

Response Evaluation	All Subjects as Treated (N=22)		
	n	%	95% CI†
Complete Response (CR)	1	4.5	(0.1, 22.8)
Partial Response (PR)	11	50.0	(28.2, 71.8)
Best Overall Response (CR+PR)	**12**	**54.5**	**(32.2, 75.6)**
Stable Disease (SD)	6	27.3	(10.7, 50.2)
Disease Control Rate (SD+CR+PR)	**18**	**81.8**	**(59.7, 94.8)**
Progressive Disease (PD)	3	13.6	(2.9, 34.9)
Non-evaluable (NE)	1	4.5	(0.1, 22.8)

†Based on binomial exact confidence interval method.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adrs]

Table 54

KEYNOTE-051
Summary of Best Overall Response Based on Lugano per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

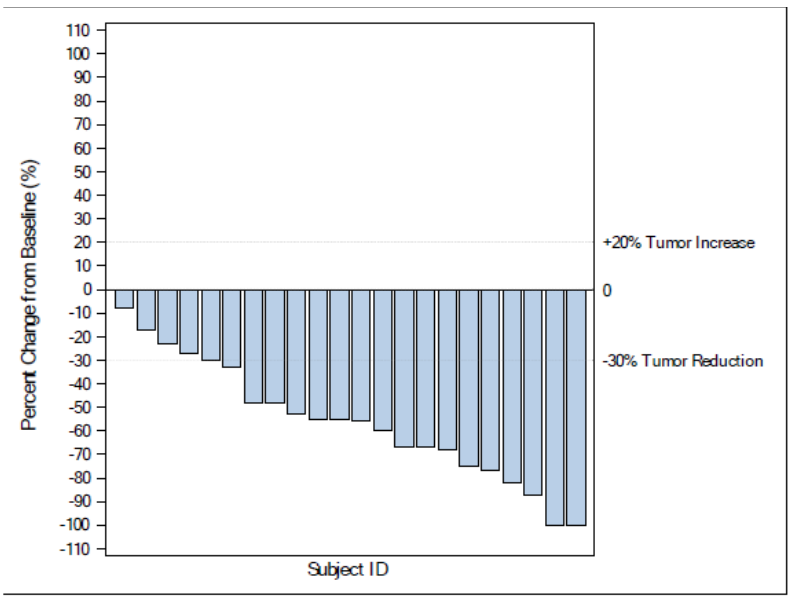
Response Evaluation	All Subjects as Treated (N=22)		
	n	%	95% CI[†]
Complete Response (CR)	4	18.2	(5.2, 40.3)
Partial Response (PR)	10	45.5	(24.4, 67.8)
Best Overall Response (CR+PR)	**14**	**63.6**	**(40.7, 82.8)**
Stable Disease (SD)	6	27.3	(10.7, 50.2)
Disease Control Rate (SD+CR+PR)	**20**	**90.9**	**(70.8, 98.9)**
Progressive Disease (PD)	2	9.1	(1.1, 29.2)

[†]Based on binomial exact confidence interval method.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adrs]

All 22 participants with HL had at least 1 post-baseline assessment of measurable tumour size in target lesions, and all had a reduction in tumour size post baseline. Eighteen participants had a maximum reduction in tumour size ≥30% (see Figure below).

Figure 34 ***waterfall plot of best tumor change from baseline per investigator assessment-R/RHL (all subjects as treated population – parts I and II)***



Percentage changes >100% were truncated at 100%.
(Data Cutoff Date: 10JAN2020)

Source: [P051V02MK3475: adam-adsl; adrs; adtl]

- All Relapsed/Refractory Tumours Except Hodgkin Lymphoma (n=139)

The ORR based on RECIST 1.1/MIBG was **5.8%** for confirmed responses (8 PRs) and 6.5% for confirmed plus unconfirmed responses (9 PRs) for 139 participants with relapsed/refractory tumors other than HL.

The 8 participants with a confirmed PR had the following tumor types by histology:

- Adenocarcinoma and mesothelioma (2 participants each); and
- Malignant ganglioma, epithelioid sarcoma, lymphoepithelial carcinoma, and malignant rhabdoid tumor (1 participant each)

The DCR was 25.9% (confirmed responses) and 28.1% (confirmed plus unconfirmed responses).

- **TTR and DOR:** rrcHL (n=22)

The median time to response based on RECIST 1.1 was 1.9 months for the 10 confirmed responders with HL. The median DOR was 17.4 months by KM estimation. Two of the 10 confirmed responses were ongoing at the time of data cutoff.

The median time to response based on IWG 2007 criteria was 2.6 months for the 3 responders in the dedicated rrcHL cohort (post Amendment 7). The DOR ranged from 0.0+ to 6.1+ months. One responder had a DOR of 6 months or longer.

Among the 12 responders by IWG 2007 criteria, the median time to response was 2.3 months and the median response duration was 17.3 months. There were 77.8% of participants with response duration ≥ 9 months. Three of the 12 responses were ongoing as of the data cutoff date [see Tables and Figure below].

Table 55

KEYNOTE-051
Summary of Time to Response and Duration of Response
Based on IWG 2007 per BICR Assessment in Subjects with a Response
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

	All Subjects as Treated (N=22)
Number of subjects with response†	12
Time to Response (months)	
Mean (SD)	2.7 (1.4)
Median (Range)	2.3 (1.1-6.2)
Response Duration‡ (months)	
Median (Range)	17.3 (0.0+ - 28.7)
Number (%‡) of Subjects with Extended Response Duration:	
≥3 months	8 (88.9)
≥6 months	8 (88.9)
≥9 months	7 (77.8)

†Includes subjects with confirmed response.
‡From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adtte]

Table 56

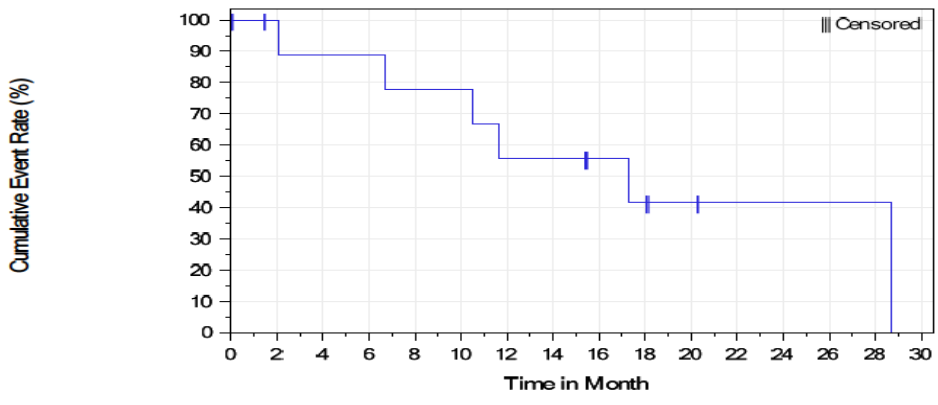
KEYNOTE-051
Summary of Response Outcome in Subjects with Censored from the DOR Analysis
Response Based on IWG 2007 per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

	MK3475 2 mg/kg Q3W (N=22)
Number of Subjects with Response[†]	12
Subjects Who Progressed or Died[‡] (%)	**6 (50.0)**
Range of DOR (months)	2.1 to 28.7
Censored Subjects (%)	**6 (50.0)**
Subjects who missed 2 or more consecutive disease assessments	0 (0.0)
Subjects who started new anti-cancer treatment	3 (25.0)
Subjects who were lost to follow-up	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	0 (0.0)
Ongoing response[§]	3 (25.0)
≥ 5 months	2 (16.7)
< 5 months	1 (8.3)
Range of DOR (months)	

[†] Includes subjects with a confirmed complete response or partial response.
[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
[§] Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.
'+' indicates there was no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Figure 35

KEYNOTE-051
Kaplan-Meier Estimates of Response and Duration of Response
Based on IWG 2007 per BICR Assessment in subjects with a response
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)



Number of subjects at risk

All Subjects as Treated	12	9	8	8	7	7	5	5	4	3	2	1	1	1	1	0

BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).
Source: [P051V02MK3475: adam-adsl; adtte]

Among the 14 responders by Lugano criteria, the median time to response was 2.1 months and the median response duration was 8.8 months. There were 45.5% of participants with response duration ≥ 9 months. Three of the 14 responses were ongoing as of the data cutoff date [see Tables and Figure below].

Table 57

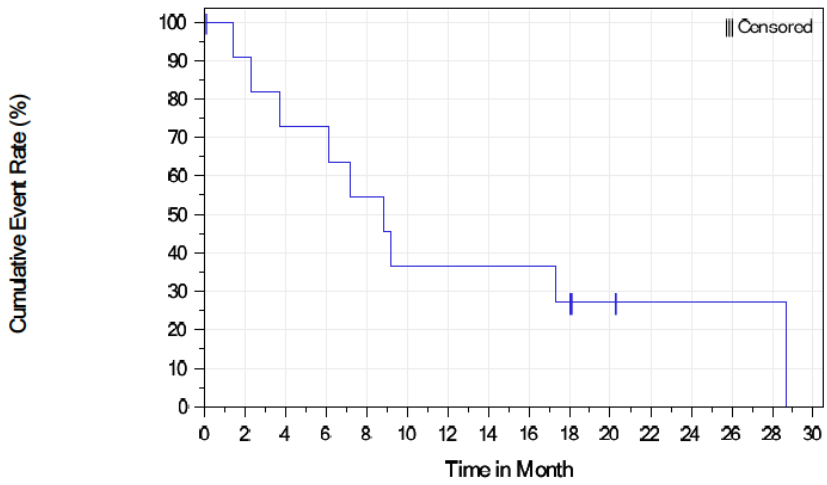
KEYNOTE-051
Summary of Time to Response and Duration of Response
Based on Lugano per BICR Assessment in Subjects with a Response
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

	All Subjects as Treated (N=22)
Number of subjects with response[†]	14
Time to Response (months)	
Mean (SD)	2.2 (0.7)
Median (Range)	2.1 (1.1-3.9)
Response Duration[‡] (months)	
Median (Range)	8.8 (0.0+ - 28.7)
Number (%[‡]) of Subjects with Extended Response Duration:	
≥3 months	9 (81.8)
≥6 months	8 (72.7)
≥9 months	

[†] Includes subjects with confirmed response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Figure 36

KEYNOTE-051
Kaplan-Meier Estimates of Response and Duration of Response
Based on Lugano per BICR Assessment in subjects with a response
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)



Number of subjects at risk

All Subjects as Treated	14	10	8	8	6	4	4	4	4	3	2	1	1	1	1	0

Table 58

KEYNOTE-051
Summary of Response Outcome in Subjects with Censored from the DOR Analysis
Response Based on IWG 2007 per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

	MK3475 2 mg/kg Q3W (N=22)
Number of Subjects with Response[†]	12
Subjects Who Progressed or Died[‡] (%)	**6 (50.0)**
Range of DOR (months)	2.1 to 28.7
Censored Subjects (%)	**6 (50.0)**
Subjects who missed 2 or more consecutive disease assessments	0 (0.0)
Subjects who started new anti-cancer treatment	3 (25.0)
Subjects who were lost to follow-up	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	0 (0.0)
Ongoing response[§]	3 (25.0)
≥ 5 months	2 (16.7)
< 5 months	1 (8.3)
Range of DOR (months)	

[†] Includes subjects with a confirmed complete response or partial response.
[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
[§] Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.
'+' indicates there was no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

PFS:

- rrcHL (n=22)

The median PFS based on IWG 2007 criteria was 11.2 months by KM estimation for the 7 participants in the dedicated rrcHL Cohort. PFS rates at 6 and 12 months were 55.6% and 27.8%, respectively.

The median PFS based on RECIST 1.1 was 12.2 months by KM estimation for 15 participants with HL in the PD-L1-positive solid tumors and other lymphoma Cohort. PFS rates at 6 and 12 months were 73.3% and 53.3%, respectively.

Among the 22 cHL participants, the median PFS based on IWG 2007 criteria was 8.3 months based on KM estimation. PFS rates at 6 and 12 months were 55.1% and 42.9% [see Table and Figure below].

Table 59

KEYNOTE-051
Summary of Progression-Free Survival (PFS) by IWG 2007 per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

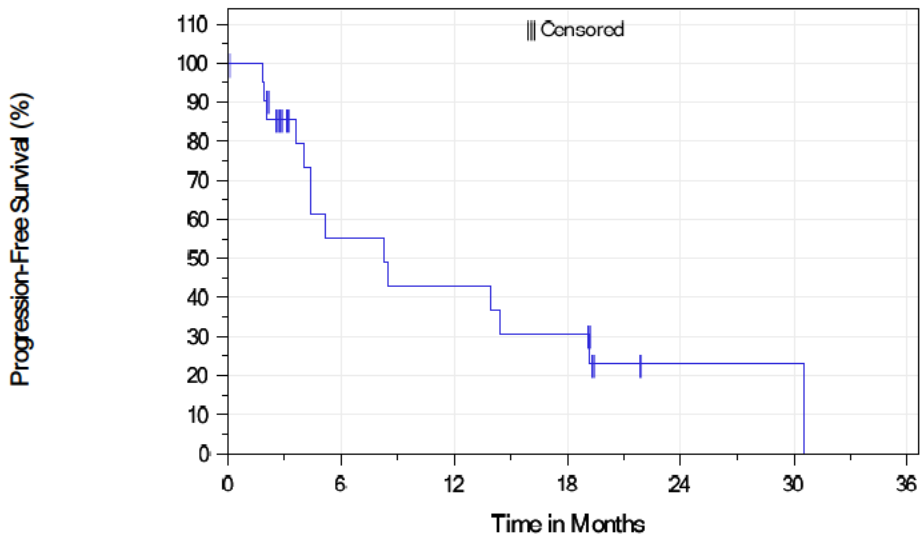
	All Subjects as Treated (N=22)
Number (%) of PFS Events	14 (63.6)
Person-Months	193
Event Rate/100 Person-Months (%)	7.2
Median PFS (Months)[§]	8.3
95% CI for Median PFS[§]	(4.0,19.2)
PFS rate at 6 Months in % [§]	55.1
PFS rate at 12 Months in % [§]	42.9

Progression-free survival is defined as time from first dose to disease progression, death or start of new anti-cancer therapy, whichever occurs first.
[§] From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adtte]

Figure 37

KEYNOTE-051
Kaplan-Meier Estimates of Progression-Free Survival (PFS) by IWG 2007 per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)



Data Cutoff Date: 10JAN2020).
Source: [P051V02MK3475: adam-adsl; adtte]

The median PFS based on Lugano criteria was 8.2 months based on KM estimation and PFS rates at 6 and 12 months were 53.0% and 24.2% [see Table and Figure below].

Table 60

KEYNOTE-051
Summary of Progression-Free Survival (PFS) by Lugano per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)

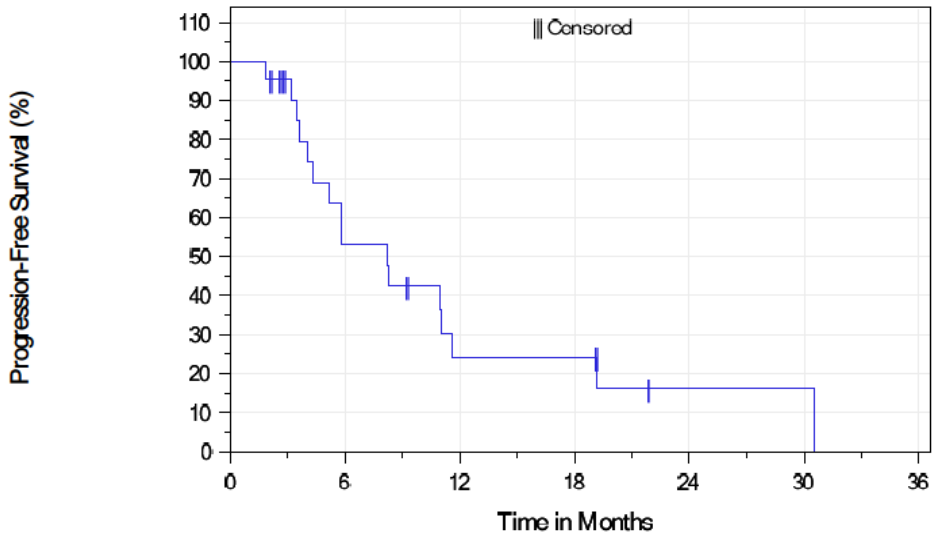
	All Subjects as Treated (N=22)
Number (%) of PFS Events	16 (72.7)
Person-Months	195
Event Rate/100 Person-Months (%)	8.2
Median PFS (Months)[§]	8.2
95% CI for Median PFS[§]	(4.0,11.6)
PFS rate at 6 Months in % [§]	53.0
PFS rate at 12 Months in % [§]	24.2

Progression-free survival is defined as time from first dose to disease progression, death or start of new anti-cancer therapy, whichever occurs first.
[§] From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded independent central review.
(Data Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adtte]

Figure 38

KEYNOTE-051
Kaplan-Meier Estimates of Progression-Free Survival (PFS) by Lugano per BICR Assessment
All Relapsed/Refractory Hodgkin Lymphoma
(All Subjects as Treated Population - Part II)



At Risk

All Subjects as Treated	22	10	4	4	1	1	0

Data Cutoff Date: 10JAN2020).
Source: [P051V02MK3475: adam-adsl; adtte]

- All Relapsed/Refractory Tumours Except Hodgkin Lymphoma (n=139)

The median PFS based on RECIST 1.1 was 1.8 months by KM estimation for 139 participants with relapsed/refractory tumors other than HL. PFS rates at 6 and 12 months were 18.7% and 13.2%, respectively.

OS:

- rrcHL (n=22)

For the 22 participants with HL, the median OS had not been reached at the time of data cutoff for this report. The OS rate was 100% at both 6 and 12 months by KM estimation. One participant died shortly after 12 months.

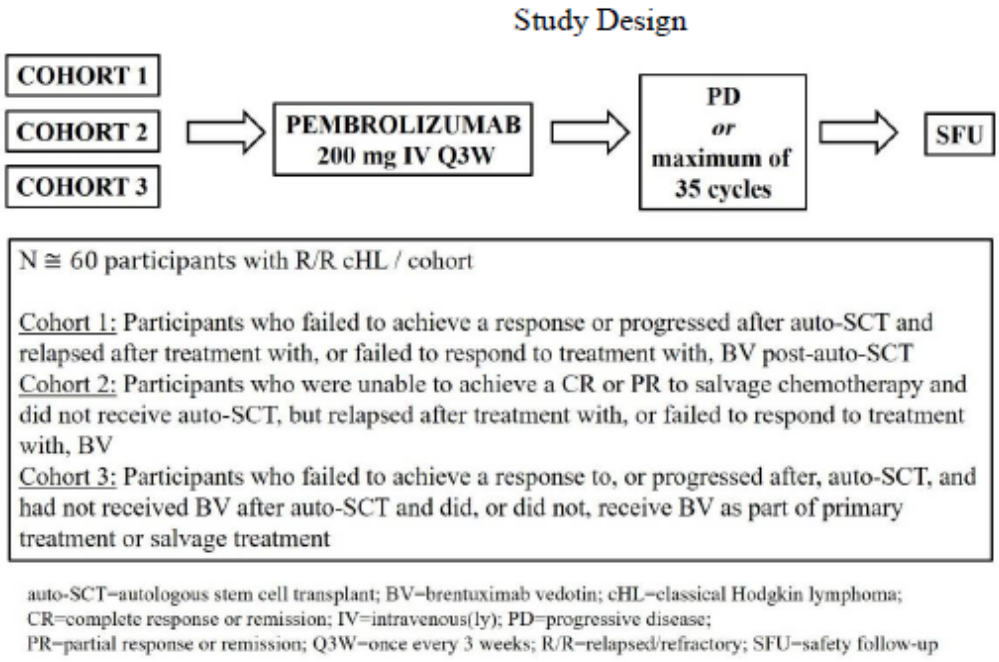
- All Relapsed/Refractory Tumors Except Hodgkin Lymphoma (n=139)

The median OS was 9.0 months by KM estimation for the 139 participants with relapsed/refractory tumors other than HL. OS rates at 6 and 12 months were 57.8% and 45.0%, respectively.

Supportive study(ies)

Keynote (KN)-087 - A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (r/r) Classical Hodgkin Lymphoma (cHL).

Figure 39 Study design



auto-SCT=autologous stem cell transplant; BV=brentuximab vedotin; cHL=classical Hodgkin lymphoma; CR=complete response or remission; IV=intravenous(ly); PD=progressive disease; PR=partial response or remission; Q3W=once every 3 weeks; R/R=relapsed/refractory; SFU=safety follow-up

Methods

Study design and population

KN-087 is an ongoing, multicenter, single-arm, multi-cohort, non-randomized Phase 2 study of IV pembrolizumab in adult patients with R/R cHL who failed to achieve a response or progressed after autologous stem cell transplant (auto-SCT) and relapsed after treatment with, or failed to respond to treatment with, brentuximab vedotin (BV) post-ASCT (Cohort 1); who were unable to achieve a complete

response (CR) or partial response (PR) to salvage chemotherapy and did not receive ASCT, but relapsed after treatment with, or failed to respond to treatment with, BV (Cohort 2); and who failed to achieve a response to, or progressed after, ASCT, and had not received BV after ASCT and did or did not, receive BV as part of primary treatment or salvage treatment (Cohort 3).

Treatment

Pembrolizumab was administered at the dose of 200 mg once every 3 weeks.

Efficacy objectives and endpoints

The study primary efficacy objective was to evaluate the objective response rate (ORR) of pembrolizumab by blinded, independent central review (BICR) according to the International Working Group (IWG) response criteria within each of the 3 cohorts of participants with R/R cHL. Secondary objectives were to evaluate: the ORR using the Lugano Classification, the CRR by the IWG criteria and the Lugano Classification, to evaluate PFS, DoR and OS.

Sample size and statistical methods

Approximately 60 participants were planned to be enrolled per cohort. The primary population for efficacy analysis was the All-Subjects-as-Treated (ASaT) population: all enrolled participants were included if they received at least 1 dose of study treatment.

ORR analysis consisted of the point estimate and 95% 2-sided exact confidence interval (CI) using the Clopper-Pearson method. An exact binomial test was conducted versus a fixed control rate. CRR analysis consisted of the point estimate and 95% 2-sided exact CI using the Clopper-Pearson method. DOR was analysed in all responders by summary statistics using the Kaplan-Meier (KM) method, with participants in response censored at their last assessment. PFS was analysed in all responders by summary statistics using the KM method, with missing data censored at last assessment. OS was analysed by summary statistics using the KM method, with missing data censored at last assessment.

Results

Disposition, Demographics, and Baseline Characteristics

Per protocol, all study participants had cHL, participants in Cohorts 1 and 3 were post-auto-SCT, and participants in Cohort 2 had not received an auto-SCT. The most common subgroup of cHL was nodular sclerosing Hodgkin Lymphoma (169 participants [80.5%]). All participants were heavily pre-treated, with a median of 4.0 prior lines of therapy (range: 1 to 12). A total of 175 participants (83.3%) had previously failed to respond to or relapsed after treatment with BV. Seventy-seven participants (36.7%) had prior radiation therapy. Median Age (Range) was 34 years (19 to 64 years) in cohort 1; 40 years (20 to 76 years) in cohorts 2; 32 years (18 to 73 years) in cohort 3.

Number of Participants Randomized/Treated/Ongoing/Discontinued

A total of 210 participants were allocated and treated in this study: 69 in Cohort 1; 81 in Cohort 2, and 60 in Cohort 3. As of the data cutoff date of 21-MAR-2019, 46 participants (21.9%) had completed the protocol-specified maximum treatment duration of 35 administrations (approximately 2 years) and 164 participants (78.1%) had discontinued study treatment. The most common reason for treatment discontinuation was disease progression (including events of clinical progression; [n=91]). The median duration of follow-up was 39.5 months (range: 1.0 to 44.8).

Outcomes

Table 61 Efficacy results

	COHORT 1	COHORT 2	COHORT 3	Total
ORR by BICR, n (%, 95% CI)	**n=69**	**n=81**	**n=60**	**N=210**
Based on IWG criteria	54 (78.3, 66.7-87.3)	52 (64.2, 52.8-74.6)	43 (71.7, 58.6-82.5)	149 (71.0, 64.3-77.0)
Based on Lugano criteria	58 (84.1, 73.3-91.8)	55 (67.9, 56.6-77.8)	41 (68.3, 55.0-79.7)	154 (73.3, 66.8-79.2)
CRR by BICR, n (%)	**n=69**	**n=81**	**n=60**	**N=210**
Based on IWG criteria	18 (26.1)	21 (25.9)	19 (31.7)	58 (27.6)
Based on Lugano criteria	25 (36.2)	23 (28.4)	21 (35.0)	69 (32.9)
DOR, months	**n=54**	**n=52**	**n=43**	**N=149**
Median (range)[a]	25.0 (0.0+, 36.1+)	11.1 (0.0+, 35.9+)	16.8 (0.0+, 39.1+)	16.6 (0.0+, 39.1+)
PFS by BICR	**n=43**	**n=54**	**n=36**	**N=133**
Median (95% CI), months	16.4 (11.3, 27.6)	11.1 (7.3,13.5)	19.4 (8.4, 22.1)	13.6 (11.1, 16.7)
Rate at 12 months[b], %	61.3	43.0	53.9	52.3
Rate at 24 months[b], %	41.6	21.9	34.0	32.2
OS	**n=69**	**n=81**	**n=60**	**N=210**
Median, months	Not reached	Not reached	Not reached	Not reached
Rate at 12 months[b], %	95.7	96.2	96.6	96.1
Rate at 24 months[b], %	92.6	91.0	89.4	91.1

a. "+" indicates there was no progressive disease at the time of the last disease assessment.

b. By KM estimation.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Pivotal study KN-204 is a phase III, randomised, open-label clinical trial designed to compare pembrolizumab vs. BV in subjects with r/r cHL. All patients with r/r cHL could be enrolled irrespectively of number of prior lines of therapy or refractory/relapsed disease status. Out of safety concerns subjects who received allogeneic HSCT within the last 5 years or had clinically relevant autoimmune conditions, active infection, CNS localization or current/previous pneumonitis were excluded: this is in line with the currently approved Keytruda SmPC and acceptable.

The study population underwent several changes over the course of the study, eventually resulting in high heterogeneity: under protocol amendment 2, e.g., subjects who previously responded to BV-containing regimens became eligible. Re-treatment of responders to BV is reflected in the current SmPC of Adcetris and is not controversial. Diverging form previous CHMP SA, however, protocol amendment 2 also allowed for the inclusion of patients with one single prior line of therapy, regardless of their transplant eligibility status. Then, following Amendment 03, patients considered by the Investigator to be eligible to ASCT/alloHSCT were definitely excluded from trial participation.

The main aim of salvage treatment in r/r cHL is to obtain a second remission and proceed to ASCT. Salvage chemotherapy followed by ASCT can allow for long-term disease control/cure in up to 50% of patients. Transplant eligibility is usually evaluated based on response to salvage treatment and residual chemosensitivity. Subjects with chemoresistant disease (i.e. patients unable to achieve a second remission or at least a significant reduction of disease bulk with salvage regimens) are not considered eligible to ASCT, since the expected benefit of transplant in this subgroup is limited. Some patients can be considered upfront ineligible to ASCT because of age and/or significant comorbidities.

Although the prognostic impact of refractoriness to frontline chemotherapy is recognised, it cannot be

considered, per se, a major criterium to define transplant ineligibility (see e.g. Hoppe RT et al, NCCN guidelines for HL v.2.2020).

Subjects were randomised 1:1 to receive up to 35 cycles of either pembrolizumab at the approved 200mg Q3W dose regimen or BV at the standard 1.8 mg/kg dose Q3W. According to the current Keytruda SmPC (section 4.2), patients are expected to continue pembrolizumab until disease progression or unacceptable toxicity. However, no subject received pembrolizumab for more than 35 cycles in study KN-204 and limited data are currently available on response duration following pembrolizumab discontinuation at cycle 35. Consistent recommendations are included in the SmPC.

BV could also be continued up to 35 cycle, yet, the currently approved SmPC for Adcetris specifies that r/r cHL patients who achieve stable disease (SD) or better could receive a minimum of 8 cycles and up to a maximum of 16 cycles of BV. Since a limited number of subjects received less than 8 or more than 16 cycles of BV in study KN-204 and no significant efficacy/safety issues have been observed in these subsets, the impact of prolonged BV administration on B/R evaluations is considered limited.

The choice of BV as comparator is acceptable for subjects not eligible to additional chemotherapy, being the current standard for patients who have failed ASCT or at least two lines of therapy.

The prognostic impact of the chosen stratification factors for randomisation (prior ASCT and disease status after frontline therapy) is recognised. The role of other factors with known prognostic relevance (e.g. presence of bulky or extranodal disease, response to prior therapy and anaemia at relapse), was also investigated in dedicated post-hoc subgroup analyses.

PFS (assessed by BICR according to IWG response criteria [Cheson, 2007], including clinical and imaging data following auto-SCT or allo-SCT) and OS were selected as dual primary efficacy endpoints to assess clinical benefit: this is agreed. Although study KN-204 was designed to claim success in the case pembrolizumab was confirmed superior to BV in either PFS or OS, consistency of results across primary endpoints is nonetheless expected. In this regard, since BV and pembrolizumab are both approved in the EU for the treatment of cHL patients in advanced settings of relapse, the possibility of a confounding effect of systematic off-study cross-over on OS cannot be excluded.

The other secondary/exploratory endpoints (e.g. ORR, CRR, DoR, ORR post-progression, PFS2 and PROs explored using the validated EQ-5D and EORTC QLQ-C30 instruments) are considered overall adequate to further characterize pembrolizumab efficacy in the target population. Although the older 2007 IWG response criteria were used for the primary efficacy analyses, additional analyses using the 2014 Lugano response criteria were also provided.

From a methodological perspective, the planned sample size (n=300) in study KN-204 is congruent with clinical assumptions and adequate to allow for the detection of a HR of 0.62 for PFS with a 85% power at alpha 1.2% (one-sided), a HR of 0.6 for OS with a 80% power at alpha 1.25% (one-sided) and a 18-20% improvement in ORR with a 90% power at alpha of 0.6% (one-sided and provided that the PFS hypothesis is rejected). Four interim analyses (IAs) and one final analysis (FA) were pre-specified. The statistical methods used to test time to event and binary endpoints are standard and the overall strategy to control multiplicity is not controversial. With respect to PROs, the EQ-5D and EORTC QLQ-C30 instruments are validated and acceptable. The 10-point change considered as minimal important difference (MID) was, however, poorly justified beyond a generic statement that this difference was perceived as clinically meaningful by the patients. Imputation under MAR was also planned to address missing data, yet no reason was provided to justify the MAR assumption. Most importantly, no strategy to control multiplicity was put in place for PROs analyses, and the open-label study design further questions results reliability.

Supportive study KN-087 is an ongoing, single-arm, multi-cohort, non-randomized Phase 2 study investigating the efficacy of pembrolizumab monotherapy in a heterogeneous population of patients with cHL in advanced settings of relapse. Cohort 3, which also included BV-naïve patients, can be considered

the most informative for the claimed indication. Results for study KN-087 were pivotal in supporting the initial indication of pembrolizumab for the treatment of r/r cHL (see EPAR for procedure EMEA/H/C/003820/II/0014).

Efficacy data and additional analyses

Three-hundred and thirty-eight subjects were screened in study KN-204 and 304/338 (~89.9%) were eventually randomised to receive either pembrolizumab (n=151) or BV (n=153). At the time of the data cut-off date the vast majority of subjects had discontinued study treatment.

Sixty-four (~21%) subjects underwent subsequent ASCT and 27 (~9%) allogeneic HSCT, with no significant differences across study arms. Considering that transplant-eligibility was an exclusion criterion, the high rate of patients receiving subsequent transplant in study KN-204 further highlights the difficulties in prospectively defining transplant eligibility in cHL.

Demographic characteristics were generally well balanced across treatment arms and overall consistent with what expected in a population of patients with r/r cHL. Nearly all subjects had a good performance status at the time of study entry (ECOG score was 0-1 in 99.7% of subjects), the majority had no B-symptoms (73.7%) and only 19.7% and 5.6% had bulky disease and bone marrow involvement, respectively.

The median number of prior lines of therapy was 2, with a median of 3 prior regimens received, and approximately 40% and 37% in both treatment arms had received prior radiotherapy (RT) and ASCT, respectively. Only a minority of patients had received prior BV (~5%, 10 patients in the BV and 5 in the pembrolizumab arm). Overall, nearly 70% of patients had primary refractory or early relapsed disease (i.e. response duration ≤12 months), identifying a high-risk clinical setting.

Taking into account the broad claimed indication and the significant heterogeneity in the study population, baseline characteristics stratified by number of prior lines of therapy and transplant eligibility were also provided. Overall, despite the fact that under protocol versions 1 and ≥3 inclusion was limited to transplant ineligible patients, only 192/304 (63%) patients in study KN204 were deemed transplant ineligible at the time of enrolment. As expected based on current guidelines, most transplant-ineligible patients (137/192 [~71%]) had received ≥2 prior lines of systemic therapy and only 55 patients (29% of all transplant-ineligible patients and 18% of the overall study population) were deemed transplant ineligible after one single line of therapy.

With respect to transplant-ineligible subjects with ≥2 prior therapies, median age was 34 years (range 18 to 83), only 10.8% of patients were aged ≥65 years (3.2% aged ≥75) and most subjects had a baseline ECOG score of 0 or 1 (58.2% and 41.4%, respectively). Approximately 30% were refractory to frontline chemotherapy and ~37% had received prior ASCT. Nodular-sclerosis was the more represented cHL histological subtype (~81%) and bulky disease, B symptoms and bone marrow involvement were present in approximately 21%, 28% and 4% of patients, respectively.

Transplant-ineligible subjects with one single prior line of therapy were older (median age at baseline was 49 years), with 40% of patients aged ≥65 years and 12.7% (7/55) ≥75 years. Baseline ECOG PS score was 0 (74.5%) or 1 (25.5%) in all subjects. The proportion of patients in this subgroup that were refractory to frontline chemotherapy was ~22% and, as expected, none had received prior ASCT. Most patients had nodular-sclerosis cHL (~82%) and only ~15% had bulky disease, 16% reported B symptoms at baseline and ~11% had bone marrow involvement.

With a median follow-up of approximately 2 years, the primary PFS analysis can be considered sufficiently mature (e.g. 55% of patents having experienced at least one PFS event). Study KN-204 met the primary PFS endpoint: pembrolizumab demonstrated a statistically significant superiority in PFS compared to BV.

Median PFS was 13.2 months (95%CI 10.9, 19.4) and 8.3 months (95%CI 5.7, 8.8) in the pembrolizumab and in the BV arms, respectively (HR 0.65, 95%CI 0.48, 0.88, p=0.00271). The external validity of the data is supported by the fact that PFS outcomes observed in the BV arm of study KN-204 were overall in line with those reported in the Adcetris registrational trial (study SG035-0003), where a ~6 months median PFS was observed in a more advanced patient population. The estimated 24-month PFS rate was 35.4% and 25.4% for pembrolizumab and BV, respectively. Results from the planned sensitivity analyses and secondary PFS endpoints were consistent with the primary analysis; in particular, results from the secondary PFS analysis censoring patients at the time of transplant confirmed study outcomes (HR 0.62, 95%CI 0.46, 0.85), showing that the impact of subsequent transplant on the relative efficacy of pembrolizumab vs. BV was overall limited.

In a population often characterised by significant chemoresistance, ORR was numerically higher with pembrolizumab compared to BV (65.6% [95%CI: 57.4, 73.1] and 54.2% [95%CI: 46.0, 62.3], respectively), yet confidence intervals largely overlapped and no significant differences could be observed in terms of CR rates (24.5% [95%CI 17.9%, 32.2%] with pembrolizumab and 24.2% [95% CI 17.6%, 31.8%] with BV). DoR data were not sufficiently mature, yet a possible trend towards longer response duration with pembrolizumab could be observed (mDoR 20.7 vs. 13.8 months). The fraction of patients with response duration longer than 24 months was, however, similar across treatment arms (47.4% vs. 42.8%, respectively).

Higher ORRs were observed in both treatment arms when the Lugano response criteria were applied: 72.8% and 67.3% with pembrolizumab and BV, respectively. The analysis applying the Lugano criteria also resulted in higher rates of remission, in particular in the BV arm (CRR 30.7%). Despite similar PFS, DoR according to the Lugano criteria was significantly shorter in both treatment arms (16.8 and 5.8 months, with pembrolizumab and BV, respectively).

Pembrolizumab and BV are both authorised in the EU for the treatment of cHL patients in advanced settings of relapse, making uncontrolled cross-over a possible issue. In this regard, PFS2 data are considered of value. Unfortunately, at the time of data cut-off date, the PFS2 analysis was still largely immature, with just 27.8% and 35.3% of events observed in the pembrolizumab and BV arms, respectively. Reassuringly, a favourable trend could still be observed (HR 0.58, 95%CI 0.38, 0.87, p=0.0037), yet updated data and detailed information on subsequent treatments are needed to exclude significant differences in treatment patterns across study arms.

The MAH remains blinded to subsequent efficacy data post-IA2 and the first planned formal OS analysis is to occur at ~91 events (IA3), which is not expected to occur until the second quarter of 2022 based on the event rate observed at the data cutoff used for IA2 (16-JAN-2020). An update for PFS2, as well as pre-planned analyses assessing effect of crossover on OS will be provided.

With respect to PROs, a trend towards an improvement could generally be observed with pembrolizumab, yet the open-label design of study KN-204 and the absence of any multiplicity control strategy do not allow to uphold formal superiority claims.

Overall, pembrolizumab demonstrated a consistent benefit across subgroups with the main exception of regional differences. Despite there were no obvious imbalances in baseline characteristics that could explain the negative trend in EU vs. ex-EU participants, subgroup analyses suggested inferior efficacy (HR 0.93) [95% CI: 0.50, 1.74], compared with for participants in the EU (n=95) compared to Ex-EU participants (n=209); HR 0.53 [95% CI: 0.37, 0.76]. Median PFS in this subgroup (16.4 months with pembrolizumab and 8.3 months in the BV arm) was in line with what observed in the overall population, yet KM plots showed that, after an initial separation, PFS curves re-joined to remain overlapped in a sort of plateau configuration. No similar trend could be observed in the overall population or in the ex-EU subset. PFS and ORR results stratified by region for the pooled HL population across studies KEYNOTE-204, KEYNOTE-087 and KEYNOTE-051 were also provided. The methodological limitations, especially

regarding interpretability of time-to-event endpoints and the overlapping of the confidence intervals, are acknowledged; nonetheless, also in the relatively large study KN-087 (n=210) a similar trend towards reduced benefit in the EU vs. ex-EU population was observed (ORR difference 7% and median PFS difference 2.5 months in the pooled dataset). Results of PFS Sensitivity Analysis 1 in KEYNOTE-204 confirmed the primary analysis by region. Since the observed regional differences appeared to be less pronounced in the PFS secondary subgroup analysis (PFS censored at the time of transplant), the MAH also evaluated the impact of SCT on PFS in the KEYNOTE-204 EU participants. However inter-treatment arm differences in the arithmetic median of "additional" PFS time after SCT (i.e. beyond the censoring date of the PFS secondary analysis that was considered based on the primary PFS definition) were only small and therefore, differences between PFS primary and secondary analyses cannot be easily explained by subsequent SCT: the observed differences across regions remain unclear.

Similar clinical outcomes were observed in subjects with 1 and ≥2 prior lines of therapy: the ORRs with pembrolizumab ranged between 61.8% and 66.7% across all subsets defined by number of prior therapies and transplant eligibility vs. 46.4%-54.4% with BV. PFS also consistently favoured the pembrolizumab arm across all prior lines of therapy subgroups, with mPFS ranging between 16.4 and 11.1 months with pembrolizumab vs. 8.4-5.7 months with BV (HR 0.62-0.70). Overall, efficacy results were usually more favourable in less pre-treated subjects with one notable exception: a lower CRR was observed with pembrolizumab in patients with 1 prior line of therapy (14.8% vs. 25.7% with BV).

Updated results with a median follow-up of approximately 40 months were also provided from the uncontrolled supportive study KN-087, showing an IWG ORR by BICR of 71% (95%CI 64.3, 77) and 71.7% (95%CI 58.6, 82.5) in the overall population and in cohort 3, respectively. CRRs were 27.6% and 31.7%, median DoR 16.6 and 16.8 months and median PFS 13.6 and 16.8 months, respectively. Median OS was not reached in all cohorts. With the limits of indirect comparisons, efficacy results in study KN-087 can be considered supportive of the activity of pembrolizumab in r/r cHL.

BV is a recognised option for subjects who have failed salvage chemotherapy +/- ASCT (i.e. 3rd line), so the ~5-month Δ in median PFS observed in the pivotal study with pembrolizumab vs. BV, which is equivalent to ~35% reduction in the risk for progression or death, can be considered of clinical relevance in such advanced clinical setting. PFS K-M plots did not show any clear plateau, however, confirming how cure is rarely achieved in advanced relapse settings. However, assessing clinical benefit with pembrolizumab in subjects who have failed one single line of therapy was, less straightforward. According to current EU guidelines (see e.g. the ESMO guidelines for cHL, Eichenauer DA et al, Ann Oncol 2018), non-cross resistant chemotherapy is still the recommended option for patients failing frontline treatment, while BV is not currently authorised in EU as 2nd line treatment. In this regard, published data show that ORR as high as 80% (CRR 20-70%) can be observed with salvage polychemotherapy, with 4-year EFS rates of 50% and 10% in transplant-naïve and non-transplant eligible patients, respectively, and 4-year OS rates as high as 70% and 30% for patients who received or not consolidation ASCT, respectively (see e.g. Bartlett NL et al, Ann Oncol. 2007; Kuruvilla J et al, Cancer 2006; Santoro A et al, JCO 2016). For less intensive regimens based on single-agent gemcitabine or bendamustine the reported ORRs were still in the range 40-55% (CRRs 7% and 37%, respectively). A median TTP of 3 months (range, 2-7 months) has been reported with single-agent gemcitabine, while the median DoR with bendamustine monotherapy was as high as 8 months, although this analysis was still immature, with all responders maintaining a continuous response at the last follow-up examination (see e.g. Ozdemir E et al, Blood 2015; Zinzani PL et al, Clin Lymphoma Myeloma Leuk 2015). Even considering patient heterogeneity and the known limits of indirect comparisons, clinical benefit with pembrolizumab in 2nd line patients not eligible to transplant is not considered established.

With respect to 2nd line patients (n=55), a heterogeneous population was included in study KN-204 encompassing both upfront transplant-ineligible patients (e.g. due to age and comorbidities) and subjects who were refractory to frontline chemotherapy. Only 34/55 2nd line patients were deemed transplant-ineligible for reasons other than chemo-refractoriness, just 22/55 (40%) were aged ≥65 and 7/55 (12.7%)

≥75 years. No information was provided on concurrent comorbidities that contraindicated ASCT and most patients (74.5%) had a baseline ECOG score of 0. Overall, it is uncertain whether 2nd line patients in study KN-204 can be considered representative of real-world transplant ineligible patients and to what extent the observed results can be generalised to such frail population.

With respect to subjects refractory to frontline chemotherapy, published data suggest that autologous transplant remains the best strategy to achieve long-term disease control (see e.g. Sibon D et al, Haematologica 2016): the need for novel salvage therapies characterised by high CRR rates to improve transplant access for primary refractory patients is recognised. In this regard, however, only 21 2nd line patients were deemed ineligible to ASCT due to primary chemoresistance in study KN-204 and the CRR rate observed in this 2nd line subgroup (14.8%) was not sufficiently compelling.

The limited available data in 2nd line transplant-ineligible patients are not considered adequate to conclude for clinical benefit in this subgroup. The indication was eventually revised to reflect this.

Assessment of paediatric data on clinical efficacy

Study KN-051 is an ongoing Phase I/II study investigating pembrolizumab monotherapy in paediatric patients with solid tumours and malignant lymphomas. Paediatric subjects with r/r cHL could be enrolled in the dedicated r/r cHL expansion cohort or in the PD-L1 positive advanced, relapsed or refractory solid tumour or other lymphoma cohort, provided that they had failed standard therapy and no other treatment option was considered appropriate. The IWG response criteria were used to assess response in the dedicated cHL cohort, while response in the PD-L1 positive cohort was assessed according to the RECIST 1.1 criteria. Efficacy data were also retrospectively re-assessed using the IWG 2007 and the 2014 Lugano response criteria for all patients.

Overall, 22 paediatric patients with r/r cHL were treated in study KN-051: 7 patients enrolled in the dedicated cHL cohort and 15 in the PD-L1 positive cohort. The median number of prior lines of therapy in the paediatric population was 2 vs. 3 in study KN-204, most patients (13/22, ~60%) had received ABVD-like regimens in first line, which is not unexpected taking into account that adolescents made up for the majority of the studied population and they are often treated according to adult standards in real world clinical practice. In line with the high-risk population studied in the KN-204 trial, most cHL patients in study KN-051 (14/22, ~64%) were refractory to frontline chemotherapy. Overall, the studied population can be considered representative of real-world cHL paediatric patients, in particular adolescents, in an advanced setting of relapse. cHL is rarer in infants and children, which are indeed poorly or not at all represented in the studied population. Clinical benefit evaluations in these settings have to rely on extrapolation from the adult and adolescent setting.

The ORR per IWG criteria observed in the 7 patients treated in the dedicated r/r cHL cohort was 42.9% (3/7), which is numerically lower than what observed in adults in pivotal study KN-204 (i.e. 65.6%). Two out of 7 subjects achieved a CR. Median DoR in this cohort was not reached due to limited follow-up (only one patient had an ongoing DoR ≥6 months). Median PFS in the r/r cHL cohort (11.2 months) was in line with that observed in study KN-204 (13.2 months), yet the estimated 12-month PFS rate was lower than that reported in adults (27.8% vs. 53.9%, respectively). The ORR per RECIST criteria was 66.7% (10/15 with only one patient reaching a CR), with median DoR and PFS of 17.4 and 12.2 months, respectively. The actual clinical value of these results is, however, unknown because of the limited generalisability of RECIST responses in cHL. OS data are still immature to draw meaningful conclusions.

With respect to the pooled population, higher ORR and CRR were observed with the Lugano criteria (54.5% [12/22] and 4.5% [1/22], respectively) compared to the IWG criteria (63.6% [14/22] and 18.2% [4/22], respectively), possibly reflecting the increased relevance of PET activity vs. TC lesion measures in the 2014 Lugano criteria. As in the adult setting, despite similar median PFS (8.3 and 8.2 months with

the IWG 2007 and Lugano criteria, respectively) a significant difference in response duration was assessed when the IWG 2007 (17.3 months) and the Lugano criteria (8.8 months) were applied. Again, increased reliance on PET activity rather than dimensional increase of target lesions with the Lugano criteria might explain the shorter response duration. The provided KM curves failed to show any clear plateau, irrespectively of response criteria.

The available efficacy data in paediatric patients with r/r cHL are limited (e.g. because of poor numbers, heterogeneity in response criteria, intrinsic difficulties in assessing time-to-event endpoints in uncontrolled studies and limited information on the possible impact of prognostic characteristics and prior treatments on the results) yet overall consistent with what observed in adults and, in principle, supportive of pembrolizumab activity in this subgroup. The totality of the information presented provides reliable evidence to support the extrapolation approach in the paediatric cHL population 3 years old and above. Based on this, the MAH conducted a model-based bridging analysis to identify a dosing regimen that would provide exposures in paediatric patients similar to those in adults as described in this submission.

In line with the framework proposed in the "Reflection paper on the use of extrapolation in the development of medicines for paediatrics" the MAH has applied the extrapolation approach based on the following comparisons between adults and paediatrics 1) similarity of HL disease, 2) similar pharmacology of drug effect, 3) similar exposure-response for efficacy and safety. The totality of evidence allowed the MAH to conduct a model-based bridging analysis to identify a dosing regimen that would provide exposures in paediatric patients similar to those in adults.

HL is recognized as a cancer that affects both children and adults. The disease has the same biology and natural history in both categories. HL has a bimodal age distribution, with peaks at 15 to 35 years of age and again after 50 years of age. While children younger than 14 years old have a higher incidence of nodular lymphocyte predominant HL, cHL is the most common histologic subtype similar to the adult population. Considering data on the incidence of HL in the paediatric population, children 3 years and older was used as an inclusion criteria in KEYNOTE-051.

Classical HL is the population being studied in adult pembrolizumab clinical studies, where the median age of enrolled participants has been in their 30s. The continuity of cHL disease across patients younger than 18 years of age and older than 18 years of age confers that it is essentially the same disease in children and adolescents as in adults. This is underscored by the same prognostic factors associated with success of therapy such as advanced stage disease, presence of B symptoms, bulky disease, ESR, haematocrit, and response to initial chemotherapy. Because of this, no difference in the mechanism of action and activity of pembrolizumab in this setting is expected to be observed between children and adults.

Historically, treatment of cHL in childhood and adults generally utilized the same strategy and agents, with high cure rates especially in younger patients. Treatment of rrcHL similarly follows adult-based strategies, with multi-agent chemotherapy followed by myeloablative high-dose chemotherapy with auto-SCT. Front-line treatment for children and adolescents with cHL is highly effective, with many patients essentially cured. However, children and adolescents with relapsed or refractory cHL need improved therapies. Their currently available treatment options are typically more multi-agent chemotherapy regimens, including high dose therapy with auto-SCT. In patients who have previously been refractory to or relapsed from 1 or 2 lines of chemotherapy, particularly those with high-risk disease, these existing treatment options are not satisfactory; while there is little expectation of potential benefit, additional toxicity is certain and unavoidable. The other option at that point is investigational agents in clinical studies. The MAH has identified a clear unmet medical need in this subset.

The IL-2 release biomarker reflects the functional blockade of the PD-1 pathway by pembrolizumab and is utilized as a measure of target engagement - in support of a similar pharmacology drug effect;. Overall, even though the data in paediatric participants are limited, the estimates of IC50 values are similar between adults and paediatric participants.

Exposure-response analysis for best percent change from baseline tumor size, demonstrated similar relationships between adult and paediatric participants with cHL.

Efficacy in cHL paediatric patients is supported by extrapolation of efficacy data in adults (KEYNOTE-204, KEYNOTE-087). In addition, KEYNOTE-051 provides supportive efficacy data in cHL paediatric patients and safety data in paediatric patients with different tumor types. Overall, the evidence supports a positive B/R in the target population of children 3 years and older.

2.4.4. Conclusions on the clinical efficacy

Based on the available efficacy data, clinical benefit with pembrolizumab vs. BV is considered established for adult patients with r/r cHL who have failed 2nd line salvage chemotherapy +/- ASCT.

Efficacy data in the paediatric setting are limited, however, when the rarity of cHL in the paediatric age and the consistent disease biology across age classes are taken into account, the available data can be considered adequate to confirm the activity of pembrolizumab in paediatric patients and support the proposed extrapolation strategy of results observed in the adult setting.

Therefore, the indication was eventually revised to *"KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option".*

The final study report for study P204 is already included as a Post-authorisation efficacy study (PAES) in the Annex II; the deadline for the submission of the CSR has been extended to Q4 of 2025 in order for the MAH to generate OS data as requested by the CHMP.

2.5. Clinical safety

Introduction

In the context of the extension of the currently approved therapeutic indication of pembrolizumab for the treatment of relapsed or refractory classical Hodgkin lymphoma (r/r cHL) in adults to an earlier line of therapy and to include paediatric patients, safety results have been presented by:

- Indication Population, including overall 300 r/r cHL patients treated in the study KEYNOTE-204, a randomized, open-label, Phase 3 trial evaluating pembrolizumab in monotherapy (KEYNOTE-204 Pembrolizumab Safety Dataset; n=148 patients) versus Brentuximab Vedotin (BV) (KEYNOTE-204 BV Safety Dataset; n=152 patients);
- cHL Safety Dataset for Pembrolizumab, a pooled safety data from KEYNOTE 204 (148 patients), updated analysis of KEYNOTE-087 (210 patients) and KEYNOTE-013 cohort 3 (31 patients);
- Pembrolizumab Monotherapy Reference Safety Dataset (RSD), a pooled population including overall 5884 patients treated with pembrolizumab in monotherapy; this dataset consists of mostly solid tumour data and represents the established safety profile for pembrolizumab;
- Cumulative Safety Dataset (CSD), a pooled population including overall 8093 patients who received pembrolizumab in other studies, including cHL in KEYNOTE-013, KEYNOTE-087 and KEYNOTE-204. The CSD was provided only to show that no clinically meaningful change from the RSD occurred, supporting the consistency of the safety data of pembrolizumab across indications.
- To support the extension of the indication to r/r cHL paediatric patients, safety data from KEYNOTE-

051 were also provided.

Table 62 ***Safety Datasets***

Dataset (N)	N	Population[1]	Nomenclature in Tables/Figures	Nomenclature in Text
KEYNOTE-204 Pembrolizumab Safety Dataset	148	Participants with relapsed or refractory cHL who received pembrolizumab in KEYNOTE-204.	KEYNOTE-204 Data for Pembrolizumab	KEYNOTE-204 Pembrolizumab Safety Dataset
KEYNOTE-204 BV Safety Dataset	152	Participants with relapsed or refractory cHL who received BV in KEYNOTE-204.	KEYNOTE-204 Data for BV	KEYNOTE-204 BV Safety Dataset
cHL Safety Dataset for Pembrolizumab	389	Participants with relapsed or refractory cHL who received pembrolizumab in KEYNOTE-204 (n=148), KEYNOTE-087 (n=210), and KEYNOTE-013, Cohort 3 (n=31).	cHL Safety Dataset for Pembrolizumab	cHL Safety Dataset
Pembrolizumab Monotherapy Reference Safety Dataset[2]	5884	Participants who received pembrolizumab in the following populations and studies: *melanoma* (n=2076) in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-054; NSCLC (n=2022) in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-024 and KEYNOTE-42; HNSCC (n=909) in KEYNOTE-012, KEYNOTE-040, KEYNOTE-048 and KEYNOTE-055; HL (n=241) in KEYNOTE-013 and KEYNOTE-087; Bladder (n=636) in KEYNOTE-045 and KEYNOTE-052.	Reference Safety Dataset for Pembrolizumab	RSD
Cumulative Safety Dataset for Pembrolizumab in Monotherapy	8093	Participants who received pembrolizumab in the following populations and studies: *advanced melanoma* in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-054; *NSCLC* in KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042; *HNSCC* in KEYNOTE-012 (Cohort B; Cohort B2), KEYNOTE-040, KEYNOTE-048, and KEYNOTE-055; *gastric cancer* in KEYNOTE-012 (Cohort D), KEYNOTE-059 (Cohort 1), and KEYNOTE-062; *cHL* in KEYNOTE-013 (Cohort 3), KEYNOTE-087, KEYNOTE-204; *bladder cancer* in KEYNOTE-012 (Cohort C, *urothelial carcinoma*), KEYNOTE-045, and KEYNOTE-052; *colorectal cancer* in KEYNOTE-164 (Cohort A); *PMBCL* in KEYNOTE-013 (Cohort 4A) and KEYNOTE-170; *cervical cancer* in KEYNOTE-028 (Cohort B4) and KEYNOTE-158 (Cohort E); *advanced HCC* in KEYNOTE-224; *MCC* in KEYNOTE-017; *esophageal cancer* in KEYNOTE-024 and KEYNOTE-028 (Cohort A4); *RCC* in KEYNOTE-427; *SCLC* in KEYNOTE-028 (Cohort C1) KEYNOTE-158 (Cohort G); *NMIBC* in KEYNOTE-057; and *TMB-H* in KEYNOTE-158.	Cumulative Running Safety Dataset for Pembrolizumab	Cumulative Safety Dataset

Abbreviations: BV=brentuximab vedotin; cHL=Classical hodgkin lymphoma; HCC=Hepatocellular carcinoma; HL=Hodgkin lymphoma; HNSCC=Head and neck squamous cell carcinoma; MCC=Merkel cell carcinoma; NMIBC=Non-muscle invasive bladder cancer; NSCLC=Non-small cell lung cancer; RCC=Renal cell carcinoma; RSD=Reference safety dataset; SCLC=Small-cell lung cancer; TMB-H=high tumor mutation burden.
[1] All participants in the listed populations received at least 1 dose of the study treatment.
[2] The Pembrolizumab Monotherapy RSD represents the established safety profile of pembrolizumab in monotherapy.

Patient exposure

Demographic and other characteristics of Study Population in the different Safety Datasets are reported in Table 2. Gender, race and ECOG performance were generally similar across the KEYNOTE-204 safety datasets, the cHL Safety Dataset and the RSD. Most patients were male, white and had an ECOG

performance status score of 0. However, differences in age and region were observed between the different datasets: in the KEYNOTE-204 and in the cHL Safety Dataset, the median age of patients was less than that in the RSD, and more than 80% of patients were <65 years old compared with 57.5% of patients in the RSD. Lower age is expected based on the epidemiology of cHL compared to solid tumors included in the RSD. In addition, in KEYNOTE-204, more patients in both arms (pembrolizumab and BV) were enrolled at ex-EU sites than in the cHL Safety Dataset (68.2% and 70.4% vs 56.8%), as observed for enrolment in the RSD (64.4%).

Table 63 ***Patients Characteristics***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
Gender										
Male	81	(54.7)	89	(58.6)	212	(54.5)	3,887	(66.1)	5,416	(66.9)
Female	67	(45.3)	63	(41.4)	177	(45.5)	1,997	(33.9)	2,677	(33.1)
Age (Years)										
<65	122	(82.4)	130	(85.5)	343	(88.2)	3,385	(57.5)	4,640	(57.3)
>=65	26	(17.6)	22	(14.5)	46	(11.8)	2,499	(42.5)	3,453	(42.7)
Mean	41.8		40.9		39.7		60.6		60.4	
SD	17.6		17.2		15.7		13.2		13.4	
Median	35.5		35.0		35.0		62.0		62.0	
Range	18 to 84		18 to 83		18 to 84		15 to 94		15 to 94	
Race										
American Indian Or Alaska Native	1	(0.7)	0	(0.0)	2	(0.5)	29	(0.5)	42	(0.5)
Asian	13	(8.8)	13	(8.6)	25	(6.4)	658	(11.2)	1,209	(14.9)
Black Or African American	4	(2.7)	8	(5.3)	11	(2.8)	108	(1.8)	138	(1.7)
Multiracial	4	(2.7)	5	(3.3)	7	(1.8)	66	(1.1)	85	(1.1)
Native Hawaiian Or Other Pacific Islander	1	(0.7)	0	(0.0)	1	(0.3)	4	(0.1)	9	(0.1)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.0)
White	116	(78.4)	114	(75.0)	330	(84.8)	4,444	(75.5)	5,957	(73.6)
Missing	9	(6.1)	12	(7.9)	13	(3.3)	575	(9.8)	649	(8.0)
Ethnicity										
Hispanic Or Latino	24	(16.2)	20	(13.2)	41	(10.5)	389	(6.6)	531	(6.6)
Not Hispanic Or Latino	109	(73.6)	114	(75.0)	288	(74.0)	4,690	(79.7)	6,588	(81.4)
Not Reported	8	(5.4)	10	(6.6)	34	(8.7)	181	(3.1)	291	(3.6)
Unknown	5	(3.4)	5	(3.3)	24	(6.2)	110	(1.9)	156	(1.9)
Missing	2	(1.4)	3	(2.0)	2	(0.5)	514	(8.7)	527	(6.5)
Age Class (Years)										
<65	122	(82.4)	130	(85.5)	343	(88.2)	3,385	(57.5)	4,640	(57.3)
65-74	17	(11.5)	16	(10.5)	36	(9.3)	1,737	(29.5)	2,419	(29.9)
75-84	9	(6.1)	6	(3.9)	10	(2.6)	663	(11.3)	905	(11.2)
>=85	0	(0.0)	0	(0.0)	0	(0.0)	99	(1.7)	129	(1.6)

Geographic Region										
EU	47	(31.8)	45	(29.6)	168	(43.2)	2,092	(35.6)	2,801	(34.6)
Ex-EU	101	(68.2)	107	(70.4)	221	(56.8)	3,792	(64.4)	5,292	(65.4)
ECOG Performance Scale										
[0] Normal Activity	84	(56.8)	99	(65.1)	200	(51.4)	2,761	(46.9)	3,723	(46.0)
[1] Symptoms, but ambulatory	63	(42.6)	53	(34.9)	187	(48.1)	2,931	(49.8)	4,059	(50.2)
Other/Missing	1	(0.7)	0	(0.0)	2	(0.5)	192	(3.3)	201	(2.5)
Not Collected per Protocol	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	110	(1.4)

Safety results from participants treated with pembrolizumab in KEYNOTE-204 was the primary focus of this submission. KEYNOTE-204 is an ongoing, Phase 3, randomized, open-label study of pembrolizumab (200 mg Q3W) compared with BV (1.8 mg/kg Q3W) in participants with cHL. All participants had either failed treatment that included auto-SCT or had received at least 1 multi-agent chemotherapy regimen if they were not candidates for auto-SCT before enrolling in KEYNOTE-204. Participants who had received BV or BV containing regimen were enrolled in the study if they had responded (partial or complete) to the BV or BV-containing regimen.

In KEYNOTE-204, the median exposure to pembrolizumab was twice as long as the median exposure to BV (10.02 months vs 4.81 months). Overall, 48% (71/148) of participants in the KEYNOTE-204 were on treatment for ≥12 months, with a median of 15 administrations compared with 11.2% (17/152) of participants in the BV group on treatment for ≥12 months and a median of 7 administrations (Table 3b). The median duration of follow-up was 24.9 months (range: 1.8 to 42.0 months) in the pembrolizumab arm and 24.3 months (range: 0.6 to 42.3 months) in the BV arm. Median exposure to pembrolizumab was similar between the KEYNOTE-204 pembrolizumab arm and the cHL Safety Dataset, in which 389 patients received at least 1 dose of pembrolizumab, 46.8% (182/389) remained on treatment for ≥12 months (median of 10.65 months) and received a median of 16 administrations. In the RSD, exposure to pembrolizumab was lower (median of 4.86 months), with 21.8% of the participants on treatment for ≥12 months and a median of 8 administrations.

Table 64 ***Summary of Drug Exposure***

	KN204 Data for Pembrolizumab‡‡ (N=148)	KN204 Data for Brentuximab Vedotin¶ (N=152)	cHL Safety Data for Pembrolizumab‖ (N=389)	Reference Safety Dataset for Pembrolizumab†† (N=5884)	Cumulative Running Safety Dataset for Pembrolizumab‡‡ (N=8093)
Duration on therapy (Months)					
Mean	12.2	6.1	12.5	7.3	7.1
Median	10.02	4.81	10.65	4.86	4.24
SD	8.18	5.43	8.25	6.79	7.20
Range	0.03 to 26.74	0.03 to 26.09	0.03 to 27.93	0.03 to 32.46	0.03 to 53.42
Number of Administrations					
Mean	18.1	9.3	19.0	11.6	11.4
Median	15.00	7.00	16.00	8.00	7.00
SD	11.61	7.32	12.16	10.17	10.65

Table 65 ***Drug Exposure by Duration***

	KN204 Data for Pembrolizumab[††] (N=148)			KN204 Data for Brentuximab Vedotin[¶] (N=152)			cHL Safety Data for Pembrolizumab[‡] (N=389)			Reference Safety Dataset for Pembrolizumab[77] (N=5884)			Cumulative Running Safety Dataset for Pembrolizumab[§§] (N=8093)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure															
>0 m	148	(100.0)	(150.7)	152	(100.0)	(76.9)	389	(100.0)	(405.8)	5,884	(100.0)	(3,555.4)	8,093	(100.0)	(4,810.6)
>=1 m	147	(99.3)	(150.7)	142	(93.4)	(76.4)	382	(98.2)	(405.7)	5,033	(85.5)	(3,527.2)	6,880	(85.0)	(4,770.3)
>=3 m	128	(86.5)	(147.3)	99	(65.1)	(68.7)	347	(89.2)	(399.3)	3,620	(61.5)	(3,291.9)	4,826	(59.6)	(4,431.0)
>=6 m	100	(67.6)	(137.1)	49	(32.2)	(49.5)	271	(69.7)	(371.3)	2,612	(44.4)	(2,926.0)	3,376	(41.7)	(3,907.0)
>=12 m	71	(48.0)	(116.9)	17	(11.2)	(27.0)	182	(46.8)	(308.2)	1,281	(21.8)	(1,915.3)	1,705	(21.1)	(2,656.3)

Adverse events

Safety and tolerability have been evaluated during the treatment period up to the cut-off date of 16-Jun-2020 for KEYNOTE-204. Adverse events, occurred from the first dose up to 30 days after the last dose, were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Most AEs were of low-grade toxicity, as evidenced by the low rate of subjects with toxicity Grade 3 to 5 drug-related AEs (62 [15.9%]) and with serious drug-related adverse events (46 [11.8%]) in the 389-subject cHL population (cHL Safety Dataset).

In study KEYNOTE-204, some differences were observed in AEs between the KEYNOTE-204 pembrolizumab safety dataset and the BV group, as the incidence of SAEs and the drug-related SAEs was higher in the pembrolizumab arm than in the BV group (SAEs 29.7% vs 21.1%, respectively; drug-related SAEs 16.2% vs 10.5%, respectively). However, when adjusted for exposure, the event rates for SAEs and drug-related SAEs were similar between groups, whereas the event rates for AEs and Grade 3 to 5 AEs were higher in the BV arm than in the KEYNOTE-204 pembrolizumab group. Deaths due to AEs occurred in 3 (2%) pembrolizumab participants vs 2 (1.3%) BV participants; for 1 (0.7%) pembrolizumab participant, death was reported as drug related, while none of the 2 BV death was attributed to the drug.

Table 66 ***Summary of Adverse Events***

	KN204 Data for Pembrolizumab[††]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‡]		Reference Safety Dataset for Pembrolizumab[77]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	145	(98.0)	143	(94.1)	381	(97.9)	5,690	(96.7)	7,811	(96.5)
with no adverse event	3	(2.0)	9	(5.9)	8	(2.1)	194	(3.3)	282	(3.5)
with drug-related[†] adverse events	110	(74.3)	117	(77.0)	285	(73.3)	4,132	(70.2)	5,578	(68.9)
with toxicity grade 3-5 adverse events	65	(43.9)	66	(43.4)	147	(37.8)	2,829	(48.1)	3,936	(48.6)
with toxicity grade 3-5 drug-related adverse events	29	(19.6)	38	(25.0)	62	(15.9)	913	(15.5)	1,297	(16.0)
with serious adverse events	44	(29.7)	32	(21.1)	104	(26.7)	2,266	(38.5)	3,090	(38.2)
with serious drug-related adverse events	24	(16.2)	16	(10.5)	46	(11.8)	656	(11.1)	917	(11.3)
who died	3	(2.0)	2	(1.3)	6	(1.5)	312	(5.3)	444	(5.5)
who died due to a drug-related adverse event	1	(0.7)	0	(0.0)	1	(0.3)	39	(0.7)	61	(0.8)
discontinued drug due to an adverse event	20	(13.5)	27	(17.8)	41	(10.5)	790	(13.4)	1,047	(12.9)
discontinued drug due to a drug-related adverse event	19	(12.8)	25	(16.4)	36	(9.3)	410	(7.0)	551	(6.8)
discontinued drug due to a serious adverse event	14	(9.5)	8	(5.3)	24	(6.2)	572	(9.7)	760	(9.4)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	13	(8.8)	6	(3.9)	20	(5.1)	245	(4.2)	334	(4.1)

[†] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[‡‡] Includes all subjects who received at least one dose of Pembrolizumab in KN204.
[¶] Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
[‖] Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
[††] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
[§§] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 67 ***Summary of Exposure-Adjusted Adverse Event***

	Event Count and Rate (Events/100 person-months)[†]				
	KN204 Data for Pembrolizumab[‡‡]	KN204 Data for Brentuximab Vedotin[¶]	cHL Safety Data for Pembrolizumab[‖]	Reference Safety Dataset for Pembrolizumab[††]	Cumulative Running Safety Dataset for Pembrolizumab[§§]
Number of subjects exposed	148	152	389	5884	8093
Total exposure[‡] in person-months	1942.88	1070.52	5242.42	47883.80	63619.08
Total events (rate)					
adverse events	1366 (70.31)	1176 (109.85)	4182 (79.77)	61624 (128.69)	81093 (127.47)
drug-related[‡] adverse events	487 (25.07)	507 (47.36)	1247 (23.79)	19294 (40.29)	24566 (38.61)
toxicity grade 3-5 adverse events	117 (6.02)	151 (14.11)	285 (5.44)	6163 (12.87)	8689 (13.66)
toxicity grade 3-5 drug-related adverse events	46 (2.37)	73 (6.82)	94 (1.79)	1375 (2.87)	1960 (3.08)
serious adverse events	69 (3.55)	48 (4.48)	163 (3.11)	4094 (8.55)	5500 (8.65)
serious drug-related adverse events	35 (1.80)	19 (1.77)	61 (1.16)	916 (1.91)	1271 (2.00)
adverse events leading to death	3 (0.15)	2 (0.19)	6 (0.11)	319 (0.67)	453 (0.71)
drug-related adverse events leading to death	1 (0.05)	0 (0.00)	1 (0.02)	39 (0.08)	61 (0.10)
adverse events resulting in drug discontinuation	20 (1.03)	30 (2.80)	43 (0.82)	863 (1.80)	1129 (1.77)
drug-related adverse events resulting in drug discontinuation	19 (0.98)	27 (2.52)	38 (0.72)	448 (0.94)	593 (0.93)
serious adverse events resulting in drug discontinuation	14 (0.72)	8 (0.75)	26 (0.50)	609 (1.27)	801 (1.26)
serious drug-related adverse events resulting in drug discontinuation	13 (0.67)	6 (0.56)	22 (0.42)	259 (0.54)	351 (0.55)

In KEYNOTE-204, participants had received a median of 2 (range: 1 to 10) or 3 (range: 1 to 11) prior lines of therapy for pembrolizumab and BV, respectively, and the percentage of patients with primary refractory disease and prior auto-SCT was 40.4% and 37.1% in the pembrolizumab arm versus 40.5% and 36.6% in the BV arm. Prior use of BV was reported for 3.3% of patients in the pembrolizumab arm vs 6.5% in the BV group. Considering the inclusion criteria, a quite heterogeneous population in terms of prior exposure and response to previous therapy (including brentuximab, radiation therapy and auto-SCT), was enrolled in the KEYNOTE-204. As only 5 participants received prior BV in the pembrolizumab arm in KEYNOTE-204, comparison of AEs by prior BV status does not allow for a meaningful comparison.

Table 68: AE summary by prior BV status (ASaT population)

	Prior BV		No Prior BV	
	n	(%)	n	(%)
Subjects in population	5		143	
with one or more adverse events	4	(80.0)	141	(98.6)
with no adverse event	1	(20.0)	2	(1.4)
with drug-related† adverse events	3	(60.0)	107	(74.8)
with toxicity grade 3-5 adverse events	4	(80.0)	61	(42.7)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	29	(20.3)
with non-serious adverse events	4	(80.0)	140	(97.9)
with serious adverse events	3	(60.0)	41	(28.7)
with serious drug-related adverse events	0	(0.0)	24	(16.8)
who died	0	(0.0)	3	(2.1)
who died due to a drug-related adverse event	0	(0.0)	1	(0.7)
discontinued drug due to an adverse event	0	(0.0)	20	(14.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	19	(13.3)
discontinued drug due to a serious adverse event	0	(0.0)	14	(9.8)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	13	(9.1)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adae]

Table 69: AEs by prior radiation status

	Prior Radiation		No Prior Radiation	
	n	(%)	n	(%)
Subjects in population	58		90	
with one or more adverse events	58	(100.0)	87	(96.7)
with no adverse event	0	(0.0)	3	(3.3)
with drug-related† adverse events	43	(74.1)	67	(74.4)
with toxicity grade 3-5 adverse events	27	(46.6)	38	(42.2)
with toxicity grade 3-5 drug-related adverse events	13	(22.4)	16	(17.8)
with non-serious adverse events	58	(100.0)	86	(95.6)
with serious adverse events	19	(32.8)	25	(27.8)
with serious drug-related adverse events	12	(20.7)	12	(13.3)
who died	2	(3.4)	1	(1.1)
who died due to a drug-related adverse event	1	(1.7)	0	(0.0)
discontinued drug due to an adverse event	9	(15.5)	11	(12.2)
discontinued drug due to a drug-related adverse event	9	(15.5)	10	(11.1)
discontinued drug due to a serious adverse event	8	(13.8)	6	(6.7)
discontinued drug due to a serious drug-related adverse event	8	(13.8)	5	(5.6)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adae]

Table 70 AEs by prior auto-SCT status.

	Prior Auto-SCT		No Prior Auto-SCT	
	n	(%)	n	(%)
Subjects in population	55		93	
with one or more adverse events	53	(96.4)	92	(98.9)
with no adverse event	2	(3.6)	1	(1.1)
with drug-related† adverse events	42	(76.4)	68	(73.1)
with toxicity grade 3-5 adverse events	26	(47.3)	39	(41.9)
with toxicity grade 3-5 drug-related adverse events	14	(25.5)	15	(16.1)
with non-serious adverse events	53	(96.4)	91	(97.8)
with serious adverse events	21	(38.2)	23	(24.7)
with serious drug-related adverse events	10	(18.2)	14	(15.1)
who died	2	(3.6)	1	(1.1)
who died due to a drug-related adverse event	1	(1.8)	0	(0.0)
discontinued drug due to an adverse event	7	(12.7)	13	(14.0)
discontinued drug due to a drug-related adverse event	6	(10.9)	13	(14.0)
discontinued drug due to a serious adverse event	7	(12.7)	7	(7.5)
discontinued drug due to a serious drug-related adverse event	6	(10.9)	7	(7.5)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adae]

Table 71 AEs by prior line of therapy

	One Prior Line		Two Prior Lines		Three or More Prior Lines	
	n	(%)	n	(%)	n	(%)
Subjects in population	27		50		71	
with one or more adverse events	27	(100.0)	49	(98.0)	69	(97.2)
with no adverse event	0	(0.0)	1	(2.0)	2	(2.8)
with drug-related† adverse events	21	(77.8)	34	(68.0)	55	(77.5)
with toxicity grade 3-5 adverse events	10	(37.0)	22	(44.0)	33	(46.5)
with toxicity grade 3-5 drug-related adverse events	1	(3.7)	12	(24.0)	16	(22.5)
with non-serious adverse events	26	(96.3)	49	(98.0)	69	(97.2)
with serious adverse events	8	(29.6)	12	(24.0)	24	(33.8)
with serious drug-related adverse events	3	(11.1)	8	(16.0)	13	(18.3)
who died	0	(0.0)	1	(2.0)	2	(2.8)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(1.4)
discontinued drug due to an adverse event	4	(14.8)	8	(16.0)	8	(11.3)
discontinued drug due to a drug-related adverse event	4	(14.8)	7	(14.0)	8	(11.3)
discontinued drug due to a serious adverse event	1	(3.7)	6	(12.0)	7	(9.9)
discontinued drug due to a serious drug-related adverse event	1	(3.7)	5	(10.0)	7	(9.9)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 16JAN2020

Summaries of AEs by subgroups (i.e., age [<65 vs ≥65 years; <65 vs ≥65 to <75 vs ≥75 to <85 years], gender, race, ECOG status and region [North America vs Europe vs Japan; US vs non-US; EU vs non-EU]) are provided in the KEYNOTE-204 CSR.

Table 72 Comparison of the safety data of KEYNOTE-204 ,KEYNOTE-087, KEYNOTE-013

	KN204 Data for Pembrolizumab[H]		KN087 Data for Pembrolizumab[k]		KN013 Data for Pembrolizumab[l]		Reference Safety Dataset for Pembrolizumab[m]		Cumulative Running Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		210		31		5,884		8,093	
with one or more adverse events	145	(98.0)	205	(97.6)	31	(100.0)	5,690	(96.7)	7,811	(96.5)
with no adverse event	3	(2.0)	5	(2.4)	0	(0.0)	194	(3.3)	282	(3.5)
with drug-related[f] adverse events	110	(74.3)	153	(72.9)	22	(71.0)	4,132	(70.2)	5,578	(68.9)
with toxicity grade 3-5 adverse events	65	(43.9)	69	(32.9)	13	(41.9)	2,829	(48.1)	3,936	(48.6)
with toxicity grade 3-5 drug-related adverse events	29	(19.6)	27	(12.9)	6	(19.4)	913	(15.5)	1,297	(16.0)
with serious adverse events	44	(29.7)	48	(22.9)	12	(38.7)	2,266	(38.5)	3,090	(38.2)
with serious drug-related adverse events	24	(16.2)	17	(8.1)	5	(16.1)	656	(11.1)	917	(11.3)
who died	3	(2.0)	3	(1.4)	0	(0.0)	312	(5.3)	444	(5.5)
who died due to a drug-related adverse event	1	(0.7)	0	(0.0)	0	(0.0)	39	(0.7)	61	(0.8)
discontinued drug due to an adverse event	20	(13.5)	18	(8.6)	3	(9.7)	790	(13.4)	1,047	(12.9)
discontinued drug due to a drug-related adverse event	19	(12.8)	14	(6.7)	3	(9.7)	410	(7.0)	551	(6.8)
discontinued drug due to a serious adverse event	14	(9.5)	10	(4.8)	0	(0.0)	572	(9.7)	760	(9.4)
discontinued drug due to a serious drug-related adverse event	13	(8.8)	7	(3.3)	0	(0.0)	245	(4.2)	334	(4.1)

Table 73 Exposure adjusted Comparison of KEYNOTE-204, KEYNOTE-087, KEYNOTE-013 safety data

	Event Count and Rate (Events/100 person-months)[r]		
	KN204 Data for Pembrolizumab[H]	KN087 Data for Pembrolizumab[k]	KN013 Data for Pembrolizumab[l]
Number of subjects exposed	148	210	31
Total exposure[s] in person-months	1942.88	2936.03	363.51
Total events (rate)			
adverse events	1366 (70.31)	2409 (82.05)	407 (111.96)
drug-related[f] adverse events	487 (25.07)	667 (22.72)	93 (25.58)
toxicity grade 3-5 adverse events	117 (6.02)	142 (4.84)	26 (7.15)
toxicity grade 3-5 drug-related adverse events	46 (2.37)	41 (1.40)	7 (1.93)
serious adverse events	69 (3.55)	72 (2.45)	22 (6.05)
serious drug-related adverse events	35 (1.80)	21 (0.72)	5 (1.38)
adverse events leading to death	3 (0.15)	3 (0.10)	0 (0.00)
drug-related adverse events leading to death	1 (0.05)	0 (0.00)	0 (0.00)
adverse events resulting in drug discontinuation	20 (1.03)	20 (0.68)	3 (0.83)
drug-related adverse events resulting in drug discontinuation	19 (0.98)	16 (0.54)	3 (0.83)
serious adverse events resulting in drug discontinuation	14 (0.72)	12 (0.41)	0 (0.00)
serious drug-related adverse events resulting in drug discontinuation	13 (0.67)	9 (0.31)	0 (0.00)

	KN204 Data for Pembrolizumab[H]		KN087 Data for Pembrolizumab[k]		KN013 Data for Pembrolizumab[l]		Reference Safety Dataset for Pembrolizumab[m]		Cumulative Running Safety Dataset for Pembrolizumab[n]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		210		31		5,884		8,093	
with one or more adverse events	53	(35.8)	72	(34.3)	14	(45.2)	1,474	(25.1)	1,973	(24.4)
with no adverse event	95	(64.2)	138	(65.7)	17	(54.8)	4,410	(74.9)	6,120	(75.6)
with drug-related[f] adverse events	43	(29.1)	68	(32.4)	12	(38.7)	1,281	(21.8)	1,718	(21.2)
with toxicity grade 3-5 adverse events	11	(7.4)	9	(4.3)	3	(9.7)	381	(6.5)	517	(6.4)
with toxicity grade 3-5 drug-related adverse events	9	(6.1)	7	(3.3)	2	(6.5)	331	(5.6)	454	(5.6)
with serious adverse events	13	(8.8)	9	(4.3)	3	(9.7)	381	(6.5)	502	(6.2)
with serious drug-related adverse events	12	(8.1)	8	(3.8)	2	(6.5)	337	(5.7)	449	(5.5)
with dose modification[t] due to an adverse event	21	(14.2)	25	(11.9)	5	(16.1)	534	(9.1)	707	(8.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
discontinued drug due to an adverse event	13	(8.8)	14	(6.7)	3	(9.7)	232	(3.9)	311	(3.8)
discontinued drug due to a drug-related adverse event	13	(8.8)	13	(6.2)	3	(9.7)	228	(3.9)	307	(3.8)
discontinued drug due to a serious adverse event	10	(6.8)	7	(3.3)	0	(0.0)	156	(2.7)	204	(2.5)
discontinued drug due to a serious drug-related adverse event	10	(6.8)	7	(3.3)	0	(0.0)	154	(2.6)	202	(2.5)

Common adverse events

In the KEYNOTE-204, the most frequent reported AEs (incidence >10%) were as follows:

- *diarrhea* (19.6%), *pyrexia* (19.6%), *hypothyroidism* (18.9%) and *upper respiratory tract infection* (18.9%) in the Pembrolizumab Safety Dataset;
- *nausea* (24.3%), *vomiting* (19.7%), *fatigue* (18.4%) and *neuropathy peripheral* (18.4%) in the BV arm.

The overall frequency and the type of AEs reported in the KEYNOTE-204 pembrolizumab arm were generally consistent with the cHL Safety Dataset.

In comparison with the RSD and the CSD, the AEs that were most frequently reported (≥5 percentage point difference) in the KEYNOTE-204 pembrolizumab arm than in the RSD were:

- *pyrexia* (19.6% vs 12.7% and 12.6%, respectively), *hypothyroidism* (18.9% vs 11.1% and 10.8%, respectively), *upper respiratory tract infection* (18.9% vs 6.6% and 6.4%, respectively) and *nasopharyngitis* (11.5% vs 6.1 and 5.8%, respectively).

Table 74 ***Subjects with Adverse Events (incidence > 0% in one or more treatment groups) by decreasing frequency of preferred term***

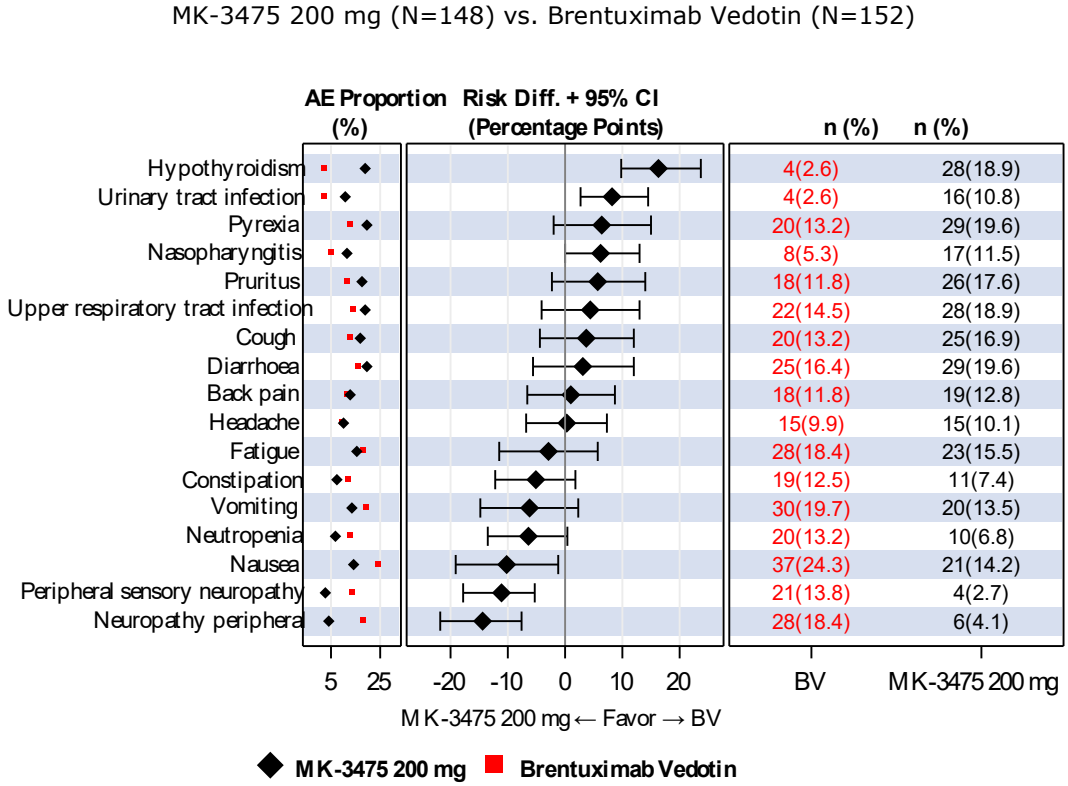
	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	145	(98.0)	143	(94.1)	381	(97.9)	5,690	(96.7)	7,811	(96.5)
with no adverse events	3	(2.0)	9	(5.9)	8	(2.1)	194	(3.3)	282	(3.5)
Diarrhoea	29	(19.6)	25	(16.4)	84	(21.6)	1,200	(20.4)	1,596	(19.7)
Pyrexia	29	(19.6)	20	(13.2)	98	(25.2)	746	(12.7)	1,021	(12.6)
Hypothyroidism	28	(18.9)	4	(2.6)	66	(17.0)	651	(11.1)	873	(10.8)
Upper Respiratory Tract Infection	28	(18.9)	22	(14.5)	74	(19.0)	387	(6.6)	518	(6.4)
Pruritus	26	(17.6)	18	(11.8)	64	(16.5)	1,060	(18.0)	1,379	(17.0)
Cough	25	(16.9)	20	(13.2)	92	(23.7)	1,148	(19.5)	1,493	(18.4)
Fatigue	23	(15.5)	28	(18.4)	76	(19.5)	1,884	(32.0)	2,462	(30.4)
Nausea	21	(14.2)	37	(24.3)	67	(17.2)	1,213	(20.6)	1,637	(20.2)
Vomiting	20	(13.5)	30	(19.7)	64	(16.5)	732	(12.4)	1,023	(12.6)
Back Pain	19	(12.8)	18	(11.8)	48	(12.3)	662	(11.3)	896	(11.1)
Nasopharyngitis	17	(11.5)	8	(5.3)	55	(14.1)	360	(6.1)	472	(5.8)
Urinary Tract Infection	16	(10.8)	4	(2.6)	31	(8.0)	384	(6.5)	519	(6.4)
Headache	15	(10.1)	15	(9.9)	47	(12.1)	711	(12.1)	870	(10.8)
Alanine Aminotransferase Increased	13	(8.8)	15	(9.9)	27	(6.9)	393	(6.7)	563	(7.0)
Arthralgia	13	(8.8)	11	(7.2)	44	(11.3)	851	(14.5)	1,073	(13.3)
Pain In Extremity	13	(8.8)	7	(4.6)	24	(6.2)	391	(6.6)	486	(6.0)
Pneumonitis	13	(8.8)	3	(2.0)	27	(6.9)	242	(4.1)	305	(3.8)
Rash	13	(8.8)	13	(8.6)	50	(12.9)	904	(15.4)	1,117	(13.8)
Aspartate Aminotransferase Increased	12	(8.1)	11	(7.2)	24	(6.2)	384	(6.5)	596	(7.4)
Oropharyngeal Pain	12	(8.1)	5	(3.3)	36	(9.3)	196	(3.3)	265	(3.3)
Pneumonia	12	(8.1)	9	(5.9)	30	(7.7)	433	(7.4)	563	(7.0)
Constipation	11	(7.4)	19	(12.5)	42	(10.8)	995	(16.9)	1,361	(16.8)
Dyspnoea	11	(7.4)	9	(5.9)	47	(12.1)	989	(16.8)	1,227	(15.2)
Abdominal Pain	10	(6.8)	15	(9.9)	27	(6.9)	480	(8.2)	762	(9.4)
Neutropenia	10	(6.8)	20	(13.2)	23	(5.9)	49	(0.8)	86	(1.1)
Weight Increased	10	(6.8)	2	(1.3)	21	(5.4)	190	(3.2)	225	(2.8)
Anaemia	9	(6.1)	13	(8.6)	36	(9.3)	836	(14.2)	1,215	(15.0)
Decreased Appetite	9	(6.1)	14	(9.2)	25	(6.4)	1,136	(19.3)	1,564	(19.3)
Thrombocytopenia	9	(6.1)	8	(5.3)	21	(5.4)	89	(1.5)	132	(1.6)
Asthenia	8	(5.4)	7	(4.6)	33	(8.5)	666	(11.3)	914	(11.3)
Hyperthyroidism	8	(5.4)	1	(0.7)	17	(4.4)	247	(4.2)	352	(4.3)
Rhinitis	8	(5.4)	5	(3.3)	19	(4.9)	107	(1.8)	137	(1.7)
Sinusitis	8	(5.4)	3	(2.0)	31	(8.0)	146	(2.5)	186	(2.3)
Anxiety	7	(4.7)	12	(7.9)	20	(5.1)	248	(4.2)	326	(4.0)
Chills	7	(4.7)	4	(2.6)	24	(6.2)	249	(4.2)	313	(3.9)
Depression	7	(4.7)	4	(2.6)	17	(4.4)	187	(3.2)	237	(2.9)
Dyspepsia	7	(4.7)	9	(5.9)	16	(4.1)	149	(2.5)	226	(2.8)
Musculoskeletal Pain	7	(4.7)	5	(3.3)	16	(4.1)	395	(6.7)	504	(6.2)
Myalgia	7	(4.7)	10	(6.6)	30	(7.7)	430	(7.3)	552	(6.8)
Nasal Congestion	7	(4.7)	3	(2.0)	34	(8.7)	150	(2.5)	192	(2.4)
Oedema Peripheral	7	(4.7)	3	(2.0)	21	(5.4)	512	(8.7)	707	(8.7)
Paraesthesia	7	(4.7)	10	(6.6)	13	(3.3)	157	(2.7)	187	(2.3)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Abdominal Pain Upper	6	(4.1)	5	(3.3)	13	(3.3)	213	(3.6)	319	(3.9)
Dizziness	6	(4.1)	5	(3.3)	15	(3.9)	430	(7.3)	543	(6.7)
Erythema	6	(4.1)	3	(2.0)	13	(3.3)	167	(2.8)	196	(2.4)
Influenza	6	(4.1)	1	(0.7)	14	(3.6)	118	(2.0)	153	(1.9)
Insomnia	6	(4.1)	7	(4.6)	31	(8.0)	429	(7.3)	569	(7.0)
Neck Pain	6	(4.1)	5	(3.3)	9	(2.3)	200	(3.4)	250	(3.1)
Neuropathy Peripheral	6	(4.1)	28	(18.4)	18	(4.6)	116	(2.0)	156	(1.9)
Productive Cough	6	(4.1)	7	(4.6)	22	(5.7)	266	(4.5)	344	(4.3)
Blood Creatinine Increased	5	(3.4)	2	(1.3)	13	(3.3)	256	(4.4)	379	(4.7)
Infusion Related Reaction	5	(3.4)	12	(7.9)	16	(4.1)	56	(1.0)	80	(1.0)
Pharyngitis	5	(3.4)	2	(1.3)	11	(2.8)	52	(0.9)	70	(0.9)
Rhinitis Allergic	5	(3.4)	2	(1.3)	8	(2.1)	69	(1.2)	86	(1.1)
Weight Decreased	5	(3.4)	11	(7.2)	14	(3.6)	561	(9.5)	746	(9.2)
Acute Kidney Injury	4	(2.7)	1	(0.7)	8	(2.1)	113	(1.9)	173	(2.1)
Blood Alkaline Phosphatase Increased	4	(2.7)	7	(4.6)	12	(3.1)	240	(4.1)	369	(4.6)
Blood Thyroid Stimulating Hormone Decreased	4	(2.7)	0	(0.0)	4	(1.0)	56	(1.0)	73	(0.9)
Blood Thyroid Stimulating Hormone Increased	4	(2.7)	0	(0.0)	11	(2.8)	97	(1.6)	132	(1.6)
Bronchitis	4	(2.7)	4	(2.6)	24	(6.2)	171	(2.9)	214	(2.6)
Chest Pain	4	(2.7)	2	(1.3)	14	(3.6)	307	(5.2)	384	(4.7)
Dry Skin	4	(2.7)	3	(2.0)	18	(4.6)	304	(5.2)	390	(4.8)
Dyspnoea Exertional	4	(2.7)	0	(0.0)	8	(2.1)	120	(2.0)	145	(1.8)
Dysuria	4	(2.7)	1	(0.7)	11	(2.8)	90	(1.5)	144	(1.8)
Gastroenteritis	4	(2.7)	0	(0.0)	13	(3.3)	50	(0.8)	65	(0.8)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Herpes Zoster	4	(2.7)	5	(3.3)	17	(4.4)	55	(0.9)	84	(1.0)
Hyperglycaemia	4	(2.7)	3	(2.0)	16	(4.1)	289	(4.9)	413	(5.1)
Lymphopenia	4	(2.7)	4	(2.6)	5	(1.3)	66	(1.1)	82	(1.0)
Muscle Spasms	4	(2.7)	6	(3.9)	19	(4.9)	147	(2.5)	188	(2.3)
Oral Herpes	4	(2.7)	1	(0.7)	11	(2.8)	49	(0.8)	65	(0.8)
Peripheral Sensory Neuropathy	4	(2.7)	21	(13.8)	13	(3.3)	64	(1.1)	90	(1.1)
Skin Lesion	4	(2.7)	1	(0.7)	7	(1.8)	89	(1.5)	107	(1.3)
Stomatitis	4	(2.7)	4	(2.6)	14	(3.6)	144	(2.4)	198	(2.4)
Dermatitis Allergic	3	(2.0)	0	(0.0)	4	(1.0)	12	(0.2)	19	(0.2)
Dry Mouth	3	(2.0)	3	(2.0)	9	(2.3)	284	(4.8)	373	(4.6)
Ear Infection	3	(2.0)	2	(1.3)	8	(2.1)	29	(0.5)	36	(0.4)
Eczema	3	(2.0)	3	(2.0)	8	(2.1)	94	(1.6)	129	(1.6)
Gastrooesophageal Reflux Disease	3	(2.0)	4	(2.6)	4	(1.0)	117	(2.0)	173	(2.1)
Haematuria	3	(2.0)	1	(0.7)	8	(2.1)	155	(2.6)	231	(2.9)
Herpes Simplex	3	(2.0)	1	(0.7)	5	(1.3)	9	(0.2)	16	(0.2)
Hyperkalaemia	3	(2.0)	1	(0.7)	4	(1.0)	149	(2.5)	212	(2.6)
Hypokalaemia	3	(2.0)	6	(3.9)	14	(3.6)	270	(4.6)	377	(4.7)
Hypotension	3	(2.0)	1	(0.7)	8	(2.1)	166	(2.8)	226	(2.8)
Immune Thrombocytopenic Purpura	3	(2.0)	0	(0.0)	3	(0.8)	3	(0.1)	7	(0.1)
Influenza Like Illness	3	(2.0)	3	(2.0)	12	(3.1)	227	(3.9)	286	(3.5)
Interstitial Lung Disease	3	(2.0)	1	(0.7)	4	(1.0)	22	(0.4)	36	(0.4)
Neutrophil Count Decreased	3	(2.0)	10	(6.6)	3	(0.8)	37	(0.6)	56	(0.7)
Pain	3	(2.0)	2	(1.3)	11	(2.8)	180	(3.1)	216	(2.7)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Pelvic Pain	3	(2.0)	0	(0.0)	4	(1.0)	43	(0.7)	60	(0.7)
Rash Maculo-Papular	3	(2.0)	5	(3.3)	9	(2.3)	202	(3.4)	282	(3.5)
Renal Impairment	3	(2.0)	0	(0.0)	3	(0.8)	18	(0.3)	25	(0.3)
Respiratory Tract Infection	3	(2.0)	2	(1.3)	14	(3.6)	95	(1.6)	115	(1.4)
Rhinorrhoea	3	(2.0)	1	(0.7)	22	(5.7)	114	(1.9)	140	(1.7)
Tachycardia	3	(2.0)	1	(0.7)	6	(1.5)	85	(1.4)	128	(1.6)
Tinnitus	3	(2.0)	1	(0.7)	8	(2.1)	53	(0.9)	64	(0.8)
Tumour Pain	3	(2.0)	0	(0.0)	5	(1.3)	97	(1.6)	128	(1.6)
Urticaria	3	(2.0)	0	(0.0)	10	(2.6)	51	(0.9)	73	(0.9)
Wheezing	3	(2.0)	2	(1.3)	8	(2.1)	88	(1.5)	107	(1.3)
Acarodermatitis	2	(1.4)	0	(0.0)	2	(0.5)	2	(0.0)	6	(0.1)
Ankle Fracture	2	(1.4)	1	(0.7)	2	(0.5)	3	(0.1)	5	(0.1)
Blood Bilirubin Increased	2	(1.4)	0	(0.0)	4	(1.0)	125	(2.1)	198	(2.4)
Confusional State	2	(1.4)	0	(0.0)	3	(0.8)	99	(1.7)	136	(1.7)
Conjunctivitis	2	(1.4)	1	(0.7)	11	(2.8)	76	(1.3)	90	(1.1)
Dehydration	2	(1.4)	3	(2.0)	6	(1.5)	208	(3.5)	293	(3.6)
Dental Caries	2	(1.4)	0	(0.0)	6	(1.5)	22	(0.4)	30	(0.4)
Dermatitis Acneiform	2	(1.4)	2	(1.3)	4	(1.0)	73	(1.2)	87	(1.1)
Dysgeusia	2	(1.4)	1	(0.7)	5	(1.3)	110	(1.9)	148	(1.8)
Febrile Neutropenia	2	(1.4)	1	(0.7)	4	(1.0)	7	(0.1)	13	(0.2)
Feeling Cold	2	(1.4)	0	(0.0)	6	(1.5)	22	(0.4)	28	(0.3)
Folliculitis	2	(1.4)	1	(0.7)	2	(0.5)	30	(0.5)	36	(0.4)
Gait Disturbance	2	(1.4)	0	(0.0)	3	(0.8)	37	(0.6)	55	(0.7)

Figure 40 ***Between-treatment Comparisons in Selected Adverse Events (incidence >=10% in one or more treatment groups) and sorted by risk difference***



The incidence of *urinary tract infection* (10.8%) reported in the KEYNOTE-204 pembrolizumab arm was higher than the cHL safety dataset (8%), the RSD (6.5%), the CSD (6.4%) and slightly higher compared to the incidence of urinary tract infection (7.1%) reported in KEYNOTE-087. This discrepancy was also observed for *pneumonitis* (8.8% in the pembrolizumab arm vs 6.9% in the cHL safety dataset, 4.1% in the RSD and 3.8% in the CSD).

Drug-related Adverse Events

In KEYNOTE-204, the most frequently reported drug-related AEs in the pembrolizumab safety dataset, compared with the BV arm, were *hypothyroidism* (15.5% vs 1.3%), *pyrexia* (12.8% vs 5.9%) and *pruritus* (10.8% vs 5.3%). Conversely, the BV group showed higher incidences of drug-related *neuropathy peripheral* (2% vs 18.4%), *nausea* (4.1% vs 13.2%) and *peripheral sensory neuropathy* (2% vs 13.2%).

Table 75 ***Subjects with Drug-related Adverse Events (incidence >5% in one or more treatment groups) by decreasing frequency of preferred term***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	110	(74.3)	117	(77.0)	285	(73.3)	4,132	(70.2)	5,578	(68.9)
with no adverse events	38	(25.7)	35	(23.0)	104	(26.7)	1,752	(29.8)	2,515	(31.1)
Hypothyroidism	23	(15.5)	2	(1.3)	57	(14.7)	565	(9.6)	759	(9.4)
Pyrexia	19	(12.8)	9	(5.9)	43	(11.1)	258	(4.4)	352	(4.3)
Pruritus	16	(10.8)	8	(5.3)	30	(7.7)	836	(14.2)	1,063	(13.1)
Diarrhoea	14	(9.5)	7	(4.6)	38	(9.8)	630	(10.7)	810	(10.0)
Fatigue	13	(8.8)	16	(10.5)	39	(10.0)	1,170	(19.9)	1,488	(18.4)
Pneumonitis	12	(8.1)	1	(0.7)	26	(6.7)	223	(3.8)	284	(3.5)
Hyperthyroidism	8	(5.4)	0	(0.0)	16	(4.1)	219	(3.7)	313	(3.9)
Rash	8	(5.4)	7	(4.6)	31	(8.0)	676	(11.5)	827	(10.2)
Arthralgia	7	(4.7)	7	(4.6)	21	(5.4)	437	(7.4)	561	(6.9)
Decreased Appetite	6	(4.1)	6	(3.9)	12	(3.1)	461	(7.8)	598	(7.4)
Nausea	6	(4.1)	20	(13.2)	25	(6.4)	535	(9.1)	662	(8.2)
Vomiting	6	(4.1)	15	(9.9)	18	(4.6)	198	(3.4)	262	(3.2)
Infusion Related Reaction	5	(3.4)	12	(7.9)	16	(4.1)	54	(0.9)	76	(0.9)
Neutropenia	5	(3.4)	15	(9.9)	16	(4.1)	30	(0.5)	54	(0.7)
Asthenia	3	(2.0)	2	(1.3)	8	(2.1)	363	(6.2)	475	(5.9)
Constipation	3	(2.0)	8	(5.3)	9	(2.3)	155	(2.6)	201	(2.5)
Headache	3	(2.0)	4	(2.6)	20	(5.1)	193	(3.3)	228	(2.8)
Neuropathy Peripheral	3	(2.0)	28	(18.4)	6	(1.5)	41	(0.7)	56	(0.7)
Neutrophil Count Decreased	3	(2.0)	10	(6.6)	3	(0.8)	26	(0.4)	36	(0.4)
Peripheral Sensory Neuropathy	3	(2.0)	20	(13.2)	6	(1.5)	29	(0.5)	40	(0.5)

Grade 3 to 5 Adverse Events

The overall incidence of Grade 3 to 5 AEs in KEYNOTE-204 was generally similar between the pembrolizumab arm (43.9%) and the BV group (43.4%). In the KEYNOTE-204, the most frequently reported Grade 3 to 5 AEs by decreasing incidence were as follows:

- *pneumonia* (5.4%), *anemia* (4.1%), *pneumonitis* (4.1%), *neutropenia* (2.7%) and *thrombocytopenia* (2.7%) for the pembrolizumab arm;
- *neutropenia* (8.6%), *neutrophil count decreased* (4.6%), *pneumonia* (3.3%), *anaemia* (3.3%) and *neuropathy peripheral* (3.3%) in the BV group.

Table 76 ***Subjects with Grade 3 to 5 Adverse Events (incidence ≥ 1% in one or more treatment groups) by decreasing frequency of preferred term***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	65	(43.9)	66	(43.4)	147	(37.8)	2,829	(48.1)	3,936	(48.6)
with no adverse events	83	(56.1)	86	(56.6)	242	(62.2)	3,055	(51.9)	4,157	(51.4)
Pneumonia	8	(5.4)	5	(3.3)	15	(3.9)	242	(4.1)	321	(4.0)
Anaemia	6	(4.1)	5	(3.3)	15	(3.9)	233	(4.0)	373	(4.6)
Pneumonitis	6	(4.1)	1	(0.7)	7	(1.8)	83	(1.4)	104	(1.3)
Neutropenia	4	(2.7)	13	(8.6)	10	(2.6)	15	(0.3)	32	(0.4)
Thrombocytopenia	4	(2.7)	0	(0.0)	7	(1.8)	16	(0.3)	24	(0.3)
Acute Kidney Injury	3	(2.0)	1	(0.7)	4	(1.0)	51	(0.9)	75	(0.9)
Diarrhoea	3	(2.0)	1	(0.7)	7	(1.8)	79	(1.3)	107	(1.3)
Weight Increased	3	(2.0)	0	(0.0)	3	(0.8)	6	(0.1)	14	(0.2)
Alanine Aminotransferase Increased	2	(1.4)	3	(2.0)	5	(1.3)	61	(1.0)	98	(1.2)
Febrile Neutropenia	2	(1.4)	1	(0.7)	4	(1.0)	7	(0.1)	12	(0.1)
Hepatic Function Abnormal	2	(1.4)	0	(0.0)	2	(0.5)	3	(0.1)	11	(0.1)
Immune Thrombocytopenic Purpura	2	(1.4)	0	(0.0)	2	(0.5)	3	(0.1)	6	(0.1)
Interstitial Lung Disease	2	(1.4)	1	(0.7)	2	(0.5)	8	(0.1)	12	(0.1)
Vomiting	2	(1.4)	0	(0.0)	2	(0.5)	42	(0.7)	68	(0.8)
Abdominal Pain	1	(0.7)	1	(0.7)	2	(0.5)	42	(0.7)	80	(1.0)
Acute Graft Versus Host Disease	1	(0.7)	0	(0.0)	4	(1.0)	3	(0.1)	4	(0.0)
Aspartate Aminotransferase Increased	1	(0.7)	2	(1.3)	2	(0.5)	65	(1.1)	123	(1.5)
Device Related Infection	1	(0.7)	2	(1.3)	2	(0.5)	8	(0.1)	11	(0.1)
Dyspnoea	1	(0.7)	1	(0.7)	3	(0.8)	131	(2.2)	169	(2.1)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypokalaemia	1	(0.7)	3	(2.0)	1	(0.3)	58	(1.0)	82	(1.0)
Neuropathy Peripheral	1	(0.7)	5	(3.3)	2	(0.5)	3	(0.1)	6	(0.1)
Neutrophil Count Decreased	1	(0.7)	7	(4.6)	1	(0.3)	8	(0.1)	18	(0.2)
Pyrexia	1	(0.7)	1	(0.7)	4	(1.0)	27	(0.5)	37	(0.5)
Asthenia	0	(0.0)	0	(0.0)	1	(0.3)	58	(1.0)	97	(1.2)
Back Pain	0	(0.0)	1	(0.7)	3	(0.8)	64	(1.1)	89	(1.1)
Blood Alkaline Phosphatase Increased	0	(0.0)	1	(0.7)	1	(0.3)	48	(0.8)	82	(1.0)
Colitis	0	(0.0)	1	(0.7)	3	(0.8)	60	(1.0)	82	(1.0)
Decreased Appetite	0	(0.0)	1	(0.7)	1	(0.3)	74	(1.3)	107	(1.3)
Dehydration	0	(0.0)	1	(0.7)	1	(0.3)	62	(1.1)	91	(1.1)
Fatigue	0	(0.0)	1	(0.7)	2	(0.5)	144	(2.4)	193	(2.4)
Hyperglycaemia	0	(0.0)	1	(0.7)	2	(0.5)	64	(1.1)	95	(1.2)
Hypertension	0	(0.0)	1	(0.7)	2	(0.5)	102	(1.7)	122	(1.5)
Hyponatraemia	0	(0.0)	0	(0.0)	1	(0.3)	153	(2.6)	213	(2.6)
Hypophosphataemia	0	(0.0)	2	(1.3)	3	(0.8)	41	(0.7)	60	(0.7)
Infusion Related Reaction	0	(0.0)	3	(2.0)	0	(0.0)	0	(0.0)	1	(0.0)
Leukopenia	0	(0.0)	3	(2.0)	3	(0.8)	7	(0.1)	8	(0.1)
Lymphopenia	0	(0.0)	2	(1.3)	1	(0.3)	16	(0.3)	17	(0.2)
Paraesthesia	0	(0.0)	2	(1.3)	0	(0.0)	5	(0.1)	6	(0.1)
Peripheral Sensory Neuropathy	0	(0.0)	2	(1.3)	0	(0.0)	1	(0.0)	2	(0.0)
Pleural Effusion	0	(0.0)	0	(0.0)	0	(0.0)	68	(1.2)	94	(1.2)
Pulmonary Embolism	0	(0.0)	2	(1.3)	1	(0.3)	91	(1.5)	121	(1.5)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Urinary Tract Infection	0	(0.0)	1	(0.7)	0	(0.0)	73	(1.2)	97	(1.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[‡‡] Includes all subjects who received at least one dose of Pembrolizumab in KN204.

[¶] Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.

[‖] Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.

[††] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

[§§] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Drug-related Grade 3 to 5 Adverse Events

Table 8 displays the number and percentage of subjects with Grade 3 to 5 drug-related AEs (incidence ≥1%) in different safety datasets. The overall incidence of Grade 3 to 5 drug-related AEs in the KEYNOTE-204 was lower in the pembrolizumab arm (19.6%) than in the BV group (25%). The most frequently reported drug-related Grade 3 to 5 AEs were:

- *pneumonitis* (4.1%), *pneumonia* (2%) and *neutropenia* (2%) in the pembrolizumab arm;
- *neutropenia* (7.2%), *neutrophil count decreased* (4.6%) and *neuropathy peripheral* (3.3%) in the BV arm.

The Grade 3 to 5 drug-related AE reported more frequently was *pneumonitis* (4.1% in the KEYNOTE-204 pembrolizumab arm vs 1.8% in the cHL Safety Dataset, 1.3% in the RSD and 1.2% in the CSD).

Table 80. Subjects with drug-related Grade 3-5 adverse events (incidence ≥ 1% in one or more treatment groups) by decreasing frequency of preferred term

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	29	(19.6)	38	(25.0)	62	(15.9)	913	(15.5)	1,297	(16.0)
with no adverse events	119	(80.4)	114	(75.0)	327	(84.1)	4,971	(84.5)	6,796	(84.0)
Pneumonitis	6	(4.1)	1	(0.7)	7	(1.8)	78	(1.3)	98	(1.2)
Neutropenia	3	(2.0)	11	(7.2)	8	(2.1)	9	(0.2)	23	(0.3)
Pneumonia	3	(2.0)	2	(1.3)	3	(0.8)	13	(0.2)	27	(0.3)
Acute Kidney Injury	2	(1.4)	0	(0.0)	2	(0.5)	8	(0.1)	15	(0.2)
Diarrhoea	2	(1.4)	0	(0.0)	4	(1.0)	55	(0.9)	74	(0.9)
Immune Thrombocytopenic Purpura	2	(1.4)	0	(0.0)	2	(0.5)	2	(0.0)	5	(0.1)
Interstitial Lung Disease	2	(1.4)	1	(0.7)	2	(0.5)	7	(0.1)	11	(0.1)
Thrombocytopenia	2	(1.4)	0	(0.0)	3	(0.8)	6	(0.1)	11	(0.1)
Neuropathy Peripheral	1	(0.7)	5	(3.3)	2	(0.5)	1	(0.0)	3	(0.0)
Neutrophil Count Decreased	1	(0.7)	7	(4.6)	1	(0.3)	4	(0.1)	9	(0.1)
Fatigue	0	(0.0)	0	(0.0)	1	(0.3)	63	(1.1)	85	(1.1)
Infusion Related Reaction	0	(0.0)	3	(2.0)	0	(0.0)	0	(0.0)	1	(0.0)
Leukopenia	0	(0.0)	3	(2.0)	0	(0.0)	3	(0.1)	3	(0.0)
Paraesthesia	0	(0.0)	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral Sensory Neuropathy	0	(0.0)	2	(1.3)	0	(0.0)	1	(0.0)	2	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Acute kidney injury was reported more frequently as Grade 3 to 5 drug-related AE in the KEYNOTE-204 pembrolizumab arm than in the cHL Safety Dataset, the RSD and the CSD (1.4%, 0.5%, 0.1% and 0.2%, respectively). The observed imbalance across the datasets may be explained by the longer duration of exposure in the KEYNOTE-204 pembrolizumab arm and cHL safety dataset (10.02 and 10.65 months, respectively) relative to the RSD and CSD (4.86 and 4.24 months, respectively. Of note, these percentages in the KEYNOTE-204 pembrolizumab arm and the cHL safety dataset are based on 2 participants in each group from populations of 148 and 389 participants, respectively. These events were resolved.

Serious adverse event/deaths/other significant events

The incidence of SAEs from 90 days of last dose in KEYNOTE-204 was higher for pembrolizumab compared with BV (29.7% vs 21.1%), but the rates were similar after adjustment for exposure. *Pneumonia*, *Pneumonitis* and *Pyrexia* were most frequently reported (incidence ≥1%) in the cHL population after pembrolizumab (5.4%, 5.4% and 2.7%, respectively in the KN-204 pembrolizumab arm), whereas *pneumonia*, *infusion related reaction*, *pulmonary embolism* and *neuropathy peripheral* were the most frequent SAEs after BV (3.3%, 2%, 1.3% and 1.3%, respectively).

Pneumonitis was the only most frequently reported SAE (≥ 2 percentage points difference) in the KEYNOTE-204 pembrolizumab group than the other safety datasets (5.4% vs 3.3% in the cHL Safety Dataset, 2.0% in the RSD and 1.8% in the CSD).

Table 771: ***Subjects with serious adverse events up to 90 days of last dose (incidence ≥ 1% in one or more treatment groups) by decreasing frequency of preferred term***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	44	(29.7)	32	(21.1)	104	(26.7)	2,266	(38.5)	3,090	(38.2)
with no adverse events	104	(70.3)	120	(78.9)	285	(73.3)	3,618	(61.5)	5,003	(61.8)
Pneumonia	8	(5.4)	5	(3.3)	16	(4.1)	246	(4.2)	323	(4.0)
Pneumonitis	8	(5.4)	1	(0.7)	13	(3.3)	117	(2.0)	148	(1.8)
Pyrexia	4	(2.7)	1	(0.7)	9	(2.3)	67	(1.1)	92	(1.1)
Acute Kidney Injury	2	(1.4)	0	(0.0)	3	(0.8)	50	(0.8)	81	(1.0)
Febrile Neutropenia	2	(1.4)	0	(0.0)	2	(0.5)	4	(0.1)	9	(0.1)
Interstitial Lung Disease	2	(1.4)	1	(0.7)	2	(0.5)	13	(0.2)	18	(0.2)
Myocarditis	2	(1.4)	0	(0.0)	3	(0.8)	5	(0.1)	9	(0.1)
Acute Graft Versus Host Disease	1	(0.7)	0	(0.0)	6	(1.5)	5	(0.1)	6	(0.1)
Anaemia	1	(0.7)	0	(0.0)	3	(0.8)	59	(1.0)	86	(1.1)
Colitis	0	(0.0)	1	(0.7)	2	(0.5)	59	(1.0)	76	(0.9)
Diarrhoea	0	(0.0)	0	(0.0)	2	(0.5)	59	(1.0)	78	(1.0)
Dyspnoea	0	(0.0)	0	(0.0)	1	(0.3)	81	(1.4)	93	(1.1)
Infusion Related Reaction	0	(0.0)	3	(2.0)	1	(0.3)	4	(0.1)	6	(0.1)
Neuropathy Peripheral	0	(0.0)	2	(1.3)	0	(0.0)	2	(0.0)	3	(0.0)
Pleural Effusion	0	(0.0)	1	(0.7)	0	(0.0)	83	(1.4)	107	(1.3)
Pulmonary Embolism	0	(0.0)	2	(1.3)	1	(0.3)	71	(1.2)	93	(1.1)

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[†]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Urinary Tract Infection	0	(0.0)	1	(0.7)	0	(0.0)	73	(1.2)	97	(1.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[‡‡] Includes all subjects who received at least one dose of Pembrolizumab in KN204.
[†] Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
[‖] Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
[††] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
[§§] Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Drug-related Serious Adverse Events

In the KEYNOTE-204, the overall incidence of drug-related SAEs from 90 days of last dose was higher for pembrolizumab than BV (16.2% vs 10.5%) but the incidences were similar after adjustment for exposure. *Pneumonitis* was the only drug-related SAE more frequently reported (≥2 percentage points differences) in the KEYNOTE-204 pembrolizumab arm than the cHL Safety dataset and the RSD (5.4% vs 3.3% and 1.9%, respectively)

Table 782: ***Subjects with drug-related serious adverse events up to 90 days of last dose (incidence ≥ 1% in one or more treatment groups) by decreasing frequency of preferred term***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[†]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	24	(16.2)	16	(10.5)	46	(11.8)	656	(11.1)	917	(11.3)
with no adverse events	124	(83.8)	136	(89.5)	343	(88.2)	5,228	(88.9)	7,176	(88.7)
Pneumonitis	8	(5.4)	1	(0.7)	13	(3.3)	111	(1.9)	141	(1.7)
Pneumonia	3	(2.0)	2	(1.3)	3	(0.8)	14	(0.2)	28	(0.3)
Acute Kidney Injury	2	(1.4)	0	(0.0)	2	(0.5)	10	(0.2)	18	(0.2)
Interstitial Lung Disease	2	(1.4)	1	(0.7)	2	(0.5)	12	(0.2)	17	(0.2)
Myocarditis	2	(1.4)	0	(0.0)	3	(0.8)	5	(0.1)	9	(0.1)
Pyrexia	2	(1.4)	0	(0.0)	2	(0.5)	17	(0.3)	28	(0.3)
Infusion Related Reaction	0	(0.0)	3	(2.0)	1	(0.3)	4	(0.1)	6	(0.1)

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Neuropathy Peripheral	0	(0.0)	2	(1.3)	0	(0.0)	1	(0.0)	2	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Deaths due to adverse events

The incidence of AEs resulting in death was low and comparable across the safety datasets. Deaths due to AEs in KEYNOTE-204 occurred in 3 patients (2%) in the pembrolizumab arm and in 2 BV patients (1.3%).

Table 793 ***Subjects with adverse events resulting in death up to 90 days of last dose (incidence > 0% in one or more treatment groups) by decreasing frequency of preferred term***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	3	(2.0)	2	(1.3)	6	(1.5)	312	(5.3)	444	(5.5)
with no adverse events	145	(98.0)	150	(98.7)	383	(98.5)	5,572	(94.7)	7,649	(94.5)
Death	1	(0.7)	1	(0.7)	1	(0.3)	42	(0.7)	63	(0.8)
Hypovolaemic Shock	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.0)
Pneumonia	1	(0.7)	0	(0.0)	1	(0.3)	36	(0.6)	48	(0.6)
Abdominal Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Accidental Death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Acute Coronary Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Acute Graft Versus Host Disease	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.0)	1	(0.0)
Acute Kidney Injury	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	5	(0.1)
Acute Left Ventricular Failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute Myocardial Infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Acute Respiratory Failure	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)	6	(0.1)
Adenocarcinoma Gastric	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Alcohol Poisoning	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Anaphylactic Shock	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Arterial Injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Aspergillus Infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Aspiration	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	5	(0.1)

Table 804 ***Subjects with adverse events resulting in death up to 90 days of last dose (incidence > 0% in one or more treatment groups)***

	MK-3475 200 mg		Brentuximab Vedotin	
	n	(%)	n	(%)
Subjects in population	148		152	
with one or more adverse events	3	(2.0)	2	(1.3)
with no adverse events	145	(98.0)	150	(98.7)
Death	1	(0.7)	1	(0.7)
Hypovolaemic shock	1	(0.7)	0	(0.0)
Pneumonia	1	(0.7)	0	(0.0)
Respiratory failure	0	(0.0)	1	(0.7)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adae]

The narratives of 2 death cases from the KEYNOTE-204 pembrolizumab arm were presented.
In One patient the primary reported cause of death was pneumonia, considered related to pembrolizumab, but interstitial myocarditis, interstitial hepatitis, and tubulointerstitial nephritis were also noted in the autopsy report. The second subject died due to hypovolemic shock (Grade 5), considered not drug-related by the investigator; however the patient also presented with autoimmune hemolytic anemia, acute kidney injury, acute GVHD, and pneumonia at the time of death. The narrative for a patient who died due to an unknown cause, was also provided.

Adverse Events of Special Interest (AEOSI)

Summary of Adverse Event of Special Interest

The summary of AEOSIs, immune-mediated events and infusion-related reactions associated with pembrolizumab, are reported below.

Table 815 ***Adverse Event Summary: AEOSI***

	KN204 Data for Pembrolizumab[22]		KN204 Data for Brentuximab Vedotin[1]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[17]		Cumulative Running Safety Dataset for Pembrolizumab[18]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	53	(35.8)	21	(13.8)	139	(35.7)	1,474	(25.1)	1,973	(24.4)
with no adverse event	95	(64.2)	131	(86.2)	250	(64.3)	4,410	(74.9)	6,120	(75.6)
with drug-related[†] adverse events	43	(29.1)	17	(11.2)	123	(31.6)	1,281	(21.8)	1,718	(21.2)
with toxicity grade 3-5 adverse events	11	(7.4)	5	(3.3)	23	(5.9)	381	(6.5)	517	(6.4)
with toxicity grade 3-5 drug-related adverse events	9	(6.1)	5	(3.3)	18	(4.6)	331	(5.6)	454	(5.6)
with serious adverse events	13	(8.8)	5	(3.3)	25	(6.4)	381	(6.5)	502	(6.2)
with serious drug-related adverse events	12	(8.1)	5	(3.3)	22	(5.7)	337	(5.7)	449	(5.5)
with dose modification[‡] due to an adverse event	21	(14.2)	13	(8.6)	51	(13.1)	534	(9.1)	707	(8.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
discontinued drug due to an adverse event	13	(8.8)	5	(3.3)	30	(7.7)	232	(3.9)	311	(3.8)
discontinued drug due to a drug-related adverse event	13	(8.8)	5	(3.3)	29	(7.5)	228	(3.9)	307	(3.8)
discontinued drug due to a serious adverse event	10	(6.8)	4	(2.6)	17	(4.4)	156	(2.7)	204	(2.5)

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	10	(6.8)	4	(2.6)	17	(4.4)	154	(2.6)	202	(2.5)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Overall Adverse Event of Special Interest (AEOSI)

The overall incidence of AEOSI was comparable between the KEYNOTE-204 pembrolizumab arm (n=53, 35.8%) and the cHL Safety Dataset (n=139, 35.7%), including those considered as drug-related (n=43, 29.1% and n= 123, 31.6%, respectively), but with a slightly higher prevalence of serious-drug related AEs compared with the cHL Safety Datase (n=12, 8.1% vs n=22, 5.7% respectively). No deaths occurred in the KEYNOTE pembrolizumab arm or in the cHL Safety Dataset, related to a fatal AEOSI.

Most immune-mediated AEOSIs were mild to moderate in severity and were managed with treatment interruptions and/or corticosteroids. At the time of the data cut-off, 50.9% of patients were reported to have AEOSIs resolved, 9.4% were resolving and 37.7% were not resolved (most AEOSIs related to endocrine abnormalities) in the KEYNOTE-204 pembrolizumab arm.

In KEYNOTE-204, a higher incidence of AEOSIs was observed in the pembrolizumab arm compared with the BV group (35.8% vs 13.8%). The most frequent AEOSIs were *hypothyroidism* (n=28 [18.9%]), *pneumonitis* (n=13 [8.8%]), and *hyperthyroidism* (n=8 [5.4%]) in the pembrolizumab arm, and *infusion-related reaction* (n=12 [7.9]), *hypothyroidism* (n=4 [2.6%]), and *pneumonitis* (n=3 [2%]) in the BV arm.

Table 826 ***Summary of outcome for subjects with AEOSI (incidence > 0% in one or more treatment groups)***

	Outcome	KN204 Data for Pembrolizumab‡‡ n	(%)	KN204 Data for Brentuximab Vedotin¶ n	(%)	cHL Safety Data for Pembrolizumab‖ n	(%)	Reference Safety Dataset for Pembrolizumab†† n	(%)	Cumulative Running Safety Dataset for Pembrolizumab§§ n	(%)
Subjects in population		148		152		389		5884		8093	
With one or more AEOSI	**Overall**	**53**	**(35.8)**	**21**	**(13.8)**	**139**	**(35.7)**	**1474**	**(25.1)**	**1973**	**(24.4)**
	Fatal	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.7)	17	(0.9)
	Not Resolved	20	(37.7)	3	(14.3)	41	(29.5)	693	(47.0)	913	(46.3)
	Resolving	5	(9.4)	0	(0.0)	9	(6.5)	97	(6.6)	154	(7.8)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)	27	(1.8)	29	(1.5)
	Sequelae	1	(1.9)	0	(0.0)	6	(4.3)	33	(2.2)	43	(2.2)
	Resolved	27	(50.9)	18	(85.7)	83	(59.7)	613	(41.6)	817	(41.4)

Table 837 ***Subjects with Adverse Events of Special Interest (incidence > 0% in one or more treatment groups) by AEOSI category and preferred term***

	KN204 Data for Pembrolizumab[22]		KN204 Data for Brentuximab Vedotin[1]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[17]		Cumulative Running Safety Dataset for Pembrolizumab[18]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	53	(35.8)	21	(13.8)	139	(35.7)	1,474	(25.1)	1,973	(24.4)
with no adverse events	95	(64.2)	131	(86.2)	250	(64.3)	4,410	(74.9)	6,120	(75.6)
Adrenal Insufficiency	**1**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.3)**	**47**	**(0.8)**	**63**	**(0.8)**
Addison's Disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Adrenal Insufficiency	1	(0.7)	0	(0.0)	1	(0.3)	42	(0.7)	53	(0.7)
Adrenocortical Insufficiency Acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Primary Adrenal Insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Secondary Adrenocortical Insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Colitis	**1**	**(0.7)**	**1**	**(0.7)**	**6**	**(1.5)**	**110**	**(1.9)**	**154**	**(1.9)**
Autoimmune Colitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	4	(0.0)
Colitis	1	(0.7)	1	(0.7)	5	(1.3)	95	(1.6)	132	(1.6)
Colitis Microscopic	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)	4	(0.0)
Enterocolitis	0	(0.0)	0	(0.0)	1	(0.3)	8	(0.1)	14	(0.2)
Immune-Mediated Enterocolitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.0)
Encephalitis	**1**	**(0.7)**	**0**	**(0.0)**	**2**	**(0.5)**	**3**	**(0.1)**	**6**	**(0.1)**
Encephalitis	0	(0.0)	0	(0.0)	1	(0.3)	3	(0.1)	5	(0.1)
Encephalitis Autoimmune	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**6**	**(0.1)**

	KN204 Data for Pembrolizumab[22]		KN204 Data for Brentuximab Vedotin[1]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[17]		Cumulative Running Safety Dataset for Pembrolizumab[18]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**6**	**(0.1)**
Axonal Neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Demyelinating Polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	4	(0.0)
Hepatitis	**1**	**(0.7)**	**0**	**(0.0)**	**2**	**(0.5)**	**56**	**(1.0)**	**80**	**(1.0)**
Autoimmune Hepatitis	0	(0.0)	0	(0.0)	1	(0.3)	25	(0.4)	35	(0.4)
Drug-Induced Liver Injury	1	(0.7)	0	(0.0)	1	(0.3)	6	(0.1)	9	(0.1)
Hepatitis	0	(0.0)	0	(0.0)	0	(0.0)	24	(0.4)	33	(0.4)
Hepatitis Acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Immune-Mediated Hepatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Hyperthyroidism	**8**	**(5.4)**	**1**	**(0.7)**	**17**	**(4.4)**	**247**	**(4.2)**	**352**	**(4.3)**
Hyperthyroidism	8	(5.4)	1	(0.7)	17	(4.4)	247	(4.2)	352	(4.3)
Hypophysitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**36**	**(0.6)**	**42**	**(0.5)**
Hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	22	(0.4)	25	(0.3)
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	14	(0.2)	17	(0.2)
Hypothyroidism	**28**	**(18.9)**	**4**	**(2.6)**	**66**	**(17.0)**	**652**	**(11.1)**	**877**	**(10.8)**
Autoimmune Hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hypothyroidism	28	(18.9)	4	(2.6)	66	(17.0)	651	(11.1)	873	(10.8)
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)

	KN204 Data for Pembrolizumab[22]		KN204 Data for Brentuximab Vedotin[1]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[17]		Cumulative Running Safety Dataset for Pembrolizumab[18]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypothyroidism	**28**	**(18.9)**	**4**	**(2.6)**	**66**	**(17.0)**	**652**	**(11.1)**	**877**	**(10.8)**
Primary Hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Infusion Reactions	**8**	**(5.4)**	**12**	**(7.9)**	**31**	**(8.0)**	**138**	**(2.3)**	**173**	**(2.1)**
Anaphylactic Reaction	0	(0.0)	0	(0.0)	0	(0.0)	10	(0.2)	11	(0.1)
Anaphylactoid Reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cytokine Release Syndrome	0	(0.0)	0	(0.0)	6	(1.5)	8	(0.1)	9	(0.1)
Drug Hypersensitivity	1	(0.7)	0	(0.0)	2	(0.5)	18	(0.3)	22	(0.3)
Hypersensitivity	2	(1.4)	0	(0.0)	9	(2.3)	47	(0.8)	53	(0.7)
Infusion Related Reaction	5	(3.4)	12	(7.9)	16	(4.1)	56	(1.0)	80	(1.0)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**4**	**(0.0)**
Myasthenia Gravis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Myasthenic Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**	**2**	**(0.0)**	**2**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.0)	1	(0.0)
Myelitis Transverse	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Myocarditis	**2**	**(1.4)**	**0**	**(0.0)**	**3**	**(0.8)**	**5**	**(0.1)**	**9**	**(0.1)**
Myocarditis	2	(1.4)	0	(0.0)	3	(0.8)	5	(0.1)	9	(0.1)
Myositis	**1**	**(0.7)**	**0**	**(0.0)**	**3**	**(0.8)**	**19**	**(0.3)**	**32**	**(0.4)**

	KN204 Data for Pembrolizumab[77]		KN204 Data for Brentuximab Vedotin[5]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[77]		Cumulative Running Safety Dataset for Pembrolizumab[88]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Myositis	**1**	**(0.7)**	**0**	**(0.0)**	**3**	**(0.8)**	**19**	**(0.3)**	**32**	**(0.4)**
Myopathy	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)	4	(0.0)
Myositis	0	(0.0)	0	(0.0)	1	(0.3)	13	(0.2)	23	(0.3)
Necrotising Myositis	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.0)	1	(0.0)
Polymyositis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	1	(0.7)	0	(0.0)	1	(0.3)	1	(0.0)	4	(0.0)
Nephritis	**1**	**(0.7)**	**1**	**(0.7)**	**2**	**(0.5)**	**23**	**(0.4)**	**36**	**(0.4)**
Acute Kidney Injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Autoimmune Nephritis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	5	(0.1)
Glomerulonephritis Membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Nephritis	1	(0.7)	0	(0.0)	1	(0.3)	3	(0.1)	11	(0.1)
Nephrotic Syndrome	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.0)	2	(0.0)
Renal Failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Tubulointerstitial Nephritis	0	(0.0)	1	(0.7)	0	(0.0)	11	(0.2)	13	(0.2)
Pancreatitis	**2**	**(1.4)**	**0**	**(0.0)**	**2**	**(0.5)**	**18**	**(0.3)**	**32**	**(0.4)**
Autoimmune Pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis	2	(1.4)	0	(0.0)	2	(0.5)	14	(0.2)	27	(0.3)
Pancreatitis Acute	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)	5	(0.1)
Pneumonitis	**16**	**(10.8)**	**4**	**(2.6)**	**31**	**(8.0)**	**264**	**(4.5)**	**341**	**(4.2)**
Interstitial Lung Disease	3	(2.0)	1	(0.7)	4	(1.0)	22	(0.4)	36	(0.4)

	KN204 Data for Pembrolizumab[77]		KN204 Data for Brentuximab Vedotin[5]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[77]		Cumulative Running Safety Dataset for Pembrolizumab[88]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Pneumonitis	**16**	**(10.8)**	**4**	**(2.6)**	**31**	**(8.0)**	**264**	**(4.5)**	**341**	**(4.2)**
Organising Pneumonia	0	(0.0)	0	(0.0)	1	(0.3)	3	(0.1)	3	(0.0)
Pneumonitis	13	(8.8)	3	(2.0)	27	(6.9)	242	(4.1)	305	(3.8)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**	**10**	**(0.2)**	**11**	**(0.1)**
Sarcoidosis	0	(0.0)	0	(0.0)	1	(0.3)	10	(0.2)	11	(0.1)
Severe Skin Reactions	**3**	**(2.0)**	**3**	**(2.0)**	**5**	**(1.3)**	**97**	**(1.6)**	**128**	**(1.6)**
Dermatitis Bullous	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)	9	(0.1)
Dermatitis Exfoliative	0	(0.0)	1	(0.7)	0	(0.0)	5	(0.1)	5	(0.1)
Dermatitis Exfoliative Generalised	0	(0.0)	1	(0.7)	0	(0.0)	2	(0.0)	2	(0.0)
Erythema Multiforme	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)	7	(0.1)
Exfoliative Rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	5	(0.1)
Lichen Planus	0	(0.0)	0	(0.0)	1	(0.3)	5	(0.1)	6	(0.1)
Oral Lichen Planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Pemphigoid	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	6	(0.1)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Pruritus	0	(0.0)	0	(0.0)	1	(0.3)	12	(0.2)	14	(0.2)
Pruritus Genital	1	(0.7)	0	(0.0)	1	(0.3)	1	(0.0)	2	(0.0)
Rash	0	(0.0)	0	(0.0)	0	(0.0)	30	(0.5)	38	(0.5)
Rash Erythematous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash Maculo-Papular	0	(0.0)	0	(0.0)	0	(0.0)	16	(0.3)	23	(0.3)
Rash Pruritic	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)

	KN204 Data for Pembrolizumab[77]		KN204 Data for Brentuximab Vedotin[5]		cHL Safety Data for Pembrolizumab[1]		Reference Safety Dataset for Pembrolizumab[77]		Cumulative Running Safety Dataset for Pembrolizumab[88]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Severe Skin Reactions	**3**	**(2.0)**	**3**	**(2.0)**	**5**	**(1.3)**	**97**	**(1.6)**	**128**	**(1.6)**
Rash Pustular	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Skin Necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Stevens-Johnson Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.0)
Toxic Skin Eruption	2	(1.4)	1	(0.7)	2	(0.5)	2	(0.0)	4	(0.0)
Thyroiditis	**2**	**(1.4)**	**0**	**(0.0)**	**5**	**(1.3)**	**58**	**(1.0)**	**76**	**(0.9)**
Autoimmune Thyroiditis	0	(0.0)	0	(0.0)	1	(0.3)	14	(0.2)	17	(0.2)
Thyroid Disorder	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)	6	(0.1)
Thyroiditis	2	(1.4)	0	(0.0)	4	(1.0)	41	(0.7)	55	(0.7)
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**20**	**(0.3)**	**28**	**(0.3)**
Diabetic Ketoacidosis	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.2)	12	(0.1)
Fulminant Type 1 Diabetes Mellitus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Type 1 Diabetes Mellitus	0	(0.0)	0	(0.0)	0	(0.0)	16	(0.3)	22	(0.3)
Uveitis	**2**	**(1.4)**	**0**	**(0.0)**	**5**	**(1.3)**	**21**	**(0.4)**	**28**	**(0.3)**
Chorioretinitis	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.0)	1	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	1	(0.3)	4	(0.1)	4	(0.0)
Iritis	0	(0.0)	0	(0.0)	1	(0.3)	3	(0.1)	4	(0.0)

Hypothyroidism

In KEYNOTE-204, the most common AEOSI reported was *hypothyroidism*, which occurred in 28 patients (18.9%) in the pembrolizumab arm compared to 4 patients (2.6%) in the BV group. Of these, 23 patients (15.5%) in the pembrolizumab arm had AEOSI assessed as drug-related and were Grade 1 or 2. *Hypothyroidism* was managed through observation and/or thyroid replacement hormone and no patients received corticosteroid treatment. Less than half of patients had a revolved or resolving status.

In KEYNOTE-204, out of 28 participants, 11 participants had a past medical history of prior radiation

therapy. In the pembrolizumab arm of KEYNOTE-204, 58 participants had received prior radiation at baseline while 93 participants had not received prior radiation in the ITT population. The incidence of *hypothyroidism* in participants who received prior radiation was thus 19.0% (11/58) compared to 18.3% (17/93) in participants who had not received prior radiation. TSH levels reported at baseline for these 28 participants were as follows: 20 participants with normal, 7 participants with high and 1 participant with low TSH levels at baseline, respectively.

Table 848 ***Adverse Event Summary: AEOSI - Hypothyroidism***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	28	(18.9)	4	(2.6)	66	(17.0)	652	(11.1)	877	(10.8)
with no adverse event	120	(81.1)	148	(97.4)	323	(83.0)	5,232	(88.9)	7,216	(89.2)
with drug-related† adverse events	23	(15.5)	2	(1.3)	57	(14.7)	566	(9.6)	763	(9.4)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)	10	(0.1)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)	10	(0.1)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)	7	(0.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)	7	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Table 859 ***Time to onset and duration of AEOSI - Hypothyroidism***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5884		8093	
Subjects with Hypothyroidism	28	(18.9)	4	(2.6)	66	(17.0)	652	(11.1)	877	(10.8)
Time to Onset of First Hypothyroidism (days)†										
Mean (Std)	138.9 (150.3)		336.5 (246.2)		133.6 (140.5)		122.7 (97.5)		123.3 (100.4)	
Median	89.5		319.0		85.0		105.0		103.0	
Range	20 to 741		64 to 644		20 to 741		1 to 664		1 to 741	
Total episodes of Hypothyroidism	33		4		76		720		965	
Average Episodes per patient	1.18		1.00		1.15		1.10		1.10	
Episode duration (days)‡										
Median	Not reached		Not reached		246.0		Not reached		Not reached	

Table 860 ***Summary of outcome for subjects with AEOSI - Hypothyroidism***

		KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	Outcome	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypothyroidism	Resolving	5	(17.9)	0	(0.0)	8	(12.1)	45	(6.9)	80	(9.1)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)	20	(3.1)	22	(2.5)
	Sequelae	0	(0.0)	0	(0.0)	4	(6.1)	14	(2.1)	14	(1.6)
	Resolved	8	(28.6)	1	(25.0)	27	(40.9)	144	(22.1)	184	(21.0)

Pneumonitis

In KEYNOTE-204, the overall incidence of *pneumonitis* was higher in the pembrolizumab arm than in the BV group (n=16, 10.8% vs n=4, 2.6%) and most cases were considered as drug-related (10.1% vs 1.3%). One-half of the patients (8/16) had Grade 3 or 4 events; no patients died due to *pneumonitis*. *Pneumonitis* was more frequent than observed in the cHL Safety Dataset (8%) and in the RSD (4.5%), but it was resolved for 12 out of 16 (75%) pembrolizumab patients in KEYNOTE-204, for 24 out of 31 patients (77.4%) in the cHL Safety Dataset and for 148 out of 264 patients (56.1%) in the RSD. The majority of patients were treated with systemic corticosteroid.

Table 871 ***Adverse Event Summary: AEOSI – Pneumonitis***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	16	(10.8)	4	(2.6)	31	(8.0)	264	(4.5)	341	(4.2)
with no adverse event	132	(89.2)	148	(97.4)	358	(92.0)	5,620	(95.5)	7,752	(95.8)
with drug-related† adverse events	15	(10.1)	2	(1.3)	30	(7.7)	244	(4.1)	318	(3.9)
with toxicity grade 3-5 adverse events	8	(5.4)	2	(1.3)	9	(2.3)	91	(1.5)	116	(1.4)
with toxicity grade 3-5 drug-related adverse events	8	(5.4)	2	(1.3)	9	(2.3)	85	(1.4)	109	(1.3)
with serious adverse events	10	(6.8)	2	(1.3)	15	(3.9)	130	(2.2)	166	(2.1)
with serious drug-related adverse events	10	(6.8)	2	(1.3)	15	(3.9)	123	(2.1)	158	(2.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.2)	14	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.2)	14	(0.2)
discontinued drug due to an adverse event	11	(7.4)	1	(0.7)	21	(5.4)	105	(1.8)	140	(1.7)
discontinued drug due to a drug-related adverse event	11	(7.4)	1	(0.7)	21	(5.4)	103	(1.8)	138	(1.7)
discontinued drug due to a serious adverse event	9	(6.1)	1	(0.7)	13	(3.3)	77	(1.3)	97	(1.2)
discontinued drug due to a serious drug-related adverse event	9	(6.1)	1	(0.7)	13	(3.3)	76	(1.3)	96	(1.2)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Table 882 ***Summary of outcome for subjects with AEOSI – Pneumonitis***

		KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab¶¶		Cumulative Running Safety Dataset for Pembrolizumab##	
	Outcome	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Pneumonitis	Resolved	12	(75.0)	4	(100.0)	24	(77.4)	148	(56.1)	189	(55.4)
Pneumonitis	**Overall**	**16**	**(10.8)**	**4**	**(2.6)**	**31**	**(8.0)**	**264**	**(4.5)**	**341**	**(4.2)**
	Fatal	0	(0.0)	0	(0.0)	0	(0.0)	9	(3.4)	14	(4.1)
	Not Resolved	3	(18.8)	0	(0.0)	6	(19.4)	81	(30.7)	106	(31.1)
	Resolving	1	(6.3)	0	(0.0)	1	(3.2)	22	(8.3)	28	(8.2)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.3)
	Sequelae	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.1)	3	(0.9)

Table 893 ***Summary of concomitant corticosteroid use for AEOSI - Pneumonitis***

	KN204 Data for Pembrolizumab‡‡ (N=148)		KN204 Data for Brentuximab Vedotin¶ (N=152)		cHL Safety Data for Pembrolizumab‖ (N=389)		Reference Safety Dataset for Pembrolizumab¶¶ (N=5884)		Cumulative Running Safety Dataset for Pembrolizumab## (N=8093)	
	n	%	n	%	n	%	n	%	n	%
Patients with one or more Pneumonitis	16		4		31		264		341	
Treated with systemic corticosteroid	15	93.8	2	50.0	29	93.5	175	66.3	241	70.7
Not treated with systemic corticosteroid	1	6.3	2	50.0	2	6.5	89	33.7	100	29.3

The number of Patients with one or more Pneumonitis is used as the denominator for the percentage calculation.

‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.

¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.

¶¶ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)

Database cutoff date for HCC (KN224: 15MAY2018)

Database Cutoff date for Merkel Cell (P017: 06FEB2018)

Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)

Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)

Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)

Database Cutoff date for TMB-H (KN158: 27JUN2019)

Source: [ISS: adam-adsl, adae, adcm]

<u>*Infusion reactions*</u>

The incidence of *infusion reactions* in the KEYNOTE-204 pembrolizumab arm was consistent with the cHL Safety Dataset and was more frequent than the RSD and the CSD. *Infusion related reactions* were more frequent in the cHL population (5.4% in the KEYNOTE-204 pembrolizumab arm, 7.9% in the BV group and 8% in the cHL Safety Dataset) than in the RSD (2.3%) and the CSD (2.1%), characterized by a very earlier median time to first occurrence (1 day vs 44.5 in the RSD and 40 days in the CSD).

Table 904 ***Adverse Event Summary: AEOSI - Infusion Reactions***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab¶¶		Cumulative Running Safety Dataset for Pembrolizumab##	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	8	(5.4)	12	(7.9)	31	(8.0)	138	(2.3)	173	(2.1)
with no adverse event	140	(94.6)	140	(92.1)	358	(92.0)	5,746	(97.7)	7,920	(97.9)
with drug-related[†] adverse events	6	(4.1)	12	(7.9)	24	(6.2)	86	(1.5)	110	(1.4)
with toxicity grade 3-5 adverse events	0	(0.0)	3	(2.0)	2	(0.5)	14	(0.2)	16	(0.2)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	3	(2.0)	1	(0.3)	5	(0.1)	6	(0.1)
with serious adverse events	0	(0.0)	3	(2.0)	2	(0.5)	21	(0.4)	24	(0.3)
with serious drug-related adverse events	0	(0.0)	3	(2.0)	1	(0.3)	9	(0.2)	12	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(0.7)	3	(2.0)	3	(0.8)	4	(0.1)	5	(0.1)
discontinued drug due to a drug-related adverse event	1	(0.7)	3	(2.0)	3	(0.8)	4	(0.1)	5	(0.1)
discontinued drug due to a serious adverse event	0	(0.0)	2	(1.3)	1	(0.3)	3	(0.1)	3	(0.0)

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin†		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab¶¶		Cumulative Running Safety Dataset for Pembrolizumab##	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	2	(1.3)	1	(0.3)	3	(0.1)	3	(0.0)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
† Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
¶¶ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Table 915 ***Time to onset and duration of AEOSI - Infusion Reactions***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin†		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab¶¶		Cumulative Running Safety Dataset for Pembrolizumab##	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5884		8093	
Subjects with Infusion Reactions	8	(5.4)	12	(7.9)	31	(8.0)	138	(2.3)	173	(2.1)
Time to Onset of First Infusion Reactions (days)†										
Mean (Std)	141.4 (227.5)		29.3 (24.2)		206.0 (287.9)		114.5 (156.2)		111.2 (161.7)	
Median	1.0		22.0		1.0		44.5		40.0	
Range	1 to 582		22 to 106		1 to 723		1 to 723		1 to 723	
Total episodes of Infusion Reactions	9		14		42		167		211	
Average Episodes per patient	1.13		1.17		1.35		1.21		1.22	
Episode duration (days)‡										
Median	1.0		1.0		3.0		2.0		2.0	

Table 926 ***Summary of concomitant corticosteroid use for AEOSI - Infusion Reactions***

	KN204 Data for Pembrolizumab‡‡ (N=148)		KN204 Data for Brentuximab Vedotin† (N=152)		cHL Safety Data for Pembrolizumab‖ (N=389)		Reference Safety Dataset for Pembrolizumab¶¶ (N=5884)		Cumulative Running Safety Dataset for Pembrolizumab## (N=8093)	
	n	%	n	%	n	%	n	%	n	%
Patients with one or more Infusion Reactions	8		12		31		138		173	
Treated with systemic corticosteroid	3	37.5	9	75.0	10	32.3	39	28.3	51	29.5
Not treated with systemic corticosteroid	5	62.5	3	25.0	21	67.7	99	71.7	122	70.5

Laboratory findings

In KEYNOTE-204, the frequency and severity of laboratory test toxicity were comparable in the pembrolizumab and BV arms, in which most shifts in the toxicity Grade from baseline were to Grades ≤2. However, in the pembrolizumab arm, shifts to Grade 3 or 4 were observed for *lymphocytes decreased* (Grade 3, n=6; 4.1% and Grade 4, n=7; 4.8%), *alanine aminotransferase increased* (Grade 3, n=8; 5.4%) and Grade 4, n=1; 0.7%), *neutrophils decreased* (Grade 3, n=8; 5.5% and Grade 4, n=4; 2.7%). Similar

shifts to Grade 3 or 4 were observed for the BV arm. The results of clinical laboratory evaluations were consistent between KEYNOTE-204, the cHL Safety Dataset and the RSD.

Table 937 ***Summary of subjects with increases in highest laboratory test toxicity Grade from baseline (subjects with baseline and post-baseline measurements)***

Laboratory test	KN204 Data for Pembrolizumab (n=148)	KN204 Data for BV (n=152)	cHL Safety Data (n=389)	Reference Safety Dataset (n=5,884)	Cumulative Running Safety Dataset (n=8,093)
APTT increased	4 (7.5)	5 (10.0)	6 (7.2)	194 (13.6)	297 (13.8)
Alanine Aminotransferase Increased	**50 (33.8)**	**69 (45.4)**	**100 (41.7)**	**261 (25.3)**	**1786 (25.4)**
Albumin decreased	24 (16.4)	29 (1 9.3)	43 (19.3)	1835 (37.3)	2398 (36.1)
Alkaline phosphatase increased	30 (20.5)	34 (22.4)	68 (27.5)	1365 (27.5)	1927 (27.5)
Amylase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)
Aspartate Aminotransferase Increased	**57 (38.5)**	**62 (40.8)**	**108 (44.8)**	**1421 (28.5)**	**2052 (29.2)**
Bilirubin increased	24 (16.2)	13 (8.6)	43 (20.2)	505 (10.2)	781 (11.1)
Calcium decreased	32 (21.6)	24 (15.8)	61 (26.2)	1228 (23.2)	1717 (23.5)
Calcium increased	20 (13.5)	17 (11.2)	44 (19.4)	615 (11.6)	805 (11.0)
Creatine kinase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Creatinine increased	42 (28.4)	21 (13.8)	65 (29.1)	951 (19.1)	1368 (19.4)
Gamma glutamyl transferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	39 (33.9)
Glucose decreased	15 (10.1)	14 (9.2)	65 (26.5)	485 (9.9)	654 (9.5)
Glucose increased	68 (45.9)	55 (36.2)	151 (57.0)	2493 (50.8)	3416 (49.4)
Haemoglobin decreased	35 (23.6)	50 (32.9)	60 (21.0)	2243 (44.4)	3083 (43.0)
Leukocytes decreased	46 (31.1)	67 (44.1)	93 (38.8)	612 (12.2)	905 (12.7)
Lymphocytes decreased	**51 (34.9)**	**48 (32.0)**	**92 (34.3)**	**1791 (38.3)**	**2529 (37.8)**
Magnesium decreased	13 (24.5)	6 (12.0)	43 (30.3)	603 (15.8)	685 (16.1)
Magnesium increased	5 (9.4)	5 (10.0)	12 (10. 4)	265 (7.0)	291 (6.9)
Neutrophils decreased	**41 (28.1)**	**64 (42.7)**	**86 (36.6)**	**349 (7.5)**	**536 (8.0)**
Phosphate decreased	44 (30.8)	27 (18.5)	90 (37.7)	1043 (22.1)	1346 (21.3)
Platelet decreased	**50 (33.8)**	**39 (25.7)**	**103 (40.6)**	**631 (12.6)**	**929 (13.0)**
Potassium decreased	19 (12.8)	21 (13.8)	46 (20.3)	682 (12.9)	965 (13.2)
Potassium increased	22 (14.9)	12 (7.9)	47 (20.6)	966 (18.2)	1306 (17.8)
Prothrombin INR increased	4 (7.4)	5 (10.4)	5 (5.8)	224 (16.0)	339 (15.6)
Sodium decreased	36 (24.5)	30 (19.7)	90 (36.1)	1932 (36.2)	2570 (34.8)
Sodium increased	12 (8.2)	8 (5.3)	25 (11. 6)	290 (5.5)	372 (5.1)
Triglycerides increased	0 (0.0)	0 (0.0)	0 (0.0)	808 (35.0)	810 (35.0)

In KEYNOTE-204, there were 10 participants in each treatment group (6.8% and 6.6% in the pembrolizumab and BV groups, respectively) who experienced "*thrombocytopenia*" or "*platelet count decreased*" as reported by the sites as an AE. Among the 10 participants in the pembrolizumab group, 9 participants had an event outcome reported as resolved, as of the data cut-off date.

Among these 10 participants in the pembrolizumab group, Grade 1 events were experienced by 4 participants, and Grade 2, 3, and 4 events were experienced by 2 participants each. There were no events that led to clinical sequelae nor had a fatal outcome. Among participants in KEYNOTE-204, 12 were treated with platelet infusions: 7 (4.7%) in the pembrolizumab group and 5 (3.3%) in the BV group. Most platelet infusions were intended for treatment of thrombocytopenia. Concomitant medications for Grade 3-4 thrombocytopenia for the 4 participants in the KEYNOTE-204 pembrolizumab arm were also provided.

In the RSD, excluding the 243 cHL participants from KEYNOTE-013 and KEYNOTE-087, a total of 140 participants out of 5643 (2.5%) experienced thrombocytopenia or platelet count decreased. Of these, there were 100 participants with Grade 1 events, 20 with Grade 2 events, 9 with Grade 3 events, and 11 with Grade 4 events. There were no events that led to clinical sequelae nor had a fatal outcome. Less than 1%

(17/5643) of patients received a platelet transfusion after starting pembrolizumab. In addition, a case of autoimmune thrombocytopenia has been reported after treatment with pembrolizumab in KEYNOTE-204.

Immunogenicity

No new immunogenicity data were available.

Analysis of Secondary Malignancies

There were no secondary malignancies identified in the KEYNOTE-204 or reported in the cHL Safety Dataset.

Safety in special populations

Age

In the KEYNOTE-204 pembrolizumab arm, the incidence of AEs was generally higher among older patients (>=65), similar to the cHL Safety Dataset. This pattern was not observed between the age groups in the RSD and in the CRS.

Table 948 ***Adverse Event Summary by Age Category (<65, ≥65 Years)***

	KN204 Data for Pembrolizumab‡‡				KN204 Data for Brentuximab Vedotin¶				cHL Safety Data for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab§§			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	122		26		130		22		343		46		3,385		2,499		4,640		3,453	
with one or more adverse events	119	(97.5)	26	(100.0)	121	(93.1)	22	(100.0)	335	(97.7)	46	(100.0)	3,268	(96.5)	2,422	(96.9)	4,476	(96.5)	3,335	(96.6)
with no adverse event	3	(2.5)	0	(0.0)	9	(6.9)	0	(0.0)	8	(2.3)	0	(0.0)	117	(3.5)	77	(3.1)	164	(3.5)	118	(3.4)
with drug-related† adverse events	87	(71.3)	23	(88.5)	97	(74.6)	20	(90.9)	245	(71.4)	40	(87.0)	2,366	(69.9)	1,766	(70.7)	3,161	(68.1)	2,417	(70.0)
with toxicity grade 3-5 adverse events	50	(41.0)	15	(57.7)	51	(39.2)	15	(68.2)	123	(35.9)	24	(52.2)	1,505	(44.5)	1,324	(53.0)	2,139	(46.1)	1,797	(52.0)
with toxicity grade 3-5 drug-related adverse events	23	(18.9)	6	(23.1)	28	(21.5)	10	(45.5)	52	(15.2)	10	(21.7)	456	(13.5)	457	(18.3)	657	(14.2)	640	(18.5)
with serious adverse events	30	(24.6)	14	(53.8)	25	(19.2)	7	(31.8)	81	(23.6)	23	(50.0)	1,182	(34.9)	1,084	(43.4)	1,634	(35.2)	1,456	(42.2)
with serious drug-related adverse events	16	(13.1)	8	(30.8)	12	(9.2)	4	(18.2)	36	(10.5)	10	(21.7)	346	(10.2)	310	(12.4)	475	(10.2)	442	(12.8)
who died	3	(2.5)	0	(0.0)	1	(0.8)	1	(4.5)	5	(1.5)	1	(2.2)	144	(4.3)	168	(6.7)	204	(4.4)	240	(7.0)
who died due to a drug-related adverse event	1	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	21	(0.6)	18	(0.7)	28	(0.6)	33	(1.0)
discontinued drug due to an adverse event	14	(11.5)	6	(23.1)	17	(13.1)	10	(45.5)	33	(9.6)	8	(17.4)	399	(11.8)	391	(15.6)	523	(11.3)	524	(15.2)
discontinued drug due to a drug-related adverse event	13	(10.7)	6	(23.1)	15	(11.5)	10	(45.5)	28	(8.2)	8	(17.4)	207	(6.1)	203	(8.1)	270	(5.8)	281	(8.1)
discontinued drug due to a serious adverse event	10	(8.2)	4	(15.4)	5	(3.8)	3	(13.6)	18	(5.2)	6	(13.0)	287	(8.5)	285	(11.4)	383	(8.3)	377	(10.9)
discontinued drug due to a serious drug-related adverse event	9	(7.4)	4	(15.4)	3	(2.3)	3	(13.6)	14	(4.1)	6	(13.0)	123	(3.6)	122	(4.9)	166	(3.6)	168	(4.9)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.
¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.
‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.
†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)
Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Database cutoff date for HCC (KN224: 15MAY2018)
Database Cutoff date for Merkel Cell (P017: 06FEB2018)
Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)
Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)
Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)
Database Cutoff date for TMB-H (KN158: 27JUN2019)

Source: [ISS: adam-adsl; adae]

The most commonly occurring AEs among participants ≥65 years (n=26) treated with pembrolizumab are provided in Table 76. Compared with participants <65 years of age treated with pembrolizumab (Table 77), participants ≥65 years of age had higher (>15 percentage point difference) rates of *peripheral oedema* (23.1% vs 0.8%), *decreased appetite* (23.1% vs 2.5%), and *pain in extremity* (23.1% vs 5.7%) (AE incidences <5% not shown in table).

Slightly higher rates of AEs for some categories were also observed among older participants compared with younger participants in the BV arm of KEYNOTE-204 (e.g., Grade 3 to 5 AEs: 68.2% vs 39.2%) and the RSD (Grade 3 to 5 AEs: 53.0% vs 44.5%).

Table 959 Subjects with Adverse Events by decreasing incidence

(Incidence ≥ 5%)
(Age >= 65 years)
(MK-3475 200 mg)
(ASaT Population)

	MK-3475 200 mg	
	n	(%)
Subjects in population	26	
with one or more adverse events	26	(100.0)
with no adverse events	0	(0.0)
Hypothyroidism	8	(30.8)
Pruritus	7	(26.9)
Decreased appetite	6	(23.1)
Diarrhoea	6	(23.1)
Oedema peripheral	6	(23.1)
Pain in extremity	6	(23.1)
Nasopharyngitis	5	(19.2)
Nausea	5	(19.2)
Pyrexia	5	(19.2)
Urinary tract infection	5	(19.2)
Fatigue	4	(15.4)
Hyperthyroidism	4	(15.4)
Rash	4	(15.4)
Vomiting	4	(15.4)
Chills	3	(11.5)
Cough	3	(11.5)
Dizziness	3	(11.5)
Dry skin	3	(11.5)
Peripheral sensory neuropathy	3	(11.5)
Pneumonia	3	(11.5)
Upper respiratory tract infection	3	(11.5)
Abdominal pain upper	2	(7.7)
Arthralgia	2	(7.7)
Blood creatinine increased	2	(7.7)
Constipation	2	(7.7)
Dehydration	2	(7.7)
Dry mouth	2	(7.7)
Dysgeusia	2	(7.7)
Dyspnoea	2	(7.7)
Dyspnoea exertional	2	(7.7)
Dysuria	2	(7.7)
Eczema	2	(7.7)
Feeling cold	2	(7.7)
Gait disturbance	2	(7.7)
Headache	2	(7.7)
Infusion related reaction	2	(7.7)
Insomnia	2	(7.7)
Interstitial lung disease	2	(7.7)
Muscle spasms	2	(7.7)
Oropharyngeal pain	2	(7.7)
Peripheral swelling	2	(7.7)
Puncture site pain	2	(7.7)
Renal impairment	2	(7.7)
Stomatitis	2	(7.7)
Tremor	2	(7.7)
Weight decreased	2	(7.7)
Wheezing	2	(7.7)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adae]

(Incidence ≥ 5%)
(Age < 65 years)
(MK-3475 200 mg)
(ASaT Population)

	MK-3475 200 mg	
	n	(%)
Subjects in population	122	
with one or more adverse events	119	(97.5)
with no adverse events	3	(2.5)
Upper respiratory tract infection	25	(20.5)
Pyrexia	24	(19.7)
Diarrhoea	23	(18.9)
Cough	22	(18.0)
Hypothyroidism	20	(16.4)
Fatigue	19	(15.6)
Pruritus	19	(15.6)
Back pain	18	(14.8)
Nausea	16	(13.1)
Vomiting	16	(13.1)
Headache	13	(10.7)
Alanine aminotransferase increased	12	(9.8)
Aspartate aminotransferase increased	12	(9.8)
Nasopharyngitis	12	(9.8)
Pneumonitis	12	(9.8)
Arthralgia	11	(9.0)
Urinary tract infection	11	(9.0)
Neutropenia	10	(8.2)
Oropharyngeal pain	10	(8.2)
Weight increased	10	(8.2)
Abdominal pain	9	(7.4)
Constipation	9	(7.4)
Dyspnoea	9	(7.4)
Pneumonia	9	(7.4)
Rash	9	(7.4)
Thrombocytopenia	9	(7.4)
Anaemia	8	(6.6)
Rhinitis	8	(6.6)
Anxiety	7	(5.7)
Asthenia	7	(5.7)
Depression	7	(5.7)
Nasal congestion	7	(5.7)
Pain in extremity	7	(5.7)
Paresthesia	7	(5.7)
Sinusitis	7	(5.7)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 16JAN2020

Source: [P204V01MK3475: adam-adsl; adae]

Gender

In the pembrolizumab arm, the events observed in males versus females were as follows:

- Drug-related AEs in 59 (72.8%) males and 51 (76.1%) females;
- Grade 3 to 5 AEs in 34 (42.0%) males versus 31 (46.3%) females;
- SAEs in 21 (25.9%) males versus 23 (34.3%) females;

- Discontinuations due to AEs in 8 (9.9%) males versus 12 (17.9%) females.

This was generally consistent across the KEYNOTE-204 pembrolizumab arm, the cHL Safety Dataset, and the RSD.

Table 96 ***Adverse Event Summary by Gender (Male, Female)***

	KN204 Data for Pembrolizumab‡‡				KN204 Data for Brentuximab Vedotin¶				cHL Safety Data for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab§§			
	M		F		M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	81		67		89		63		212		177		3,887		1,997		5,416		2,677	
with one or more adverse events	79	(97.5)	66	(98.5)	86	(96.6)	57	(90.5)	207	(97.6)	174	(98.3)	3,756	(96.6)	1,934	(96.8)	5,215	(96.3)	2,596	(97.0)
with no adverse event	2	(2.5)	1	(1.5)	3	(3.4)	6	(9.5)	5	(2.4)	3	(1.7)	131	(3.4)	63	(3.2)	201	(3.7)	81	(3.0)
with drug-related† adverse events	59	(72.8)	51	(76.1)	71	(79.8)	46	(73.0)	151	(71.2)	134	(75.7)	2,710	(69.7)	1,422	(71.2)	3,691	(68.1)	1,887	(70.5)
with toxicity grade 3-5 adverse events	34	(42.0)	31	(46.3)	39	(43.8)	27	(42.9)	75	(35.4)	72	(40.7)	1,894	(48.7)	935	(46.8)	2,659	(49.1)	1,277	(47.7)
with toxicity grade 3-5 drug-related adverse events	15	(18.5)	14	(20.9)	24	(27.0)	14	(22.2)	33	(15.6)	29	(16.4)	630	(16.2)	283	(14.2)	910	(16.8)	387	(14.5)
with serious adverse events	21	(25.9)	23	(34.3)	18	(20.2)	14	(22.2)	55	(25.9)	49	(27.7)	1,534	(39.5)	732	(36.7)	2,105	(38.9)	985	(36.8)
with serious drug-related adverse events	14	(17.3)	10	(14.9)	10	(11.2)	6	(9.5)	28	(13.2)	18	(10.2)	448	(11.5)	208	(10.4)	644	(11.9)	273	(10.2)
who died	1	(1.2)	2	(3.0)	1	(1.1)	1	(1.6)	4	(1.9)	2	(1.1)	221	(5.7)	91	(4.6)	326	(6.0)	118	(4.4)
who died due to a drug-related adverse event	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	25	(0.6)	14	(0.7)	40	(0.7)	21	(0.8)
discontinued drug due to an adverse event	8	(9.9)	12	(17.9)	17	(19.1)	10	(15.9)	21	(9.9)	20	(11.3)	529	(13.6)	261	(13.1)	717	(13.2)	330	(12.3)
discontinued drug due to a drug-related adverse event	8	(9.9)	11	(16.4)	16	(18.0)	9	(14.3)	18	(8.5)	18	(10.2)	278	(7.2)	132	(6.6)	380	(7.0)	171	(6.4)
discontinued drug due to a serious adverse event	6	(7.4)	8	(11.9)	5	(5.6)	3	(4.8)	14	(6.6)	10	(5.6)	386	(9.9)	186	(9.3)	523	(9.7)	237	(8.9)
discontinued drug due to a serious drug-related adverse event	6	(7.4)	7	(10.4)	4	(4.5)	2	(3.2)	11	(5.2)	9	(5.1)	167	(4.3)	78	(3.9)	232	(4.3)	102	(3.8)

† Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

‡‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.

¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.

ECOG PS

The incidence of AEs with pembrolizumab was similar between subjects with an ECOG performance status of 1 and an ECOG performance status of 0. Nevertheless drug-related AEs, Grade 3-5 AEs, deaths and SAEs were higher in subjects with ECOG PS 1. This was consistent across the KEYNOTE-204 pembrolizumab arm, the cHL Safety Dataset and the RSD.

Table 971 ***Adverse Event Summary by ECOG Status Category (0, 1)***

	KN204 Data for Pembrolizumab‡‡				KN204 Data for Brentuximab Vedotin¶				cHL Safety Data for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab§§			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	84		63		99		53		200		187		2,761		2,931		3,723		4,059	
with one or more adverse events	81	(96.4)	63	(100.0)	94	(94.9)	49	(92.5)	195	(97.5)	184	(98.4)	2,671	(96.7)	2,835	(96.7)	3,589	(96.4)	3,923	(96.6)
with no adverse event	3	(3.6)	0	(0.0)	5	(5.1)	4	(7.5)	5	(2.5)	3	(1.6)	90	(3.3)	96	(3.3)	134	(3.6)	136	(3.4)
with drug-related† adverse events	57	(67.9)	52	(82.5)	81	(81.8)	36	(67.9)	139	(69.5)	144	(77.0)	2,085	(75.5)	1,940	(66.2)	2,734	(73.4)	2,642	(65.1)
with toxicity grade 3-5 adverse events	33	(39.3)	31	(49.2)	43	(43.4)	23	(43.4)	60	(30.0)	86	(46.0)	1,112	(40.3)	1,605	(54.8)	1,526	(41.0)	2,243	(55.3)
with toxicity grade 3-5 drug-related adverse events	14	(16.7)	14	(22.2)	28	(28.3)	10	(18.9)	27	(13.5)	34	(18.2)	410	(14.8)	471	(16.1)	561	(15.1)	671	(16.5)
with serious adverse events	25	(29.8)	19	(30.2)	18	(18.2)	14	(26.4)	48	(24.0)	56	(29.9)	872	(31.6)	1,294	(44.1)	1,182	(31.7)	1,761	(43.4)
with serious drug-related adverse events	16	(19.0)	8	(12.7)	12	(12.1)	4	(7.5)	26	(13.0)	20	(10.7)	311	(11.3)	325	(11.1)	419	(11.3)	456	(11.2)
who died	1	(1.2)	2	(3.2)	1	(1.0)	1	(1.9)	2	(1.0)	4	(2.1)	79	(2.9)	217	(7.4)	121	(3.3)	304	(7.5)
who died due to a drug-related adverse event	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	14	(0.5)	25	(0.9)	21	(0.6)	39	(1.0)
discontinued drug due to an adverse event	12	(14.3)	8	(12.7)	20	(20.2)	7	(13.2)	19	(9.5)	22	(11.8)	304	(11.0)	452	(15.4)	407	(10.9)	585	(14.4)
discontinued drug due to a drug-related adverse event	11	(13.1)	8	(12.7)	18	(18.2)	7	(13.2)	16	(8.0)	20	(10.7)	193	(7.0)	200	(6.8)	257	(6.9)	261	(6.4)
discontinued drug due to a serious adverse event	9	(10.7)	5	(7.9)	6	(6.1)	2	(3.8)	11	(5.5)	13	(7.0)	198	(7.2)	350	(11.9)	265	(7.1)	460	(11.3)

	KN204 Data for Pembrolizumab‡				KN204 Data for Brentuximab Vedotin¶				cHL Safety Data for Pembrolizumab‖				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab§§			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued drug due to a serious drug-related adverse event	8	(9.5)	5	(7.9)	4	(4.0)	2	(3.8)	9	(4.5)	11	(5.9)	106	(3.8)	130	(4.4)	142	(3.8)	176	(4.3)

† Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

‡ Includes all subjects who received at least one dose of Pembrolizumab in KN204.

¶ Includes all subjects who received at least one dose of Brentuximab Vedotin in KN204.

‖ Includes all subjects who received at least one dose of Pembrolizumab in KN204, KN087 and KN013 Cohort 3.

†† Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

§§ Includes all subjects who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, ; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (cHL) and KN013 Cohort 4A (PMBCL), KN024, KN028 Cohort A4 (Esophageal), KN028 Cohort B4 (Cervical) and KN028 Cohort C1 (SCLC), KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 Cohort 1, KN062, KN087, KN204, KN158 Cohort C (Cervical), KN158 Cohort G (SCLC) and KN158 TMB-H, KN164 Cohort A, KN170, KN180, KN181, KN224, KN427, and P017.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052:26SEP2018)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)

Database cutoff date for HCC (KN224: 15MAY2018)

Database Cutoff date for Merkel Cell (P017: 06FEB2018)

Database Cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Database Cutoff date for Renal Carcinoma (KN427: 07SEP2018)

Database Cutoff date for SCLC (KN158-Cohort G: 27JUN2019, KN028-Cohort C1: 31JUL2018)

Database Cutoff date for NMIBC (non-muscle invasive bladder cancer) (KN057: 24MAY2019)

Database Cutoff date for TMB-H (KN158: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Complications Following Post-Allogeneic Stem Cell Transplantation (SCT)

In KEYNOTE-204, 14 and 13 patients in the pembrolizumab and BV arms respectively, underwent allo-SCT after stopping treatment. Of these, 12 (85.7%) in the pembrolizumab arm and 7 (53.8%) in the BV group experienced a post allo-SCT AE. The most common AE was *GVHD* for 8 patients (57.1%) in the pembrolizumab arm (n=1 Grade 1, n=5 Grade 2, n=1 Grade 3, n=1 Grade 4) and for 5 patients (38.5%) in the BV group (n=1 Grade 2, n=3 Grade 3, n=1 Grade 4). No participants experienced *hepatic veno-occlusive disease*.

Two patients, both in the pembrolizumab arm, died due to AEs: *hypovolemic shock* and *hypoxic respiratory failure*, both of which were reported by the MAH as not related to the study treatment.

In KEYNOTE-087, 32 patients (15.2%) underwent allo-SCT; 20 of these patients experienced a post-allo-SCT AE. The most common AE was *GVHD* (n=18): *acute GVHD* (n=11, including 1 hyperacute), *chronic GVHD* (n=2), or both (n=5). Eight patients had more than 1 event of *GVHD* (acute and/or chronic). Among the 30 events of *GVHD*, most events were Grade 1 (11 events), 13 were Grade 2, 4 were Grade 3 and 2 were Grade 5. No participants experienced *hepatic veno-occlusive disease*. Four patients died due to post allo-SCT AEs: *acute GVHD*, *hyperacute GVHD*, *pneumonia* and *sepsis* (n=1 each). None was considered by the MAH related to the study treatment.

In KEYNOTE-051, 2 cHL paediatric patients received an allo-SCT after treatment with pembrolizumab. Both patients developed a post allogeneic SCT complication: Grade 2 *chronic GVHD* in 1 patient and Grade 2 *acute GVHD* in the other, approximately 4 months post-allogeneic SCT. At the time of the study, both patients were alive and the *GVHD* was not resolved. The investigators considered the *chronic* and *acute GVHD* as not related to pembrolizumab.

For the 48 cHL participants in KEYNOTE-051, KEYNOTE-087 and KEYNOTE-204 who received an allo-SCT after on-study pembrolizumab, a summary of the time from the last dose of on-study pembrolizumab to allo-SCT is presented for the overall population as well as whether the participant experienced a *GVHD*

(either acute or chronic) or not. Of note, there is one participant excluded in the analysis of time since last dose of pembrolizumab to first allo-SCT due to insufficient data in the date of the allo-SCT as the month of transplant was missing. Also in KEYNOTE-051, there is only 1 participant in the analysis with *GVHD* compared to 2 who was excluded from the AE summary tables because the onset date of *GVHD* (12.01.2020) occurred after the data cut-off (10.01.2020).

Table 982 Time to allo-SCT after the last dose of on-study pembrolizumab

	GVHD		No GVHD		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	28		20		48	
Study						
3475-051	1	(3.6)	1	(5.0)	2	(4.2)
3475-087	18	(64.3)	14	(70.0)	32	(66.7)
3475-204	9	(32.1)	5	(25.0)	14	(29.2)
Time since Last Dose of Pembrolizumab to First Allogeneic HSCT (Months)						
Subjects with data	28		19		47	
Mean	6.9		9.2		7.8	
SD	6.8		8.3		7.4	
Median	4.5		5.5		4.6	
Range	1 to 30		1 to 33		1 to 33	

Source: [PMR: adam-adsl; adbase]

In KEYNOTE-204, additional information on the 10 allo-SCT participants post-pembrolizumab who experienced a *GVHD* event are provided. Also, details on the mortality status for all pembrolizumab participants receiving allo-SCT, where 'transplant-related' death was considered as any death that was not reported as progressive disease, is provided and includes additional information on all 14 allo-SCT participants, such as the last known contact date and follow-up time since allo-SCT. These preliminary data confirm that *GVHD* is a frequent AE post pembrolizumab, especially as *acute GVHD* (reported 8 out of 11 patients, including the subject excluded from the analysis), Grade 2 or Grade 3 predominantly. However, also *chronic GVHD* mild/moderate/severe has been observed (in 3 out of 11 patients). Of the fourteen transplanted patients, two patients died, and the cause of death was *respiratory failure* and *hypovolaemic shock*, respectively.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction (DDI) studies have been performed. However, as pembrolizumab is an IgG antibody administrated parenterally and cleared by catabolism, food and DDI are not able to influence exposure, and drugs that affect cytochrome P450 enzymes are not expected to interfere with the metabolism of pembrolizumab. Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, the use of systemic corticosteroids or other immunosuppressive drugs should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab, although these drugs can be used to treat immune-related adverse reactions during the pembrolizumab treatment.

Discontinuation due to adverse events

Adverse Events and Drug-related Adverse Events leading to Treatment Discontinuation

Adverse Events Leading to Treatment Discontinuation

The incidence of AEs leading to discontinuation of study treatment in KEYNOTE-204 was similar for the pembrolizumab and BV groups (13.5% vs 17.8%), with the exception of *neuropathy peripheral* (0% pembrolizumab, 5.3% BV), *peripheral sensory neuropathy* (0% pembrolizumab, 3.9% BV), and *pneumonitis* (6.1% pembrolizumab, 0% BV). The incidence of AEs leading to discontinuation was lower in the pembrolizumab arm respect to the BV group, after adjustment for exposure (1.03 vs 2.80 events/100 person-months). The overall incidence of AEs leading to pembrolizumab discontinuation in KEYNOTE-204 was consistent with the cHL Safety Dataset and the RSD, except for *pneumonitis* (6.1% in KEYNOTE-204 pembrolizumab arm, 4.4% in the cHL Safety Dataset and 1.6% in the RSD).

Table 993 ***Subjects with adverse events resulting in treatment discontinuation (the most frequent AEs leading to treatment discontinuation)***

	KN204 Data for Pembrolizumab‡‡		KN204 Data for Brentuximab Vedotin¶		cHL Safety Data for Pembrolizumab‖		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	20	(13.5)	27	(17.8)	41	(10.5)	790	(13.4)	1,047	(12.9)
with no adverse events	128	(86.5)	125	(82.2)	348	(89.5)	5,094	(86.6)	7,046	(87.1)
Pneumonitis	9	(6.1)	0	(0.0)	17	(4.4)	96	(1.6)	124	(1.5)
Interstitial Lung Disease	2	(1.4)	1	(0.7)	3	(0.8)	8	(0.1)	15	(0.2)
Acute Kidney Injury	1	(0.7)	0	(0.0)	1	(0.3)	6	(0.1)	10	(0.1)
Bacteraemia	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Blood Bilirubin Increased	1	(0.7)	0	(0.0)	1	(0.3)	4	(0.1)	11	(0.1)
Encephalitis Autoimmune	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Escherichia Infection	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Infusion Related Reaction	1	(0.7)	3	(2.0)	3	(0.8)	2	(0.0)	3	(0.0)
Nephropathy	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Respiratory Tract Infection Fungal	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Squamous Cell Carcinoma Of The Cervix	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Abdominal Distension	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Abdominal Pain Upper	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Accidental Death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Acute Coronary Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Acute Myocardial Infarction	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Acute Respiratory Failure	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)	5	(0.1)
Addison's Disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)

Drug-related Adverse Events Leading to Treatment Discontinuation

Drug-related AEs that resulted in treatment discontinuation were reported in 12.8% of patients in the pembrolizumab arm and in 16.4% of patients in the BV group. The incidence of drug-related AEs leading to treatment discontinuation was similar except for *neuropathy peripheral* (0% pembrolizumab, 5.3% BV), *peripheral sensory neuropathy* (0% pembrolizumab, 3.9% BV) and *pneumonitis* (6.1% pembrolizumab, 0% BV). The incidence of drug-related AEs leading to discontinuation was lower in the pembrolizumab arm compared with BV group, after adjustment for exposure (0.98 vs 2.52 events/100 person-months). The overall incidence of drug-related AEs leading to discontinuation was higher than in the cHL Safety Dataset and the RSD (12.8% in the KEYNOTE-204 pembrolizumab arm, 9.3% in the cHL Safety dataset and 7% in the RSD). *Pneumonitis* was the only drug-related AE leading to discontinuation with a greater than 2 percentage point difference in KEYNOTE-204 compared with the RSD (6.1% vs 1.6%).

Table 1004 ***Subjects with drug-related adverse events resulting in treatment discontinuation (the most frequent drug-related AEs leading to treatment discontinuation)***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	19	(12.8)	25	(16.4)	36	(9.3)	410	(7.0)	551	(6.8)
with no adverse events	129	(87.2)	127	(83.6)	353	(90.7)	5,474	(93.0)	7,542	(93.2)
Pneumonitis	9	(6.1)	0	(0.0)	17	(4.4)	94	(1.6)	122	(1.5)
Interstitial Lung Disease	2	(1.4)	1	(0.7)	3	(0.8)	8	(0.1)	15	(0.2)
Acute Kidney Injury	1	(0.7)	0	(0.0)	1	(0.3)	5	(0.1)	9	(0.1)
Bacteraemia	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Blood Bilirubin Increased	1	(0.7)	0	(0.0)	1	(0.3)	3	(0.1)	6	(0.1)
Encephalitis Autoimmune	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Escherichia Infection	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Infusion Related Reaction	1	(0.7)	3	(2.0)	3	(0.8)	2	(0.0)	3	(0.0)
Nephropathy	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Respiratory Tract Infection Fungal	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Addison's Disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Adrenal Insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)	7	(0.1)
Adrenocorticotropic Hormone Deficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alanine Aminotransferase Increased	0	(0.0)	0	(0.0)	0	(0.0)	18	(0.3)	21	(0.3)
Anaphylactoid Reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Aptyalism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Arterial Thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Arthralgia	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)	6	(0.1)

Adverse Events and Drug-related Adverse Events leading to Treatment Interruption

Adverse Events Leading to Treatment Interruption

The incidence of AEs leading to treatment interruption was similar in the KEYNOTE-204 pembrolizumab and BV arms (29.7% vs 33.6%). The most frequent AEs leading to treatment interruption were *pneumonia* (3.4%) and *upper respiratory tract infection* (3.4%) in the pembrolizumab arm, *neuropathy peripheral* (5.9%) and *infusion-related reactions* (4.6%) in the BV arm. The incidence of AEs leading to interruption of pembrolizumab was consistent between KEYNOTE-204, the cHL safety dataset and the RSD.

Table 1015 ***Subjects with AEs resulting in treatment interruption (most frequent AEs leading to treatment interruption)***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	44	(29.7)	51	(33.6)	117	(30.1)	1,492	(25.4)	2,077	(25.7)
with no adverse events	104	(70.3)	101	(66.4)	272	(69.9)	4,392	(74.6)	6,016	(74.3)
Pneumonia	5	(3.4)	2	(1.3)	14	(3.6)	95	(1.6)	129	(1.6)
Upper Respiratory Tract Infection	5	(3.4)	6	(3.9)	13	(3.3)	39	(0.7)	51	(0.6)
Aspartate Aminotransferase Increased	4	(2.7)	1	(0.7)	8	(2.1)	62	(1.1)	102	(1.3)
Cough	4	(2.7)	3	(2.0)	5	(1.3)	23	(0.4)	38	(0.5)
Pneumonitis	4	(2.7)	1	(0.7)	11	(2.8)	85	(1.4)	107	(1.3)
Alanine Aminotransferase Increased	3	(2.0)	1	(0.7)	9	(2.3)	73	(1.2)	105	(1.3)
Diarrhoea	3	(2.0)	0	(0.0)	12	(3.1)	112	(1.9)	149	(1.8)
Pyrexia	3	(2.0)	1	(0.7)	10	(2.6)	31	(0.5)	44	(0.5)
Confusional State	2	(1.4)	0	(0.0)	2	(0.5)	6	(0.1)	9	(0.1)
Infection	2	(1.4)	1	(0.7)	2	(0.5)	4	(0.1)	7	(0.1)
Abscess	1	(0.7)	0	(0.0)	1	(0.3)	1	(0.0)	2	(0.0)
Acarodermatitis	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Acute Kidney Injury	1	(0.7)	0	(0.0)	2	(0.5)	15	(0.3)	28	(0.3)
Blood Albumin Decreased	1	(0.7)	0	(0.0)	1	(0.3)	1	(0.0)	2	(0.0)
Blood Alkaline Phosphatase Increased	1	(0.7)	1	(0.7)	1	(0.3)	18	(0.3)	29	(0.4)
Blood Creatine Phosphokinase Increased	1	(0.7)	0	(0.0)	2	(0.5)	8	(0.1)	11	(0.1)
Bronchial Obstruction	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Bronchitis	1	(0.7)	1	(0.7)	10	(2.6)	24	(0.4)	29	(0.4)
Cardiac Failure	1	(0.7)	0	(0.0)	1	(0.3)	3	(0.1)	5	(0.1)

Drug-related Adverse Events Leading to Treatment Interruption

Drug-related AEs leading to dose interruption occurred in 18.9% of patients in the pembrolizumab arm and in 28.9% of patients in the BV group. *Diarrhea* (n=3, 2%), *AST increased* (n=3, 2%) and *pneumonitis* (n=3, 2%) were the most common AEs leading to dose interruption in the pembrolizumab arm; *neuropathy peripheral* (n=9, 5.9%), *infusion reaction* (n=7, 4.6%) and *neutropenia* (n=4, 2.6%) were the most common AEs in the BV arm (Table 31). The incidence and types of drug-related AEs leading to the interruption of pembrolizumab in KEYNOTE-204 were consistent with the cHL Safety Dataset and the RSD.

Table 1026 ***Subjects with drug-related adverse events resulting in treatment interruption (the most frequent drug-related AEs leading to treatment interruption)***

	KN204 Data for Pembrolizumab[‡‡]		KN204 Data for Brentuximab Vedotin[¶]		cHL Safety Data for Pembrolizumab[‖]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	148		152		389		5,884		8,093	
with one or more adverse events	28	(18.9)	44	(28.9)	64	(16.5)	837	(14.2)	1,127	(13.9)
with no adverse events	120	(81.1)	108	(71.1)	325	(83.5)	5,047	(85.8)	6,966	(86.1)
Aspartate Aminotransferase Increased	3	(2.0)	1	(0.7)	6	(1.5)	42	(0.7)	71	(0.9)
Diarrhoea	3	(2.0)	0	(0.0)	8	(2.1)	82	(1.4)	114	(1.4)
Pneumonitis	3	(2.0)	1	(0.7)	10	(2.6)	79	(1.3)	98	(1.2)
Alanine Aminotransferase Increased	2	(1.4)	1	(0.7)	5	(1.3)	50	(0.8)	72	(0.9)
Confusional State	2	(1.4)	0	(0.0)	2	(0.5)	2	(0.0)	4	(0.0)
Pneumonia	2	(1.4)	2	(1.3)	3	(0.8)	10	(0.2)	19	(0.2)
Upper Respiratory Tract Infection	2	(1.4)	2	(1.3)	4	(1.0)	4	(0.1)	6	(0.1)
Blood Albumin Decreased	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Blood Alkaline Phosphatase Increased	1	(0.7)	1	(0.7)	1	(0.3)	10	(0.2)	15	(0.2)
Bronchial Obstruction	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Cardiac Failure	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.0)
Colitis	1	(0.7)	0	(0.0)	3	(0.8)	29	(0.5)	41	(0.5)
Gamma-Glutamyltransferase Increased	1	(0.7)	1	(0.7)	1	(0.3)	7	(0.1)	10	(0.1)
H1n1 Influenza	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.0)
Herpes Virus Infection	1	(0.7)	1	(0.7)	1	(0.3)	0	(0.0)	1	(0.0)
Infusion Related Reaction	1	(0.7)	7	(4.6)	3	(0.8)	21	(0.4)	27	(0.3)
Interstitial Lung Disease	1	(0.7)	0	(0.0)	1	(0.3)	8	(0.1)	11	(0.1)
Lower Respiratory Tract Infection	1	(0.7)	1	(0.7)	1	(0.3)	1	(0.0)	2	(0.0)
Neuropathy Peripheral	1	(0.7)	9	(5.9)	1	(0.3)	4	(0.1)	7	(0.1)

Assessment of paediatric data on clinical safety

To support the safety of pembrolizumab (2mg/kg Q3W) in the paediatric population, long-term data from KEYNOTE-051 were presented. KEYNOTE-051 is an ongoing, 2-part Phase 1-2, nonrandomized, open-label, single arm in paediatric population (aged between 6 months to <18 years) with advanced melanoma, relapsed or refractory, PD-L1-positive malignant solid tumours, or cHL (the 22 participants with HL ranged in age from 10 to 17 years: four participants were 10 to 13 years of age and 18 participants were 14 to 17 years of age). A total of 162 paediatric patients were enrolled, 161 of whom (22 with cHL) received at least 1 dose of pembrolizumab.

At the cut-off date (10.01.2020), the median duration of exposure to pembrolizumab was 8-fold-longer for cHL patients (344 days) compared with patients with other tumours (43 days), with a median number of 17 pembrolizumab administrations in cHL patients vs 3 administrations in participants with relapsed/refractory tumours other than cHL. The percentage of patients who received pembrolizumab for ≥6 months and ≥12 months was 3-4-fold higher in cHL than the other patients (72.7% and 40.9% in cHL patients vs 18% and 12.9% in the others participants). The median duration of follow-up was approximately 3-fold longer for participants with cHL (23.7 months, range 4-43.2 months) than for participants with all other tumors types (8.3 months, range 0.4-56 months), primarily due to the large number of early deaths among the other tumour types.

The types and incidences of the most frequently reported AEs in KEYNOTE-051 were consistent with a heavily pre-treated paediatric population with advanced cancers. Although the majority of participants (57.8%) had treatment-related AEs, the proportions of participants with Grade 3 to 5 treatment-related AEs was 8.7%, with treatment-related SAEs was 9.9%, and with treatment-related AEs leading to discontinuation of study treatment was 3.7%.

The most frequently reported AEs (≥20% of participants) were *pyrexia* (32.9%), *vomiting* (29.8%), *headache* (25.5%), *abdominal pain* (22.4%), *anaemia* (21.1%), *cough* (20.5%), and *constipation* (19.9%), the majority of them with Grade 1-2 toxicity.

Table 1037 ***Subjects with Adverse Events by Decreasing Incidence (Incidence ≥ 10%) (All Subjects as Treated Population - Parts I and II)***

	All Subjects as Treated	
	n	(%)
Subjects in population	161	
with one or more adverse events	155	(96.3)
with no adverse events	6	(3.7)
Pyrexia	53	(32.9)
Vomiting	48	(29.8)
Headache	41	(25.5)
Abdominal pain	36	(22.4)
Anaemia	34	(21.1)
Cough	33	(20.5)
Constipation	32	(19.9)
Fatigue	31	(19.3)
Nausea	31	(19.3)
Diarrhoea	30	(18.6)
Decreased appetite	22	(13.7)
Aspartate aminotransferase increased	21	(13.0)
Alanine aminotransferase increased	20	(12.4)
Arthralgia	20	(12.4)
Lymphocyte count decreased	20	(12.4)
Asthenia	19	(11.8)
Back pain	19	(11.8)
Pain in extremity	19	(11.8)
Pruritus	19	(11.8)
White blood cell count decreased	18	(11.2)
Dyspnoea	17	(10.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adae]

The most frequently reported treatment-related AEs (>5% of participants) were *fatigue* (8.7%), *anemia* (8.1%), *pyrexia* (7.5%), *aspartate aminotransferase increased* (6.8%), *lymphocyte count decreased* (6.8%), *diarrhea* (6.2%), *alanine aminotransferase increased* (5.6%), and *hypothyroidism* (5.6%), the majority of them with Grade 1-2 toxicity.

Table 1048. ***Subjects with Drug-related Adverse Events by Decreasing Incidence (Incidence ≥ 5%) (All Subjects as Treated Population - Parts I and II)***

	All Subjects as Treated	
	n	(%)
Subjects in population	161	
with one or more Adverse Events	93	(57.8)
with no Adverse Events	68	(42.2)
Fatigue	14	(8.7)
Anaemia	13	(8.1)
Pyrexia	12	(7.5)
Aspartate aminotransferase increased	11	(6.8)
Lymphocyte count decreased	11	(6.8)
Diarrhoea	10	(6.2)
Alanine aminotransferase increased	9	(5.6)
Hypothyroidism	9	(5.6)
Nausea	8	(5.0)
Rash maculo-papular	8	(5.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 10JAN2020).

Source: [P051V02MK3475: adam-adsl; adae]

The most frequently reported Grade 3 to 5 AEs (>5% of participants) were *anemia* (8.1%) and *lymphocyte count decreased* (5.6%).

Table 1059 ***Subjects with Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 5%) (All Subjects as Treated Population - Parts I and II)***

	All Subjects as Treated	
	n	(%)
Subjects in population	161	
with one or more Adverse Events	76	(47.2)
with no Adverse Events	85	(52.8)
Anaemia	13	(8.1)
Lymphocyte count decreased	9	(5.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 10JAN2020).

The most frequently reported SAEs (≥2% of participants) were *pyrexia* (6.8%), *pneumonia* (3.7%), *pleural effusion* (3.1%), *device related infection* (2.5%), *seizure* (1.9%), *sepsis* (1.9%), and *vomiting* (1.9%).

Table 106 ***Subjects with Serious Adverse Events by Decreasing Incidence Up to 90 Days from Last Dose (Incidence ≥ 1%) (All Subjects as Treated Population - Parts I and II)***

	All Subjects as Treated	
	n	(%)
Subjects in population	161	
with one or more adverse events	62	(38.5)
with no adverse events	99	(61.5)
Pyrexia	11	(6.8)
Pneumonia	6	(3.7)
Pleural effusion	5	(3.1)
Device related infection	4	(2.5)
Seizure	3	(1.9)
Sepsis	3	(1.9)
Vomiting	3	(1.9)
Dyspnoea	2	(1.2)
Headache	2	(1.2)
Hypertension	2	(1.2)
Nausea	2	(1.2)
Pneumonitis	2	(1.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 10JAN2020).

The most frequently reported treatment related SAEs (>1% of participants) were *pyrexia* in 4 participants (2.5%), *hypertension* in 2 participants (1.2%), and *pleural effusion* in 2 participants (1.2%).

Death: five participants (3.1%) had 1 or more AEs that resulted in death up to 90 days after receiving the last dose of pembrolizumab. Two participants had fatal AEs reported by the investigator as treatment related: 1 participant had *pulmonary edema* and 1 participant had *pneumonitis and pleural effusion*. The fatal, treatment-related AE of *pulmonary edema* occurred in a participant experiencing concomitant *sepsis*. The fatal, treatment-related AEs of *pneumonitis* and *pleural effusion* occurred in a participant with extensive right chest involvement of the underlying epithelioid sarcoma.

One participant with a primary diagnosis of solid tumour NOS developed a secondary malignancy of Grade 5 *adenocarcinoma gastric*, reported by the investigator as not treatment related. No other secondary malignancies were identified.

Two out of 4 participants with MSI-H solid tumours had a serious neurologic AE during the first 2 treatment cycles. Both SAEs (*seizure and myoclonus*) were reported as non-treatment related by the investigator, and no action was taken with pembrolizumab in response to the events.

AEOSIs: thirty (18.6%) participants had at least 1 AEOSI. The most frequently reported AEOSI (in ≥2.5% of participants) were *hypothyroidism* (8.1%), *hyperthyroidism* (3.7%), *hypersensitivity* (2.5%), and *pneumonitis* (2.5%). Four (2.5%) participants had a Grade 3 to 5 AEOSI: 3 participants with a Grade 3 AEOSI (*colitis, myelitis, and pruritus*) and 1 participant with Grade 5 *pneumonitis*. The AEOSIs were manageable with standard therapeutic strategies or concomitant corticosteroids and among the 30 participants who had at least 1 AEOSI, 13 (43.3%) participants had resolution of an event by the time of data cutoff.

Treatment with pembrolizumab was well tolerated; most AEs did not lead to **treatment interruption**. Among the 21 (13.0%) participants who had at least 1 AE resulting in treatment interruption, the most common AE and drug-related AE was *alanine aminotransferase increased* in 3 (1.9%) participants.

An **update on immunological analyses** has been also provided by the MAH for paediatric cHL patients included in KEYNOTE-051. Vaccinated antibody concentrations and memory B- and T-cell counts were collected as part of the secondary objectives of KEYNOTE-051. Analyses of pooled KEYNOTE-051 participants indicate an upward trend from pre-treatment to post-treatment Cycle 4 in memory B- and T-cell counts through. Minimal changes were observed in the concentration of vaccinated antibodies from pre-treatment to post-treatment Cycle 4.

In KEYNOTE-051, 3 patients received an allo-SCT after treatment with pembrolizumab (2 paediatric patients with cHL). One cHL patient was treated with pembrolizumab for 12 weeks, then discontinued treatment while continuing to receive an "immune checkpoint blockade" (but the name and duration were unknown). The allo-SCT was performed 11 months after stopping the pembrolizumab treatment. Approximately 4 months post-allogeneic SCT, the patient developed a Grade 2 *chronic GVHD*; the patient was alive, approximately 10 months after allo-SCT.

The other cHL patient underwent allo-SCT after receiving treatment with pembrolizumab (30 doses). On Day 644, the patient discontinued pembrolizumab and on Day 736 (about after 3 months of interruption) had an allo-SCT. GVHD prophylaxis included anti-thymocyte immunoglobulin and methotrexate. On Day 846, the patient developed a Grade 2 *acute GVHD*, treated with steroid; at the cut-off date, the patient was alive, but *acute GVHD* was not resolved. The investigator considered the *chronic* and *acute GVHD* as not related to pembrolizumab.

No additional participants in KEYNOTE-051 have received an allo-SCT after the cut-off data (10 Jan 2020).

Comparison of cHL paediatric safety data to cumulative paediatric safety data:

AEs among participants with rrcHL and other tumour types in KEYNOTE-051, are provided by key categories: overall AE summary (Table 79), and overall summary of AEOSI. The data provided by the MAH showed that the patients with cHL had higher rates of drug-related AEs and dose modifications due to AEs compared with other tumour types while participants with other tumor types had higher rates of Grade 3-5 AEs and SAEs. They experienced higher rates of overall AEOSI and drug-related AEOSI compared with participants with other tumor types. Nevertheless, the duration of exposure to pembrolizumab was approximately 8-fold longer for participants in KEYNOTE-051 with cHL.

Comparison of cHL paediatric safety data to the cHL safety profile in adults:

While the number of cHL participants in KEYNOTE-051 is small (N=22), a comparison of AE rates in KEYNOTE-051 versus cHL participants in KEYNOTE-204 and the cHL Safety Dataset shows consistently lower rates for all AE categories in the KEYNOTE-051 cHL dataset (except for AEOSI).

Table 1071 KEYNOTE-051 Adverse events summary, all subjects Parts I, II

	Hodgkin Lymphoma		Other Tumor Types		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	22		139		161	
with one or more adverse events	21	(95.5)	134	(96.4)	155	(96.3)
with no adverse event	1	(4.5)	5	(3.6)	6	(3.7)
with drug-related† adverse events	15	(68.2)	78	(56.1)	93	(57.8)
with toxicity grade 3-5 adverse events	6	(27.3)	70	(50.4)	76	(47.2)
with toxicity grade 3-5 drug-related adverse events	2	(9.1)	12	(8.6)	14	(8.7)
with serious adverse events	4	(18.2)	58	(41.7)	62	(38.5)
with serious drug-related adverse events	2	(9.1)	14	(10.1)	16	(9.9)
with dose modification‡ due to an adverse event	6	(27.3)	21	(15.1)	27	(16.8)
who died	0	(0.0)	5	(3.6)	5	(3.1)
who died due to a drug-related adverse event	0	(0.0)	2	(1.4)	2	(1.2)
discontinued drug due to an adverse event	1	(4.5)	9	(6.5)	10	(6.2)
discontinued drug due to a drug-related adverse event	1	(4.5)	5	(3.6)	6	(3.7)
discontinued drug due to a serious adverse event	1	(4.5)	7	(5.0)	8	(5.0)
discontinued drug due to a serious drug-related adverse event	1	(4.5)	3	(2.2)	4	(2.5)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
Reporting for serious adverse events and serious drug-related adverse events goes through 90 days.
(Data Cutoff Date: 10JAN2020).

Table 1082 KEYNOTE-051 Adverse events summary for AEOSI, all subjects Parts I, II

	Hodgkin Lymphoma		Other Tumor Types		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	22		139		161	
with one or more adverse events	9	(40.9)	21	(15.1)	30	(18.6)
with no adverse event	13	(59.1)	118	(84.9)	131	(81.4)
with drug-related† adverse events	6	(27.3)	15	(10.8)	21	(13.0)
with toxicity grade 3-5 adverse events	1	(4.5)	3	(2.2)	4	(2.5)
with toxicity grade 3-5 drug-related adverse events	1	(4.5)	3	(2.2)	4	(2.5)
with serious adverse events	0	(0.0)	4	(2.9)	4	(2.5)
with serious drug-related adverse events	0	(0.0)	3	(2.2)	3	(1.9)
with dose modification‡ due to an adverse event	1	(4.5)	4	(2.9)	5	(3.1)
who died	0	(0.0)	1	(0.7)	1	(0.6)
who died due to a drug-related adverse event	0	(0.0)	1	(0.7)	1	(0.6)
discontinued drug due to an adverse event	0	(0.0)	2	(1.4)	2	(1.2)
discontinued drug due to a drug-related adverse event	0	(0.0)	2	(1.4)	2	(1.2)
discontinued drug due to a serious adverse event	0	(0.0)	2	(1.4)	2	(1.2)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	2	(1.4)	2	(1.2)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
Reporting for serious adverse events and serious drug-related adverse events goes through 90 days.
(Database Cutoff Date: 10JAN2020).

Post marketing experience

Data from post marketing experience have been included in the latest submitted PSURs.

2.5.1. Discussion on clinical safety

In the context of extension of the currently approved therapeutic indication of pembrolizumab for the treatment of relapsed or refractory classical Hodgkin lymphoma (rrcHL) in adults, to an earlier line of therapy and to include paediatric patients, safety results have been presented from study KEYNOTE-204, evaluating pembrolizumab in monotherapy versus Brentuximab Vedotin (BV), in parallel to the cHL Safety Dataset, the Reference Safety Dataset (RSD) and the Cumulative Safety Dataset (CSD). To support the extension of the indication to rrcHL paediatric patients, safety data from KEYNOTE-051 have been also provided. KEYNOTE-087 was the pivotal study supporting the initial rrcHL indication in the adults. In order to evaluate potential differences in the pembrolizumab safety profile, the updated data from KEYNOTE-013 and KEYNOTE-087 have been presented separately from the overall cHL Safety Dataset, and the safety analysis from these studies have been compared with KEYNOTE-204. Some differences were observed in AEs between the KEYNOTE-204 pembrolizumab safety dataset and the study KEYNOTE-087, as the incidence of SAEs and drug-related SAEs was higher in KN-204 than in the KN-087 (SAEs 29.7% vs 22.9%, respectively; drug-related SAEs 16.2% vs 8.1%, respectively). However, when adjusted for exposure, the event rates were similar. Analysis of AEOSIs revealed a similar incidence (<5% difference) for all categories, including Grade 3 to 5 events, SAEs, and AEs leading to discontinuation. The overall AE profile observed in the KEYNOTE-204 pembrolizumab arm was generally consistent with KEYNOTE-013 for both overall AEs and AEOSIs, except for a higher incidence of SAEs in KEYNOTE-013 than in KEYNOTE-204 (SAEs 38.7% vs 29.7%, respectively). However, in agreement with the MAH, differences observed for some categories (all ≤10%) are likely due to small participant numbers in KEYNOTE-013 (n=31) and should be interpreted with caution. In conclusion, when comparing the safety data of KEYNOTE-204 with KEYNOTE-087 and KEYNOTE-013, no significant differences emerged for using pembrolizumab across this cHL patient population.

In line with the Hodgkin lymphoma, the Indication Population was younger compared to the RSD and the CSD, with a median age of 35.5 years (*vs.* 62 years in the other safety datasets). This population was quite heterogeneous in terms of prior exposure and response to previous therapy (in median 2 prior lines of therapy, range 1-10 in pembrolizumab arm), including previous BV or auto-SCT. In terms of prior exposure and response to previous therapy, the MAH underlined that: i) comparison of AEs by prior BV status does not allow for a meaningful comparison, as only 5 participants received prior BV in the pembrolizumab arm in KEYNOTE-204; ii) rates of AEs were generally similar between participants with and without prior radiation; iii) most categories of AEs occurred at similar rates, when examined by prior auto-SCT status, although a higher percentage of participants with prior auto-SCT experienced SAEs (38.2% vs 24.7%), but the percentage of participants experiencing drug-related SAEs was similar (18.2% vs 15.1%); iv) participants with one prior line of therapy experienced fewer Grade 3 to 5 drug-related AEs compared with participants with 2 lines or 3 or more lines of therapy; v) although the subgroup analyses were notable for some numerical differences within several AE sub-categories (i.e., age [<65 vs ≥65 years; <65 vs ≥65 to <75 vs ≥75 to<85 years], gender, race, ECOG status and region [North America vs Europe vs Japan; US vs non-US; EU vs non-EU]), the smaller number of participants within these subgroups does not allow for a meaningful comparison and no definitive conclusion can be drawn.

In terms of exposure to pembrolizumab, a longer median time on therapy was reported for cHL patients compared to the RSD and the CSD (10.02 months in the KN-204 pembrolizumab arm and 10.65 months in the cHL Safety Dataset vs 4.86 months in the RSD and 4.24 months in the CSD), with a higher number of doses administered (15 doses in KN-204 and 16 doses in the cHL Safety Dataset vs 8 doses in the RSD and 7 doses in the CSD). Overall, 67.6% of cHL population in KN-204 (n=100) were exposed to pembrolizumab for at least 6 months (vs 32.2%, n=49 in BV arm) and safety data with treatment exposure ≥12 months were available for 71 patients (48%) for pembrolizumab (vs only 17 patients, 11.2% in the BV group).

In general, pembrolizumab was well tolerated among subjects with cHL. Most AEs were of low-Grade toxicity as evidenced by the low rate of subjects with toxicity Grade 3 to 5 drug-related AEs (62 [15.9%]) and with serious drug-related adverse events (46 [11.8%]) in the 389-subject cHL population.

The overall AE profile in the KEYNOTE-204 pembrolizumab group was generally consistent with the cHL Safety Dataset, except for such categories of AES (SAEs, drug-related SAEs, Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs). The incidence of Grade 3 to 5 AEs generally differed by less than 2 percentage points between the KEYNOTE-204 pembrolizumab arm and the cHL Safety Dataset, except for the observed rate of *pneumonitis* (4.1% vs 1.8%, respectively). The only Grade 3 to 5 drug-related AE and SAE reported more frequently (≥2 percentage points difference) in the KEYNOTE-204 pembrolizumab arm than in the cHL Safety Dataset was *pneumonitis* (Grade 3 to 5 drug-related AE 4.1% vs 1.8%; SAE 5.4% vs 3.3%, respectively). The frequency and type of drug-related SAEs reported in the KEYNOTE-204 pembrolizumab arm were generally consistent with the cHL Safety Dataset, generally differing by less than 1 percentage point except for *pneumonitis* (5.4% vs 3.3%) and *pneumonia* (2.0% vs 0.8%).

Patients enrolled in KEYNOTE-204 had relapsed or refractory disease and were heavily pre-treated with chemotherapeutic agents that have a known association with pulmonary toxicities, including prior radiation exposure, bleomycin (a prior treatment in 89.2% of participants in the pembrolizumab group has been reported), and melphalan in those participants who underwent previous SCT. These findings may have contributed to the observed high rate of *pneumonitis*, a known immune-related event, in KEYNOTE-204 patients who received pembrolizumab. As these heavily pre-treated patients have all weakened immune systems, opportunistic infections, including *pneumonia*, might be a risk.

However, after adjustment for exposure, event rates in the KEYNOTE-204 and cHL Safety Dataset were similar for all AE categories.

In Keynote-204, the AEs with a notable risk difference included *hypothyroidism* and *urinary tract infection* in the pembrolizumab arm, and *peripheral neuropathy*, *nausea* and *peripheral sensory neuropathy* in the BV arm. These AEs were consistent with the established safety profiles of pembrolizumab in monotherapy and BV. An exception was noted for *urinary tract infection* and for *pneumonitis* with higher incidence in the KEYNOTE-204 pembrolizumab arm than the other datasets. While no definitive explanation for the imbalance observed between the safety datasets was identified, the higher incidence of *urinary tract infection* observed in the pembrolizumab arm may be partly explained by the slightly higher proportion of females in the KEYNOTE-204 pembrolizumab arm relative to the RSD and the CSD (45.3%, 33.9% and 33.1% respectively). Women are more prone to *urinary infections* than men. Additionally, the higher incidence of *urinary tract infection* could be also related to the median duration of exposure in the KEYNOTE-204 pembrolizumab arm, twice as long compared with the RSD and the CSD (10.02 vs 4.86 and 4.24 months, respectively). Similarly, the higher rates of *pneumonitis* in the KEYNOTE-204 pembrolizumab arm than those observed in cHL safety dataset, RSD and CSD (8.8%, 6.9%, 4.1% and 3.8% respectively) may also be explained by the median duration of exposure and/or by prior radiation/melphalan/bleomycin exposure in patients in KEYNOTE-204 who received pembrolizumab, as these agents all have a known association with pulmonary toxicity

The most frequently reported drug-related AEs in the pembrolizumab arm, compared with the BV arm, were *hypothyroidism* (15.5% vs 1.3%), *pyrexia* (12.8% vs 5.9%) and *pruritus* (10.8% vs 5.3%), whereas the BV group showed higher incidences of drug-related *neuropathy peripheral* (2% vs 18.4%), *nausea* (4.1% vs 13.2%) and *peripheral sensory neuropathy* (2% vs 13.2%). The incidence and types of drug-related AEs reported in the KEYNOTE-204 pembrolizumab safety dataset were generally consistent with the other datasets, except for *pyrexia* and *hypothyroidism*. This could be expected because *pyrexia* is a common B symptom associated with cHL and an increased risk of *hypothyroidism* could be due to previous treatment with radiation therapy. Also, *acute kidney injury* was reported more frequently as Grade 3 to 5 drug-related AE in the KEYNOTE-204 pembrolizumab arm than in the cHL Safety Dataset, the RSD and the CSD (1.4%,

0.5%, 0.1% and 0.2%, respectively). Of note, the percentages in the KEYNOTE-204 pembrolizumab arm and the cHL safety dataset were based on 2 patients in each group from populations of 148 and 389 participants, respectively. Details on these patients have been provided by the MAH. Both participants' clinical courses were marked by numerous AEs that developed concurrently with *acute kidney injury*. In both cases, the events of acute kidney injury were treated and resulted in resolution. *Acute kidney injury* is a known immune-related AE of pembrolizumab. Renal adverse events with PD-1 inhibitors consist mainly of elevated serum creatinine levels, and *nephritis* has been reported in 0.3%–1.2% of patients across clinical trials (*Vardhana S et al. The Oncologist 2019;24:86–95*). In agreement with the MAH, the observed imbalance across the datasets may be explained by the longer duration of exposure in the KEYNOTE-204 pembrolizumab arm and cHL safety dataset (10.02 and 10.65 months, respectively) compared with RSD and CSD (4.86 and 4.24 months, respectively).

SAEs were consistent across population, with *pneumonia* (5.4%), *pneumonitis* (5.4%) and *pyrexia* (2.7%) most frequently reported. *Pneumonitis* was the only more frequently reported SAE (≥2 percentage points difference) in the KEYNOTE-204 pembrolizumab group than the other safety datasets, for which the contribution of the immune dysregulation induced by lymphoma cannot be excluded.

Deaths due to AEs in KEYNOTE-204 occurred in 3 patients (2%) in the pembrolizumab arm and in 2 BV patients (1.3%), compared with 6 (1.5%) patients in the cHL Safety Dataset and 312 (5.3%) patients in the RSD. One death in the pembrolizumab group of KEYNOTE-204 was attributed to drug-related AE of *pneumonia*. More details have been required for all participants in KEYNOTE-204 pembrolizumab arm who died due to AEs, also providing the narrative of death that occurred in the third patient. In the case of one participant, although autopsy confirmed that *pneumonia* was the primary cause of death with microbiology positive for *E.coli*, diagnostic imaging was suggestive of *pneumonitis*, for which related relation to pembrolizumab, as AEOSI, cannot be excluded. In addition, during the clinical course, the patient was treated with antibiotics and steroids that did not result in clinical improvement and, therefore, the exact aetiology of the pulmonary compromise is not clear. Similarly, for the AE of cardiac failure (reported as *myocarditis*), without information on the clinical status at baseline and with only an echocardiogram revealing an aortic and mitral valve disease, it is difficult to understand the exact aetiology of such *myocarditis*. However, the prior oncology treatment history included treatment with doxorubicin and bleomycin that could be a potential contributing factor to the reported *cardiac failure* and *pneumonitis*.

For another participant, in agreement with the MAH, the AEs including *acute GVHD*, *autoimmune hemolytic anemia* and *infections* should be considered as complications associated with stem cell transplant.

The narrative for the third participant, who died due to an unknown cause, was also provided. However, for this case, the insufficient clinical information provided do not allow to assess a potential causal role for pembrolizumab and the reported events.

The incidence of AEOSI in the cHL population in KEYNOTE-204 has been reported as comparable to that in the cHL Safety Dataset (35.8% and 35.7%, respectively) but higher compared to the RSD (25.1%) and to the CSD (24.4%), which could be due to longer exposure and follow-up. In KEYNOTE-204, the most frequent AEOSIs were *hypothyroidism* (n=28 [18.9%]), *pneumonitis* (n=16 [10.8%]), and *hyperthyroidism* (n=8 [5.4%]) in the pembrolizumab arm; *infusion-related reaction* (n=12 [7.9]), *hypothyroidism* (n=4 [2.6%]), and *pneumonitis* (n=3 [2%]) in the BV arm. Most immune-mediated AEOSIs were mild to moderate in severity and were managed with treatment interruptions and/or corticosteroids.

Hypothyroidism was the most frequently observed AEOSI across populations. The higher rate of events in cHL patients (Grade 1 and 2), as well as the shorter time to onset of the first *hypothyroidism* event can be justified by the frequent prior exposure to mediastinal radiation therapy. None of the events was treated with corticosteroids. In the pembrolizumab arm of KEYNOTE-204, 58 participants had received prior radiation at baseline while 93 participants had not received prior radiation in the ITT population. Considering that an AEOSI of *hypothyroidism* occurred in 28 (18.9%) patients in the pembrolizumab arm and, of these

28 participants, 11 patients had a past medical history of prior radiation therapy, the incidence of *hypothyroidism* in participants who received prior radiation was 19.0% (11/58) compared to 18.3% (17/93) in participants who had not received prior radiation. The TSH levels reported at baseline were normal for 20 out of 28 patients, high for 7 patients and low for 1 patient, suggesting that a pre-existing *hypothyroidism* was not present for the majority of these patients. The longer duration of exposure for patients in KEYNOTE-204 may also explain the higher overall incidence of hypothyroidism compared to the RSD.

No major differences specific for the cHL population were observed in terms of events outcome, except for a higher rate of patients with a resolved status in the cHL Safety Dataset (40.9%) compared to the patients in the KEYNOTE-204 pembrolizumab arm (28.6%). A clarification has been provided by the MAH to explain the higher rate of *hypothyroidism* with unresolved status in KEYNOTE-204: the longer duration of follow-up in KEYNOTE-013 and KEYNOTE-087 (included in cHL Safety Dataset) allowed for additional information to be collected on the complete clinical course with respect to the outcome of events, in contrast to the shorter duration of follow-up in KEYNOTE-204 that may explain the higher rate of *hypothyroidism* with unresolved status. An additional aspect to consider regarding the resolution status may be related to medical judgment: while some investigators may consider an event resolved once the participant is stable on thyroid hormone replacement, others may consider the event unresolved since the requirement for treatment is still present. However, overall experience with pembrolizumab and *hypothyroidism* indicates that physician monitoring and thyroid hormone replacement are sufficient to manage this risk without requiring discontinuation of therapy and for this reason, the MAH's conclusion is endorsed.

Sixteen (10.8%) participants experienced an AEOSI of *pneumonitis* in the pembrolizumab arm compared to 4 (2.6%) in the BV arm. The incidence of *pneumonitis* and the characteristics of events, in terms of time to onset, duration and type of outcome, were as expected, considering that the prior radiation exposure and the use of bleomycin may be contributing factors for the observed incidence of *pneumonitis* in cHL population. The majority of *pneumonitis* events were Grade 3 and below and resolved with systemic corticosteroids. There were no fatal events of pneumonitis.

Infusion related reactions were more frequent in the cHL population, especially in the BV arm (5.4% in the KEYNOTE-204 pembrolizumab arm, 7.9% in the BV group and 8% in the cHL Safety Dataset) than in the RSD (2.3%) and the CSD (2.1%), characterized by a very earlier median time to first occurrence (1 day in KN-204 vs 44.5 in RSD and 40 days in CSD). The majority of infusion reaction events did not require corticosteroid treatment.

Changes in laboratory findings in the cHL population were in line with those reported in the larger cHL datasets, mostly related with Hodgkin lymphoma and prior anti-lymphoma treatment. Further investigation has been requested on potential immunogenicity related to pembrolizumab, particularly with respect to ANA, ASMA and anti-neutrophil cytoplasmic antibodies. Rheumatic and/or systemic irAEs may occur across all classes of check point inhibitor (CPI), including pembrolizumab, most frequently and severely with combination treatments and may be associated with other organ-specific irAEs. Since autoantibodies are not found in the majority of patients experiencing CPI-induced rheumatic and systemic disease, there is no indication to test every patient at baseline. More generally, the pre-existing antinuclear antibodies revealed no significant difference in the development of irAEs between the positive and negative ANA groups (*Sakaklda T et al. Clinical and Translation Oncology 2020).* In the absence of clinical biomarkers predicting the occurrence of irAEs after use of PD-1/PD-L1 blockade for cancer immunotherapy, in line with the EULAR recommendation (*Kostine M et al. Ann Rheum Dis 2020*), the detection of autoantibodies in an asymptomatic patient would not preclude the start of CPI therapy. However, there is the particular situation of patients with *thymoma* who develop CPI-induced *myositis* and who all have anti-acetylcholine receptor and antistriated muscle antibodies detected in serum sample obtained prior to CPI therapy (*Mammen AL et al. Ann Rheum Dis 2019*). Accordingly, as *myositis* may evolve into a severe irAE, testing for the presence of these antibodies before starting CPI in a patient with *thymoma* is recommended to identify a high risk of

myositis (*Kostine M et al. Ann Rheum Dis 2020*). To date, the MAH' explanation that there is no rationale for the screening or long-term monitoring of autoimmunity (e.g. ANA, ANCA, ASMA) prior to treatment with pembrolizumab is accepted.

The MAH has also focused on laboratory data pertaining to "*platelet count decreased*" or "*thrombocytopenia*" that are reported as AEs for which clinically meaningful data including outcome, treatments received, and clinical sequelae were presented. In KEYNOTE-204, the incidence of "*thrombocytopenia*" or "*platelet count decreased*" were 6.8% and 6.6% in the pembrolizumab and BV groups, respectively, compared to the RSD in which a total of 140 participants out of 5643 (2.5%) experienced these AEs. Based on the data provided, no evidence of significant concern on laboratory data pertaining to "*platelet count decreased*" or "*thrombocytopenia*" as AEs was highlighted during the pembrolizumab treatment for the cHL patient population. Myelosuppression is a common toxicity associated with cytotoxic chemotherapy, but *thrombocytopenia* as immune-related adverse events (irAEs) commonly occur during the administration of immune checkpoint inhibitors (ICI) (*Delanoy N et al. Lancet Haematol. 2019*). In the KEYNOTE-204 pembrolizumab arm, all four participants were treated for Grade 3-4 thrombocytopenia, including one participant who received systemic corticosteroids and no participants received immunoglobulin. In addition, a case of autoimmune thrombocytopenia was reported after treatment with pembrolizumab in KEYNOTE-204. However, in this case, the assessment for thrombocytopenia is confounded by disseminated intravascular coagulation in the setting of patient's underlying progressive malignant disease that are considered as risk factors for thrombocytopenia. In conclusion, the management by platelet transfusion is a main issue in patients with severe thrombocytopenia secondary to cytotoxic chemotherapy, whereas systemic steroid and immunoglobulin administration is identified as a reasonable choice in those, due to immunotherapy. The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions, as reported in section 4.4 of the SmPC.

No major and unexpected differences in the tolerability of pembrolizumab treatment were observed across the different ECOG PS categories, while an increased rate of drug-related AEs was observed in females compared to males (76.1% vs 72.8%). The Grade 3-5 AEs and the SAEs were slightly higher in the female population and the rate of discontinuation due to an AE was almost doubled compared to the male population. Considering the small sample size and low number of participants in the pembrolizumab treatment arm by gender (81 males and 67 females), this does not represent a clinically meaningful comparison. Nevertheless, the gender differences in incidences AEs should be further evaluated in future procedures.

The incidence of drug-related AES, SAEs, serious drug-related AEs in the cHL population ≥ 65 years of age was higher than in subjects <65 years of age in the BV arm of KEYNOTE-204 (e.g., Grade 3 to 5 AEs: 68.2% vs 39.2%) and the RSD (Grade 3 to 5 AEs: 53.0% vs 44.5%). Compared with participants <65 years of age treated with pembrolizumab, patients ≥65 years of age had higher (>15 percentage point difference) rates of *peripheral oedema* (23.1% vs 0.8%), *decreased appetite* (23.1% vs 2.5%), and *pain in extremity* (23.1% vs 5.7%), which are expected AEs in an older population, who generally have more comorbidities compared to younger patients. However, the relatively small number of subjects who were ≥ 65 years old in the cHL Population (n=26 in the KN-204 pembrolizumab arm; n=46 in the cHL Safety Dataset) is not sufficient for a meaningful comparison with the cHL Population < 65 years of age, or the larger datasets at this time and any definitive conclusion can be drawn. In section 4.2 of the SmPC, it is already reported that "*Data from patients ≥ 65 years are too limited to draw conclusions on cHL population*".

Overall, 48 cHL patient treated with pembrolizumab (from KEYNOTE-204, KEYNOTE-087 and KEYNOTE-051) received allogenic SCT. PD-1 inhibition prior to allo-SCT may enhance allogeneic T-cell responses and

augment the graft-versus-tumour effect. However, prior immunomodulation may also increase risk of GVHD. Complications were experienced by 34 of them (with *acute* and/or *chronic GVHD* as the most common AEs post allo-SCT) and a fatal outcome was reported in 6 patients (two patients, both in the KEYNOTE-204 pembrolizumab arm, died for *hypovolemic shock* and *hypoxic respiratory failure*; four patients in KEYNOTE-087 for *acute GVHD*, *hyperacute GVHD*, *pneumonia* and *sepsis*), but none of these post allo-SCT AEs were considered by the MAH related to study treatment.

Allo-SCT after PD-1 blockade appears feasible with a low rate of relapse. However, there may be an increased risk of early immune toxicity, which could reflect long-lasting immune alterations triggered by prior PD-1 blockade, as *acute* and *chronic GVHD* post allo-transplant. Approximately 30-50% of patients with cHL experience *GVHD* after allo-transplant (*Sure A et al. J Clin Oncol 2008*). Several studies have reported a higher rate of *acute GVHD* among patients who were exposed to check point inhibitor therapy before receiving allo-SCT and the median interval between exposures to the last dose of CPI and allo-HSCT was variable, ranging between 28 and 62 days, depending on the half-life of the checkpoint inhibitor. Regardless of the mechanism of PD-1 depletion, it has been demonstrated that anti-PD-1 therapy creates a long-lasting disturbance in the composition of circulating T-cell populations. These findings would explain the absence of any apparent association between the time interval from PD-1 to transplantation and early toxicity and suggests that the use of a window period to delay HSCT for even several months after PD-1 therapy may not mitigate the impact of this therapy on allo-SCT outcomes (*Merryman RW et al, Blood 2017*).

From the data provided by the MAH, it is highlighted that: i) overall, the median times from last dose of pembrolizumab to allo-SCT were similar, differing by ~1 month between those with *GVHD* and those who did not have *GVHD*. This suggests that the timing of the last dose of pembrolizumab in relation to the SCT could not influence the occurrence of post-transplant *acute* or *chronic GVHD*; ii) based on these limited data from KEYNOTE-204, an association between the time from last dose of pembrolizumab and *GVHD* is not supported.

While it was not possible to create a control cohort for this analysis that perfectly matched with all possible salient characteristics that could influence the occurrence of *acute* and/or *chronic GVHD* after pembrolizumab (e.g., age, disease, sex, donor, graft source, *GVHD* prophylaxis), we acknowledge that many possible factors could be involved in the occurrence of *GVHD* and it is difficult to determine because participants who receive an allo-SCT do not represent a homogeneous population. However, these data confirm that prior PD-1 blockade should not be considered a contraindication to allo-SCT in this patient population.

Otherwise, treatment with pembrolizumab in the post-alloSCT disease relapse setting is feasible but can induce early and severe AEs. Caution and careful monitoring are warranted, particularly in patients who have a history of *GVHD*, but additional long-term data are needed to fully evaluate the risks and benefits of using PD-1 inhibitor therapy after allo-SCT.

There were no secondary malignancies in KEYNOTE-204.

Information on *pneumonits* in cHL patients has been included in the SmPC (section 4.8)

Assessment of paediatric data on clinical safety

In the KEYNOTE-051 study most participants had at least 1 AE. The types and incidences of the most frequently reported AEs were consistent with a heavily pretreated paediatric population with advanced cancers. No new safety signals were observed.

Although the majority of participants had treatment-related AEs, pembrolizumab was well tolerated as

evidenced by the small proportions of participants with Grade 3 to 5 treatment-related AEs, treatment-related SAEs, and treatment-related AEs leading to discontinuation of study treatment. Approximately half of the participants had at least one Grade 3 to 5 AE. The most frequently reported treatment-related Grade 3 to Grade 5 AEs were *lymphocyte count decreased* and *anemia*.

Approximately one-third of the participants had at least 1 SAE up to 90 days after receiving the last dose of pembrolizumab. The most frequently reported treatment related SAEs were *pyrexia*, *hypertension*, and *pleural effusion*, each occurring in ≤4 participants. Five participants had 1 or more AEs that resulted in death. For 1 participant with fatal *pulmonary edema* and 1 participant with *fatal pneumonitis* and *pleural effusion*, AEs were deemed as drug-related by the investigator.

Thirty (18.6%) participants had at least 1 AEOSI. Four participants had a Grade 3 to 5 AEOSI: *colitis, myelitis, pruritus* (each Grade 3) and *pneumonitis* (Grade 5). Two participants had an AEOSI that led to discontinuation of the study treatment: Grade 3 *myelitis* and Grade 5 *pneumonitis*. Among the participants with 1 or more AEOSI, 13 (43.3%) had resolution of an event by the time of data cut-off. Among the events that had not resolved, 12 were endocrinopathies (ie, *hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency*) that required long-term hormone replacement therapy.

Most AEs did not lead to treatment interruption. The most frequently reported AE and treatment-related AE resulting in treatment interruption was *alanine aminotransferase increased* in 3 participants. Three participants (2 with cHL, 1 with solid tumour NOS) received an allogeneic SCT after discontinuing treatment with pembrolizumab. Both participants with cHL received alternative systemic anticancer therapy before the allogeneic SCT and developed GVHD post allogeneic SCT. Investigators deemed the GVHD not related to pembrolizumab.

The safety results from KEYNOTE-051 were generally consistent with those reported for pembrolizumab in monotherapy in adult patients, as demonstrated in a head-to-head comparison of frequencies of AEs in KEYNOTE-051 vs the pembrolizumab monotherapy adult safety database (RSD) in May 2019, within variation EMEA/H/C/003820/II/0071. To support the submission of a Type II variation with the proposed indication extended to paediatric cHL patients, safety data from cHL children should be presented separately and comparison between the safety data of cHL paediatrics *vs.* the cumulative safety data from KEYNOTE-051 and the safety profile in adults (particularly *vs*. the safety profile in cHL adults from the KEYNOTE-204 and the cumulative cHL Safety Dataset) should be provided, also considering differences in the therapeutic history of these patients (e.g., prior lines of therapy, more frequent radiotherapy in paediatric patients). The MAH acknowledges the question about limited paediatric data in the KEYNOTE-051 HL cohort that includes only 22 patients: the small sample size and the differences in prior therapies received compared with adult cHL patients limits the conclusions that can be drawn when comparing this cohort to other datasets. However, the data provided by the MAH comparing the cHL paediatric safety profile to cumulative paediatric safety data, showed that the patients with cHL had higher rates of drug-related AEs and dose modifications due to AEs compared with other tumour types, while participants with other tumor types had higher rates of Grade 3-5 AEs and SAEs. They experienced higher rates of overall AEOSI and drug-related AEOSI compared with participants with other tumor types. Nevertheless, the duration of exposure to pembrolizumab was approximately 8-fold longer for participants in KEYNOTE-051 with cHL. Compared to the cHL safety profile in adults, consistent lower rates for all AE categories (except for AEOSI) could be observed.

Treatment with pembrolizumab in paediatric participants could affect the immunological competence, not only in terms of *decreased number of lymphocytes* (one of the most frequently reported Grade 3 to 5 AEs in paediatric patients) but also of influencing the immunological functional activities, especially in paediatric patients with a less mature immune system. The MAH provided an update of immunological analyses for paediatric cHL patients included in KEYNOTE-051. Vaccinated antibody concentrations and memory B- and T-cell counts were collected as part of the secondary objectives of KEYNOTE-051 (data cut-off of January

2020). An upward trend in memory B- and T-cell counts and minimal changes in the concentration of vaccinated antibodies from pre-treatment to post-treatment Cycle 4 were observed. Taken together, these data indicate that treatment with pembrolizumab does not appear to affect immunological competence in this paediatric patient population.

The outcomes after transplant have been presented only for 2 cHL patients. This point is of importance in paediatric patients as the cure rate after allo-SCT is higher than in adults. After the cut-off date (10-JAN-2020), no additional patients in KEYNOTE-051 received an allo transplant, so that an evaluation of potential cure rate in cHL paediatric patients (n=2) compared to adults is not possible.

For KEYNOTE-204, the MAH provided additional information on all 14 allo-SCT participants, such as the last known contact date, the follow-up time since the allo-SCT and details on the mortality status. In particular, the MAH provided data on the allo-SCT participants post-pembrolizumab who experienced a *GVHD* event. These preliminary data confirm that *GVHD* is a frequent AE post pembrolizumab, especially as *acute GVHD* (reported 8 out of 11 patients), Grade 2 or Grade 3 predominantly. However, also *chronic GVHD* mild/moderate/severe has been observed (in 3 out of 11 patients). Of the fourteen transplanted patients, two patients died, and the cause of death was *respiratory failure* and *hypovolaemic shock*, respectively. An interim analysis report of the comprehensive and detailed safety analysis of adult participants with hematologic malignancies enrolled in MSD-sponsored studies who received an allo-SCT following therapy with pembrolizumab was submitted in December 2020. The was recommended to share the final analysis report across haematological malignancies, including paediatric and adult participants.

As of the database cut-off date of 10-JAN-2020 in KEYNOTE-051, there was no additional data available of secondary malignancy, and only one participant with a primary diagnosis of solid tumour NOS developed a secondary malignancy of Grade 5 *adenocarcinoma gastric*, reported by the investigator as not treatment related. There were no secondary malignancies identified in KEYNOTE-204 and KEYNOTE-087. For KEYNOTE-051 the MAH will plan to enrol a minimum of 20 patients within the r/r cHL cohort, for which the next data cut-off for the analysis is planned in March 2024.

2.5.2. Conclusions on clinical safety

The incidence of most AEs did not differ significantly between study arms, with the exception of *hypothyroidism* and *urinary tract infection* in the pembrolizumab arm and higher incidences of *nausea* and *peripheral neuropathy* in the BV group. The overall AE profile observed in the KEYNOTE-204 pembrolizumab group was generally consistent with the cHL Safety Dataset and the RSD. Despite the limited sample size, from KEYNOTE-051 study no unexpected safety signal was reported in cHL paediatric patients.

The MAH will plan to enrol a minimum of 20 patients within the r/r cHL cohort in KEYNOTE-051, for which the next data cut-off for the analysis is planned in March 2024; this study is part of the PIP agreed with the PDCO.

Finally, the MAH was recommended to share the final analysis report across haematological malignancies, including paediatric and adult participants.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 30 is acceptable.

The CHMP endorsed the Risk Management Plan version 30 with the following content:

Safety concerns

Table 1093

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Based on the data supporting the new indication, the existing list of safety concerns remains unchanged.

Existing pharmacovigilance plan and risk minimisation measures remains sufficient to mitigate the risk of keytruda in all approved indications.

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table 1104: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		

Table 1104: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: • The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Table 1104: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trials (KN087, KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet has been updated accordingly. The Annex II was amended to reflect extended deadline for the submission of the PAES study KN-204.

2.7.1. User consultation

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

The changes to the package leaflet are limited; in particular, the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, these proposed revisions do not constitute significant changes that would require the need to conduct a new user consultation or abridged focus testing.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved therapeutic indication is: KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory cHL who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

3.1.2. Available therapies and unmet medical need

The majority of patients with cHL can achieve long-term disease control/cure with frontline chemotherapy (e.g. ABVD, Stanford V or BEACOPP), yet 10 to 40% of patients still experience relapse or are refractory to the initial therapy. Salvage therapy is currently based on non cross-resistant chemotherapy regimens (e.g. DHAP, IGeV, GemOX plus dexamethasone, ICE etc.) that can re-induce remission in approximately 50-70% of patients. Long-term disease control following conventional therapy alone is, however, uncommon, and further consolidation with high dose chemotherapy and ASCT is usually administered to fit patients. Consolidation with ASCT has been associated with long-term disease control/cure in approximately 50% of patients.

BV is approved in the EU for the treatment of adult patients with r/r cHL following ASCT or at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. The ORR with BV in this setting has been shown to be as high as 60-75% (CRR 30-34%). 5-year OS was 41% (65% for patients who obtained a CR) and 5-year PFS was 22% (52% for patients in CR). However, exposure to BV is not devoid of toxicities: peripheral sensory neuropathy (overall incidence ~40%) is the most relevant non-hematologic adverse event (AE) (see Adcetris EPAR and SmPC). BV also proved to be an effective "bridge" to transplant (see e.g. Chen R et al, Blood 2016; Younes A et al, JCO 2012).

Prognosis after failure of salvage chemotherapy, including BV, and/or ASCT is poor. A selected subset of young and fit patients might be eligible to allogeneic hematopoietic stem cell transplant (allo-HSCT), which can still result in long-term remission in a subset of patients. However, transplant-related mortality and toxicity is not negligible.

Overall, an unmet medical need for r/r cHL patients who failed or are unfit for ASCT can be recognised.

3.1.3. Main clinical studies

The efficacy of pembrolizumab in the claimed indication is mainly supported by the Interim Analysis 2 results (data cutoff 16-JAN-2020, median survival follow-up of about 24.6 months) from Phase III study KN-204 (pivotal trial) comparing PFS (primary endpoint) as assessed by blinded independent central review (BICR), according to the IWG response criteria [Cheson, 2007], between pembrolizumab and BV treatment arms.

Efficacy data from paediatric study KN-051 were also submitted to support the proposed extrapolation strategy using a model-based PK bridging analysis to include paediatric patients aged ≥3 years. Study KN-051 was a Phase I/II study investigating pembrolizumab monotherapy in paediatric patients with solid tumours and malignant lymphomas.

Updated efficacy data from phase II study KN-087 were provided to further characterise the efficacy of pembrolizumab in r/r cHL. This is a single-arm, multi-cohort, non-randomized Phase 2 study investigating the efficacy of pembrolizumab monotherapy in a heterogeneous population of patients with cHL in advanced settings of relapse. Results for study KN-087 were pivotal in supporting the currently approved indication of pembrolizumab for the treatment of r/r cHL.

3.2. Favourable effects

In adults (Pivotal study KN-204) pembrolizumab provided a statistically significant improvement in PFS (including clinical and imaging data post-SCT): median PFS in the ITT population of pivotal study KN-204 was 13.2 months (95%CI 10.9, 19.4) and 8.3 months (95%CI 5.7, 8.8) with pembrolizumab and BV, respectively (HR 0.65, 95%CI 0.48, 0.88, p=0.00271). The estimated 24-month PFS rates were 35.4% and 25.4% with pembrolizumab and BV, respectively. Secondary PFS analysis (excluding clinical and imaging data post-SCT), PFS sensitivity analyses and analyses based on investigator assessment were consistent.

The point estimation for ORR was numerically higher with pembrolizumab compared to BV: 65.6% (95%CI: 57.4, 73.1) vs. 54.2% (95%CI: 46.0, 62.3), respectively. The CRR was not different between treatment arms (24.5% for pembrolizumab and 24.2% for BV). The proportion of patients who received subsequent ASCT (~20%) or allogeneic HSCT (~9%) did not differ between pembrolizumab and BV. For pembrolizumab, median duration of response (DoR) was 20.7 months (range: 0.0+ to 33.2+ months) versus a median of 13.8 months (range: 0.0+ to 33.9+) with BV. The fraction of patients with response duration longer than 24 months was similar across treatment arms (47.4% vs. 42.8%).

The results from the provided preliminary PFS2 analysis were in favour of pembrolizumab (HR 0.58, 95%CI 0.38, 0.87, p=0.0037).

Regarding PRO, with respect to the EORTC QLQ-C30, from baseline to Week 24 a trend towards an improvement could generally be observed with pembrolizumab while, conversely, a trend towards deterioration was reported in the BV arm. The prespecified time to deterioration analysis also showed an improvement with pembrolizumab in the GHS/QOL (HR 0.40, 95%CI 0.22, 0.74) and physical functioning scores (HR 0.56, 95%CI 0.32, 0.97). Results with the EQ-5D instrument were consistent with those reported for the QLQ-C30 questionnaire: a significant difference in the LS means favouring pembrolizumab was observed at Week 24 for the utility (Δ 0.09 points, 95%CI 0.04, 0.14) and VAS scores (Δ 6.12 points, 95%CI 1.91, 10.34).

Clinical outcomes in subjects with ≥2 prior lines of therapy were consistent with the primary analysis in the ITT population: the ORRs with pembrolizumab was 65.3% (95%CI 56.3, 73.6) vs. 54.4% (95%CI 45.3, 63.3). The CRR was 26.6% (95%CI 19.1, 35.2) and 21.6% (95%CI 14.7, 29.8) with pembrolizumab and BV, respectively. PFS also consistently favoured the pembrolizumab arm (HR 0.66, 95%CI 0.47, 0.92): the mPFS was 12.6 months (95%CI 8.7, 19.4) with pembrolizumab and –8.2 months with BV (95%CI 5.6, 8.8) HR 0.62-0.70). No DoR and OS data by line of therapy were provided.

Updated results from the supportive study KN-087with a median duration of follow-up of 39.5 months showed an IWG ORR by BICR of 71% (95%CI 64.3, 77) and 71.7% (95%CI 58.6, 82.5) in the overall population and in cohort 3 (BV-naïve patients), respectively. CRRs were 27.6% and 31.7%, median DoR 16.6 and 16.8 months and median PFS 13.6 and 16.8 months, respectively. Median OS was still not reached in all cohorts.

In paediatric patients (paediatric study KN-051) the ORR per IWG criteria observed in patients treated in the dedicated r/r cHL cohort (n=8) was 42.9% (3/7). Two out of 7 subjects achieved a CR. Median DoR in this cohort was not reached and median PFS (11.2 months) was overall in line with that observed in adults.

The ORR per RECIST criteria in the 15 patients treated in the PD-L1 positive tumours cohort was 66.7% (with one patient reaching a CR), the median DoR and PFS were 17.4 and 12.2 months, respectively.

Among the 22 cHL participants, the ORR was 54.5% based on IWG 2007 criteria and 63.6% based on Lugano criteria. The CRR was 4.5% and 18.2% based on the IWG 2007 and Lugano criteria, respectively. Among the 12 responders by IWG 2007 criteria, the median time to response was 2.3 months and the median response duration was 17.3 months. Among the 14 responders by Lugano criteria, the median time to response was 2.1 months and the median response duration was 8.8 months. Among the 22 cHL participants, the median PFS was 8.3 months based on IWG 2007 criteria and 8.2 months based on Lugano criteria.

3.3. Uncertainties and limitations about favourable effects

The OS data from KEYNOTE-204 are still immature and have not been statistically tested. Immaturity of PFS2 data and limited information on subsequent treatment make difficult to assess the impact of uncontrolled cross-over. The provided DoR analysis was not sufficiently mature (only 40% of patient were informative). Updated results from the final CSR of KEYNOTE-204 - listed as a PAES (Annex IID) - will be submitted for review in accordance with agreed timelines. Data in HL patients ≥ 65 years are limited; however this is adequately reflected in sections 4.2. and 5.1 of the SmPC.

Regarding the efficacy in paediatric patients, the main uncertainty is the limited number (22) of r/r cHL paediatric patients treated in study KN-051. No clinical and no PK data are available below the age of 10 with cHL. Descriptive statistics of predicted individual exposure parameters for paediatrics and adult patients shows that Cmin is about 50% higher in the 3-6 age group, although the median value is within the Q3 for adults. Further, there is a limited follow-up in the r/r cHL cohort and limited clinical data for paediatric patients who received subsequent SCT.

3.4. Unfavourable effects

The median duration of exposure was twice as long for patients in the pembrolizumab arm compared with the BV arm. When adjusted for exposure, event rates for most AEs tended to be higher with BV.

In KEYNOTE-204, the most frequently reported drug-related AEs in the pembrolizumab arm were *hypothyroidism* (15.5%), *pyrexia* (12.8%) and *pruritus* (10.8%), whereas the BV group showed higher incidences of drug-related *neuropathy peripheral* (18.4%), *nausea* (13.2%) and *peripheral sensory neuropathy* (13.2%). The incidence and types of drug-related AEs reported in the KEYNOTE-204 pembrolizumab arm were generally consistent with the cHL Safety Dataset and with the RSD (74.3%, 73.3% and 70.2%).

The overall incidence of Grade 3 to 5 drug-related AEs in KEYNOTE-204 was lower in the pembrolizumab arm (19.6%) than in the BV group (25%). The most frequently reported drug-related Grade 3 to 5 AEs were *pneumonitis* (4.1%), *pneumonia* (2%) and *neutropenia* (2%) in the pembrolizumab arm; *neutropenia* (7.2%), *neutrophil count decreased* (4.6%) and *neuropathy peripheral* (3.3%) in the BV arm. A higher difference in the incidence rates of the other safety datasets was noted for *pneumonitis* (4.1% in the KEYNOTE-204 pembrolizumab arm, 0.7% in the BV group, 1.8% in the cHL Safety Dataset, 1.3% in the RSD and 1.2% in the CSD).

The incidence of Serious drug-related AEs was 16.2%, with *pneumonitis* as the most frequently occurring AE (5.4%).

The most frequent AEOSIs were *hypothyroidism* (18.9%), *pneumonitis* (8.8%) in the pembrolizumab arm and *infusion-related reaction* (7.9%), *hypothyroidism* (2.6%), and *pneumonitis* (2%) in the BV arm. Most

immune-mediated AEOSIs were mild to moderate in severity and were managed with treatment interruptions and/or corticosteroids. At the time of data cut-off, 50.9% of patients were reported to have AEOSIs resolved, 9.4% were resolving and 37.7% were not resolved.

Complications to allogenic HSCT (i.e, acute/chronic GVHD) were experienced in 34 out of 48 pembrolizumab treated patients who received transplantation after progression, and a fatal outcome was reported in 6 of them.

The types and incidences of the most frequently reported AEs in paediatric patients in KEYNOTE-051 were consistent with a heavily pre-treated paediatric population with advanced cancers. Although the majority of participants (57.8%) had treatment-related AEs, pembrolizumab was well tolerated as evidenced by the small proportions of participants with Grade 3 to 5 treatment-related AEs (8.7%), treatment-related SAEs (9.9%), and treatment-related AEs leading to discontinuation of the study treatment (3.7%). The most frequently reported treatment-related AEs were *fatigue* (8.7%), *anaemia* (8.1%), *pyrexia* (7.5%), *aspartate aminotransferase increased* (6.8%), *lymphocyte count decreased* (6.8%), *diarrhoea* (6.2%), *alanine aminotransferase increased* (5.6%), and *hypothyroidism* (5.6%), the majority of them with Grade 1-2 toxicity. The most frequently reported Grade 3 to 5 AEs were *anaemia* (8.1%) and *lymphocyte count decreased* (5.6%). The most frequently reported drug-related SAEs were *pyrexia* (2.5%), *hypertension* (1.2%), and *pleural effusion* (1.2%). The most frequently reported AEOSI were *hypothyroidism* (8.1%), *hyperthyroidism* (3.7%), *hypersensitivity* (2.5%), and *pneumonitis* (2.5%).

As of the database cut-off date of 10-JAN-2020 in KEYNOTE-051, there was no additional data available of secondary malignancy, and only 1 participant with a primary diagnosis of solid tumour NOS developed a secondary malignancy of Grade 5 *adenocarcinoma gastric*. There were no secondary malignancies identified in KEYNOTE-204 and KEYNOTE-087. For KEYNOTE-051, the MAH will plan to enrol a minimum of 20 patients within the r/r cHL cohort, for which the next data cut-off for the analysis is planned in March 2024.

Complications after allogenic HSCT (*acute/chronic GVHD*) were experienced in 2 cHL patients after discontinuing treatment with pembrolizumab. Both patients were alive but *acute/chronic GVHD* was not resolved.

3.5. Uncertainties and limitations about unfavourable effects

Considering the recognized risk of exacerbating GVHD related to checkpoint inhibition, data on the feasibility of allogeneic HSCT after pembrolizumab are still limited, as indicated in the sections 4.4 and 4.8 of the SmPC. After the cut-off date (10-JAN-2020), no additional patients in KEYNOTE-051 received an allo transplant, so that an evaluation of potential cure rate in cHL paediatric patients (n=2) compared to adults is not possible. An interim analysis report of the safety analysis of adult participants with hematologic malignancies enrolled in MSD-sponsored studies who received an allo-SCT following therapy with pembrolizumab was submitted in December 2020 and is currently under assessment.

The MAH is also requested to share the final analysis report across haematological malignancies, including paediatric and adult participants by December 2024. - related to the following: FDA PMR 3188-2: Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following pembrolizumab in at least 90 patients with hematologic malignancies, of which at least 30% had received pembrolizumab alone or in combination as the regimen immediately prior to the allogeneic HSCT conditioning regimen. Evaluate toxicities at least through transplant Day 180. Include details of prior pembrolizumab treatment and the transplant regimen. Characterize toxicities including hyperacute graft-versus-host disease (GVHD), severe (Grade 3-4) acute GVHD, febrile syndromes treated with steroids, immune mediated adverse events, pulmonary complications, hepatic veno-occlusive disease and/or

sinusoidal obstruction syndrome, critical illness, and transplant-related mortality. Toxicities may be characterized prospectively, or through a combination of prospective and retrospective data analysis.

3.6. Effects Table

Effects Table for Keytruda (pembrolizumab) as monotherapy for the treatment of adult and paediatric patients aged ≥3 years with cHL who have failed ASCT or when ASCT is not a treatment option (data cut-off: 16 Jan 2020)- study KN-204

Effect	Short description	Unit	Treatment (Pembro 200 mg 3QW)	Control (BV)	Uncertainties / Strength of evidence	References
Favourable Effects						
Adults						
PFS by BICR (ITT population)	Time from randomization to PD or death whichever occurred first including clinical and imaging data following ASCT or allogeneic HSCT	months (95% CI)	13.2 (10.9, 19.4)	8.3 (5.7, 8.8)	Consistency of results across most subgroups and sensitivity analyses in study KN-204 Clinically meaningful results vs. BV in the overall population of study KN-204 Consistency of results across pivotal and supportive studies Uncertainty regarding potentially lower benefit in European population	(1)
	Time from randomization to PD or death whichever occurred first	months (95% CI)	13.6 (11.1, 16.7)	NA		(2)
PFS by BICR secondary (ITT population)	Time from randomization to PD or death whichever occurred first excluding clinical and imaging data following ASCT or allogeneic HSCT	months (95% CI)	12.6 (13.1, 22.6)	8.2 (5.6, 8.4)		(1)
PFS by BICR (patients with ≥2 prior therapies)	Time from randomization to PD or death whichever occurred first	months (95% CI)	12.6 (8.7, 19.4)	8.2 (5.6, 8.8)		
ORR (ITT population)	CR+PR rate by BICR	% (95% CI)	65.6% (57.4, 73.1)	54.2% (46.0, 62.3)	The majority of patients was able to obtain a clinical response despite the advanced setting of relapse The 95% CIs for ORR and CRR with pembrolizumab and BV in study KN-204 largely overlapped The ORR/CCR observed in the BV arm of study KN-204 were slightly inferior to those reported in the Adcetris EPAR (i.e. ORR 75% and CRR 33% by IRF analysis)	(1)
			71% (64.3, 77.0)	NA		(2)
ORR (patients with ≥2 prior therapies)	CR+PR rate by BICR	% (95% CI)	65.3% (56.3, 73.6)	54.4% (45.3, 63.3)		(1)
CRR (ITT population)	CR rate by BICR	% (95% CI)	24.5%, (17.9%, 32.2%)	24.2% (17.6%, 31.8%)		(1)
			27.6	NA		(2)
CRR (patients with ≥2 prior therapies)	CR rate by BICR	% (95% CI)	26.6 (19.1, 35.3)	21.6 (14.7, 29.8)		(1)
DoR	Time from first response to PD or death due to any cause, whichever occurs first in subjects who achieve a PR or better.	Months (range)	20.7 (0.0+, 33.2+)	13.8 (0.0+, 33.9+)	DoR in study KN-204 was not sufficiently mature The actual clinical benefit in 2nd line non transplant eligible patients is not established	(1)
			16.6 (0.0+, 39.1+)	NA		(2)
Paediatric patients						
ORR	CR+PR rate by BICR using the IWG 2007 response criteria	n % (95% CI)	N=7 42.9% (9.9, 81.6)	NA	Anti-tumour activity overall consistent with those observed in adults Efficacy in paediatric patients based on extrapolation from adults and limited paediatric data from 22 participants with HL in	(3)
			N=22 54.5% (32.3, 75.6)	NA		
	CR+PR rate by BICR using the RECIST 1.1 response		N=15 66.7%	NA		

Effect	Short description	Unit	Treatment (Pembro 200 mg 3QW)	Control (BV)	Uncertainties / Strength of evidence	References
	criteria		(38.4, 88.2)		the age from 10 to 17 years (Study KEYNOTE-051)	
	CR+PR rate by BICR using the 2014 Lugano response criteria		N=22 63.6% (40.7, 82.8)	NA		
CRR	CR rate by BICR using the IWG 2007 response criteria	N % (95% CI)	N=7 28.% (3.7, 71.0)	NA		(3)
			N=22 4.5% (0.1, 22.8)	NA		
	CR rate by BICR using the RECIST 1.1 response criteria		N=15 6.7% (0.2, 31.9)	NA		
	CR rate by BICR using the 2014 Lugano response criteria		N=22 18.2% (5.2, 40.3)	NA		
PFS	Time from randomization to PD or death whichever occurred first using the IWG 2007 response criteria	months	N=22 8.3	NA		
	Time from randomization to PD or death whichever occurred first using the RECIST 1.1 response criteria	months	N=15 12.2	NA	Median PFS consistent with that observed in adults Limited sample size	(3)
	Time from randomization to PD or death whichever occurred first using the 2014 Lugano response criteria	months	N=22 8.2	NA		
OS	Time from randomization to death	months	NR	NA	Limited sample size The analysis is not mature	(3)
Unfavourable Effects						
Tolerability	Drug-related Grade ≥3 AE	%	19.6	25	Pembrolizumab safety profile was generally in line with that reported in the cHL Safety Dataset and the Reference Safety Dataset, except for hypothyroidism and pneumonitis	(1)
	Drug-related SAEs	%	16.2	10.5		
	Death-drug related	%	0.7	0		
	Discontinuation drug-related SAEs	%	8.8	3.9		
	Incidence of Hypothyroidism	%	15.5	1.3		
Drug-related AEs	Incidence of Pyrexia		12.8	5.9	Considering the recognized risk of exacerbating GVHD related to checkpoint inhibition, data on the feasibility of allogeneic HSCT are still limited especially for paediatric cHL population	
	Incidence of Pruritus	%	10.8	5.3		
	Incidence of Diarrhoea	%	9.5	4.6		
	Incidence of Pneumonitis	%	8.1	0.7		
	Incidence of Hyperthyroidism	%	5.4	0		
	Hypothyroidism	%	18.6	2.6		
	Pneumonitis	%	10.8	2.6		
AEOSI					Hypothyroidism is reported in higher incidences than in the Reference Safety Population; Pneumonitis is reported in higher incidences than in the Reference Safety Population	

Abbreviations: AE(s): Adverse event(s); CR/CRR: Complete Response/Complete Response Rate; DoR: Duration of Response; ORR: Objective Response Rate; OS: Overall Survival; PD: Progressive Disease; PFS: Progression Free Survival; PR: Partial Response; AEOSI: Adverse Event of Special Interest.

References: (1) KEYNOTE-204 CSR. (2) KEYNOTE-087 CSR. (3) KEYNOTE-051 CSR

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

High rates of long-term disease control/cure are usually obtained with frontline chemotherapy in cHL. Approximately half of the patients who experience relapse or have refractory disease can still achieve cure with high-dose chemotherapy followed by ASCT. The outcomes of patients who fail salvage therapy or ASCT are, however, unsatisfactory, and an unmet medical need can be recognised in this clinical setting.

The approximate 5-month gain in median PFS observed with pembrolizumab in pivotal study KN-204, which is equivalent to almost 35% reduction in the risk for progression or death, can be considered of clinical relevance. PFS K-M plots did not show, however, any clear plateau, confirming that long-term disease control is rarely achieved in advanced stages of relapse.

Resistance to treatment is an important issue in advanced settings of r/r cHL, and ORR data showed a favourable trend with pembrolizumab, although CR rates and the % of patients who were able to received subsequent transplant were not improved compared to BV. Preliminary survival data from pivotal trial KN-204 and PFS2 data, although immature, were supportive of the efficacy of pembrolizumab in this advanced setting. Further data will be provided with the submission of the final CSR as a PAES (already included in the Annex II).

With respect to safety, the incidence of most AEs did not differ significantly across treatment arms, with the exception of hypothyroidism and urinary tract infection that were more common in the pembrolizumab arm, and nausea and peripheral neuropathy that were more frequent with BV. The safety profile observed in pivotal study KN-204 was generally consistent with the overall cHL Safety Dataset and the RSD. No new safety concerns were identified.

The available efficacy data from paediatric study KN-051 are limited, as expected due to the rarity of cHL in children. On the other hand, the high unmet medical need in paediatric patients for whom chemotherapy is no longer an option is recognised and, despite the limited available data, the proposed extrapolation of treatment effect from adults to paediatric patients with cHL in advanced settings of relapse can be considered acceptable on the basis of similar prognostic and clinical characteristics of the disease, pharmacological drug effect and exposure-response relationship across all age classes.

3.7.2. Balance of benefits and risks

The available efficacy data from study KN-204 support the superiority of pembrolizumab vs. BV in subjects who have failed salvage chemotherapy +/- ASCT, with an acceptable safety profile.

Clinical data in paediatric patients are limited, yet the anti-tumour activity of pembrolizumab is confirmed and the overall safety profile did not differ significantly compared to what observed in adults. An extrapolation of treatment effect from adults to paediatric patients with cHL in advanced settings of relapse is considered acceptable.

3.7.3. Additional considerations on the benefit-risk balance

The limited available data in 2nd line transplant-ineligible patients were not adequate to establish a positive B/R in this subgroup. Overall, the available data convincingly demonstrated the superiority of pembrolizumab vs. BV in subjects who have failed salvage chemotherapy and/or ASCT (i.e. subjects with $\geq$2 prior therapies).

3.8. Conclusions

The overall B/R of Keytruda as monotherapy for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option is positive.

4. Recommendations

Outcome

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

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

Extension of the currently approved therapeutic indication for the treatment of relapsed or refractory classical Hodgkin lymphoma (rrcHL) in adults to an earlier line of therapy and to include paediatric patients - as follows:
KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The Annex II was revised to reflect extended deadline for the submission of the PAES KN-204. Revised RMP Version 30 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0008/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Keytruda is not similar to Adcetris within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Keytruda-H-C-3820-II-0090.