23 March 2017
EMA/252426/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0014

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplant
APaT/ASaT	All Patients as Treated/ All Subjects as Treated
APTT	Activated Partial Thromboplastin Time
ASCT	Autologous Stem Cell Transplant
AUC	Area under the concentration versus time curve
BIL	Bilirubin
BV	Brentuximab vedotin
CL	Clearance
CMax	Peak serum concentration
CMT	Compartment
CR/CRR	Complete Response/Complete Response Rate
CV	Percent coefficient of variation = [standard deviation/mean] x 100
CTCAE	Common Terminology Criteria for Adverse Events
Df	Degree of freedom
DLT	Drug tolerance level
DOR	Duration of Response
DV	Dependent variable (observed concentration)
ECL	Electrochemiluminescense
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Reasearch and Treatment of Cancer
GVHD	Graft-Versus-Host-Disease
H	hour
HEV	Hepatitis E Virus
HL	Hodgkin Lymphoma
HNSCC	Head and Neck squamous-cell carcinoma
IV	intravenous
IIV	Inter-individual variability
MDV	Missing concentration (dependent variable)
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	High level microsatellite instability
NM-TRAN	NONMEM translator
NONMEM	Nonlinear mixed-effects modeling software
NSCLC	Non Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
Pop-PK	Population Pharmacokinetic
PR	Partial Response
PRED	Population predicted concentration
PT	Preferred Term
Q	Intercompartmental flow rate
rrcHL	Relapsed or refractory classical Hodgkin Lymphoma
RSE	Percent relative standard error = [standard error/population mean estimate] x 100
RV	Residual variability
SCT	Stem Cell Transplantation
SD	Standard deviation
%SE	Relative standard error
SOC	System Organ Class
t1/2	Terminal elimination half-life
UC	Urothelial Cancer
VOD	veno-occlusive disease
WT	Body weight

ω^2	Variance of the interindividual variability
σ^2	Variance of the residual variability

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 Limited submitted to the European Medicines Agency on 12 October 2016 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 Indication to include the treatment of classical Hodgkin Lymphoma (cHL) in adults who have refractory disease, or who have relapsed after greater than 3 prior lines of therapy, based on the results from study KEYNOTE-087, an open-label Phase II trial of pembrolizumab in subjects with relapsed or refractory cHL and study KEYNOTE-013, a Phase Ib multi-cohort trial of pembrolizumab in subjects with hematologic malignancies. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly.

An updated RMP version 5.0 was provided as part of the application.

The requested variation proposed 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 Decision(s) P/0204/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0204/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

Scientific Advice (SA) related to clinical development of pembrolizumab in relapsed/refractory cHL was received from the CHMP (EMEA/H/SA/2437/9/2015/II).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniela Melchiorri Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	12 October 2016
Start of procedure	29 October 2016
CHMP Rapporteur Assessment Report	23 December 2016
CHMP Co-Rapporteur Assessment Report	22 December 2016
PRAC Rapporteur Assessment Report	3 January 2017
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	12 January 2017
CHMP members comments	18 January 2017
CHMP Rapporteur joint Assessment Report	19 January 2017
CHMP Request for Supplementary Information (RSI)	26 January 2017
Submission of responses	1 February 2017
CHMP Rapporteur joint response Assessment Report	21 February 2017
PRAC Rapporteur response Assessment Report	23 February 2017
Comments from PRAC	N/A
Updated PRAC Rapporteur response Assessment Report	N/A
PRAC outcome	9 March 2017
Comments from CHMP	15 March 2017
Updated CHMP Rapporteur joint response Assessment Report	16 March 2017
CHMP Opinion	23 March 2017
The CHMP adopted a report on similarity of Keytruda with Adcetris on (Appendix 1)	23 March 2017

2. Scientific discussion

2.1. Introduction

Hodgkin lymphoma (HL) is a lymphoid malignancy characterised by the presence of multinucleated Reed-Sternberg cells, which usually account for only 1% to 10% of the cells in the tumour tissue. The majority of cells in HL tumour tissue are a mixed infiltrate of various lymphoid cells, including effector and regulatory T-cells and macrophage. The updated 2008 WHO classification recognizes 2 histologic groups: nodular lymphocyte predominant, which accounts for about 5% of all HL cases and classical HL (cHL) which accounts for the remaining 95%.

From a histological point of view, cHL is characterised by the presence of the pathognomonic Reed-Sternberg (RS) cells 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, particularly the number of infiltrating macrophages and eosinophils, has prognostic value. In fact, based on the histological pattern, cHL is further classified into 4 distinct subtypes: nodular sclerosis (70%), mixed cellularity (20-25%), lymphocyte rich (5%) and lymphocyte depleted (<1%). The rare lymphocyte depleted variant is associated with the most aggressive behaviour and worst prognosis.

There are marked geographic epidemiologic differences in HL with highly variable incidence rates due to age, ethnicity, region, prior infections and other factors. The incidence in Europe is approximately 2.4 cases per 100.000 persons, and presents a characteristic bimodal age distribution curve, with one peak in young adults (median age of onset 20 years) and one in older adults (median age of onset 65 years). Overall, the majority of patients are young adults, with a slightly higher prevalence in males. cHL accounts for approximately 10% of all lymphomas and 0.6% of all cancers.

Treatment of cHL is primarily based on disease stage and the presence or absence of certain clinical features (i.e. B symptoms and bulky disease). Localised, early stage cHL is usually treated with a combination of abbreviated chemotherapy and low dose involved-site radiation therapy: cure rates with this approach are significantly high, approximating 90% in some studies. Advanced cHL is usually treated with upfront combination chemotherapy (e.g. ABVD, BEACOPP or STANFORD-V) ± involved-field radiation therapy (especially in presence of bulky disease and residual mass). Most patients with cHL will attain an initial remission, however relapse/refractoriness rates are known to range from 10 to 20% in early stages to 30-40% (according to treatment and baseline characteristics) in more advanced settings. For patients who relapse, treatment of choice consists of a chemotherapy regimen (different than that used in the first line) followed by high dose chemotherapy and autologous stem cell rescue with or without radiation therapy. After the initial multi-drug treatment regimen, approximately 5% to 10% of patients with HL suffer from primary refractory disease, defined as no response or progression within 90 days of treatment, and an additional 10 to 30% will relapse. In this population, an additional 10% to 30% will relapse. Once a subject undergoes ASCT and subsequently relapses, the outcomes are generally poor and efficacious therapeutic options are limited. The median OS of patients who relapse after ASCT was initially reported to be < 1 year; more recent data suggests that the median OS is evolving and may be closer to 2 years because of the availability of newer therapies like brentuximab vendotin.

Salvage therapy is currently based on the use of non-cross-resistant regimens (i.e. DHAP, IGeV, GemOX plus dexamethasone, ICE etc.) and can achieve responses in approximately 50% of patients. Unfortunately,

long-term disease control following conventional therapy alone is uncommon, and further consolidation is needed. Fit patients are candidates for high dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT). The German Hodgkin's Lymphoma Study Group (GHSG) has identified three adverse risk factors predictive of second relapse following salvage therapy (including ASCT): time to first recurrence ≤12 months, stage III or IV at first relapse and haemoglobin <10.5 (females) or <12.0 (males) g/dL at the time of first relapse (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% overall (Böll B et al, JCO 2013).

Brentuximab vedotin (BV), an immunotoxin comprised of a CD30-directed antibody linked to an anti-tubulin agent (MMAE), is currently 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 relapsed or refractory HL after prior autologous HCT were treated with brentuximab vedotin (1.8 mg/kg every three weeks for up to 16 cycles) the overall response rate (ORR) was 75% (34% CR). Five years OS was 41% (65% for patients who obtained a CR) and progression-free survival (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 (Chen R et al, Blood 2016; Younes A et al, JCO 2012).

Prognosis after failure of 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. Other treatment options (i.e. lenalidomide, bortezomib etc.) should still be considered experimental and are not usually associated with long-term clinical benefit.

Programmed death 1 (PD-1) ligands, PD-L1 and PD-L2, frequently responsible of cancer cell evasion of immune surveillance, have been shown to be over-expressed by Reed-Sternberg cells, making PD-1 an attractive target in r/r cHL. In this regard, check-point inhibitors such pembrolizumab, directly acting on the PD-1 blockade, might prove effective in this heavily pre-treated population. Opdivo (nivolumab), a human IgG4 anti-PD-1 monoclonal antibody, has been recently granted an indication for the treatment of adult patients with r/r cHL after ASCT and treatment with BV.

Keytruda (pembrolizumab, MK-3475) is a humanized monoclonal antibody blocking the interaction between the programmed death-1 (PD-1) receptor and its ligands PD-L1 and PDL2. As a consequence, the functional activity of the target lymphocytes is enhanced to facilitate immune-mediated anti-tumour activity. An EU Marketing Authorization (MA) was granted on 17 July 2015 as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults.

In this application it is proposed for the treatment of classical Hodgkin Lymphoma (cHL) in adults who have refractory disease, or who have relapsed after greater than or equal to 3 prior lines of therapy.

The recommended dose of KEYTRUDA in cHL is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

Pembrolizumab is a protein, which is expected to biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), it is unlikely to result in a significant risk to the environment and as such a justification is provided for not submitting an Environmental Risk Assessment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Table 1. Tabular overview of clinical studies

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-3475-P013V01 [Ref. 5.3.5.2: P013V01MK3475]	Ib	Canada France Italy USA	A Phase Ib Multi-cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies	Unblinded Open-Label No Treatment Control	MK-3475 10 mg/kg every 2 weeks IV infusion up to two years	Males/females Age: 20-67 Cohort 3 Relapsed or Refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma subjects	10 mg/kg every 2 weeks 31 subjects (Cohort 3)

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
KEYNOTE-087 [Ref. 5.3.5.2: P087V01MK3475]	II	Australia, Canada, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Netherlands, Norway, Russia, Spain, Sweden, UK, US	A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL)	Open-label, single-arm, multi-cohort, multicenter 24 months	Pembrolizumab 200 mg IV every 3 weeks	Males/females age ≥ 18 years with R/R de novo cHL	210 subjects allocated and treated

2.3.2. Pharmacokinetics

Clinical pharmacology results specific to rrcHL indication derive from two clinical studies (KEYNOTE-013 and KEYNOTE-087) and are supported by available data from other indications previously approved with pembrolizumab.

Pharmacokinetics in target population

A pooled population PK analysis using data from the KN001, KN002 and KN006 studies was performed to characterize serum pembrolizumab concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications has been discussed in previous applications.

In support of this specific submission, a focused PK analysis was conducted primarily to show the similarity of observed concentrations in subjects with rrcHL cancer in KN013 (10 mg/kg Q2W) and KN087 (200 mg Q3W) with the predictions from the definitive population PK analysis. The definitive population PK model was adequate to describe the PK data in subjects with rrcHL (see section on PK/PD Modelling).

Pharmacokinetics of pembrolizumab in HL as compared to other tumour indications

The similarity of pembrolizumab pharmacokinetics in HL as compared to other tumour indications (melanoma and NSCLC) was assessed in the Population Pharmacokinetic Model for Pembrolizumab (MK-3475) to Subjects with Hodgkin Lymphoma (HL) report.

Previously, a pooled population PK analysis (report 04DDV3) using KN001, KN002 and KN006 studies was performed to characterize serum concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications. This analysis is considered the definitive population PK analysis to characterize pembrolizumab PK and inform the label for pembrolizumab.

The structure of the definitive population PK model for pembrolizumab has 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, as follows:

$$P^* = \theta_x \cdot \left(\frac{WT}{MedianWT} \right)^{\theta_y}$$

where θx is a typical value of a pharmacokinetic parameter P*, and θy is the fixed-effect parameter to be estimated. WT is the individual body weight, and MedianWT is the median body weight across the analysis population.

In addition to body weight, the existing population PK model contained several more covariate relationships, which were established through a stepwise covariate search. The covariate relationships used the following generic form for continuous covariates, similar to the relationships for body weight.

$$P^* = \theta_x \cdot \left(\frac{Cov}{MedianCov} \right)^{\theta_y}$$

The following function was used to describe the effects of categorical covariates:

$$P^* = \theta_x \cdot (1 + Q \cdot \theta_y)$$

Where θx is a typical value of a pharmacokinetic parameter P*, and θy is the fixed-effect parameter to be estimated, and Cov is the (continuous) covariate value and Q is the indicator variable denoting the category of the (categorical) covariate.

Inter-individual variability (IIV) of the PK parameters (CL, Volume of distributions (Vc and Vp) and inter-compartmental clearance Q) was included using a lognormal random effects model.

Residual variability (RV), a composite measure of assay error, dose/sample time collection errors, model misspecification, and any other unexplained variability within a subject, was modeled using a log-transformed

additive error model. (for the Assessment of the population PK analysis, please refer to the variation II/11 of Keytruda).

No additional model development was performed in the current analysis, and the definitive population PK was used as is. For this updated PK evaluation, the data from HL patients from studies KN013 and KN087 were added to the dataset. Therefore, the consistency of pembrolizumab PK in patients with Hodgkin Lymphoma from studies KN013 and KN087 with the established definitive population PK analysis was analyzed. Furthermore, comparisons were made of observed peak and trough concentrations between Japanese and non-Japanese HL patients.

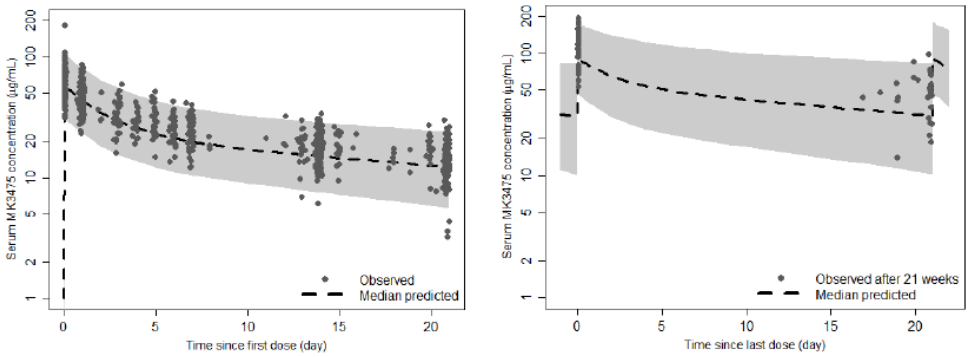
The final analysis data set from studies KN001, KN002, KN006, KN013 and KN087 used for the population PK based comparisons comprised of a total of 13771 pembrolizumab concentrations from 2417 patients.

The figures below report the Pembrolizumab serum concentrations for the HL subjects treated with 200 mg Q3W or 10 mg/kg Q2W, together with a predicted concentration range (median and 90% prediction interval) from the definitive population PK model, based on the data from patients with melanoma or NSCLC.

Near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the median C_{min} at 18 weeks was approximately 28 mcg/mL at a dose of 200 mg every 3 weeks. The median area under the concentration-time curve at steady state over 3 weeks ($AUC_{0\text{-}3weeks}$) was 658 mcg·day/mL at a dose of 2 mg/kg every 3 weeks and 876 mcg·day/mL at a dose of 200 mg every 3 weeks.

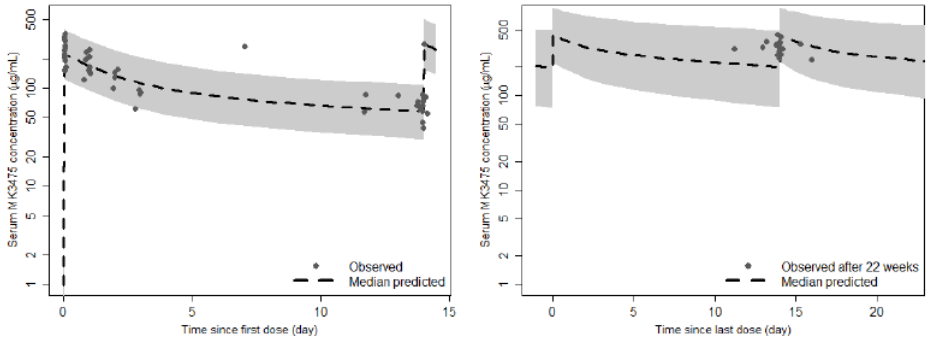
Figure 1 and 2: Pembrolizumab concentration profiles in HL patients

Consistency of Observed Concentrations in HL Subjects with Predictions Based on Definitive Population PK Model: Pembrolizumab (MK-3475) Concentration-Time Profiles during the First Dose (left panel) and at Steady State (right panel) at 200 mg Q3W



Dots are individual data from HL patients; Solid line is median prediction from the model for a regimen of 200 mg Q3W and the shaded area represents the 90% prediction interval. Reviewed per SOP-QP2-005
Data source: [04GZG6: analysis-p1p2p6p13p87p24p55pk]

Consistency of Observed Concentrations in HL Subjects with Predictions Based on Definitive Population PK Model: Pembrolizumab (MK-3475) Concentration-Time Profiles during the First Dose (left panel) and at Steady State (right panel) at 10 mg/kg Q2W

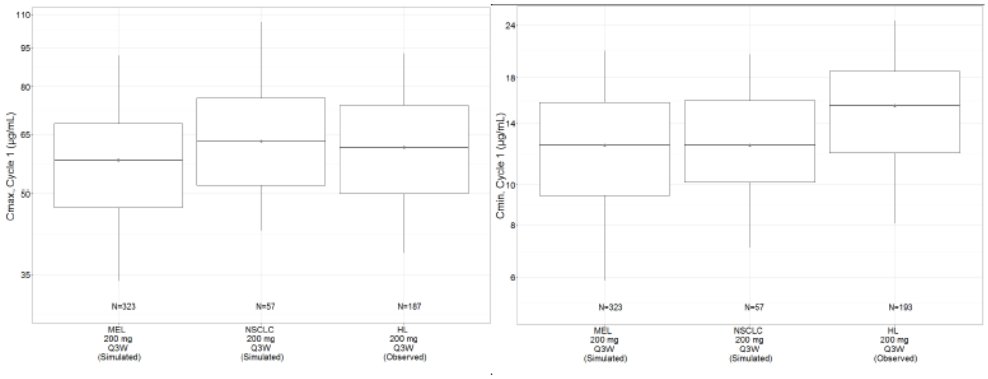


Dots are individual data from HL patients; Solid line is median prediction from the model for a regimen of 10 mg/kg Q2W and the shaded area represents the 90% prediction interval.
Reviewed per SOP-QP2-005

To further establish the similarity in pembrolizumab exposures across indications, several comparisons have been made of peak and trough concentrations between indications.

Figures 3- 4: Observed peak and trough concentrations in HL vs predicted in melanoma and NSCLC

Comparison of Distributions of Observed Peak and Trough Concentrations (Cycle 1) in HL Patients at 200 mg Q3W with Predicted Concentrations in Melanoma and NSCLC Patients at the Same Dose Regimen



Reviewed per SOP-QP2-005

Descriptive Statistics of Observed Peak and Trough Concentrations (Cycle 1) in HL Patients at 200 mg Q3W and Predicted Peak and Trough Concentrations in Melanoma and NSCLC Patients at the Same Dose Regimen

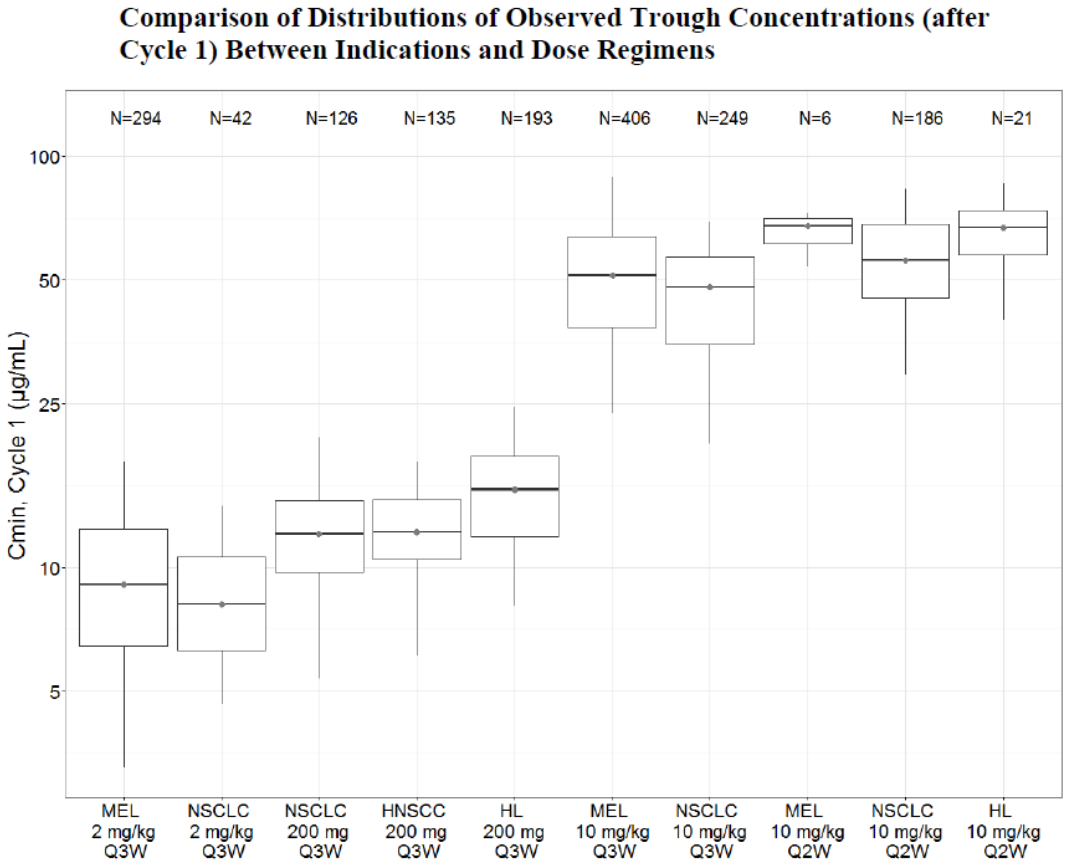
Parameter	HL (observed)				Melanoma and NSCLC (predicted)			
	N	Mean	Median	SD	N	Mean	Median	SD
Cmax[a] (µg/mL)	187	62.95	61.3	18.38	380	61.47	58.59	18.27
Cmin[b] (µg/mL)	193	15.52	15.4	5.06	380	13.78	12.4	4.67

[a] Cmax is concentration at time of peak sample in Cycle 1
[b] Cmin is trough concentration following Cycle 1

Reviewed per SOP-QP2-005

The observed median steady-state trough concentrations (C_{min}) in cHL is up to 40% higher than that in other tumour types; however, the range of trough concentrations are similar. There are no notable differences in median peak concentrations (C_{max}) between cHL and other tumour types. As a further comparison, distributions of observed peak and trough concentrations for the different dose regimens and indications have been compared.

Figure 5: trough concentrations (after Cycle 1) presented by indication and dose regimen.

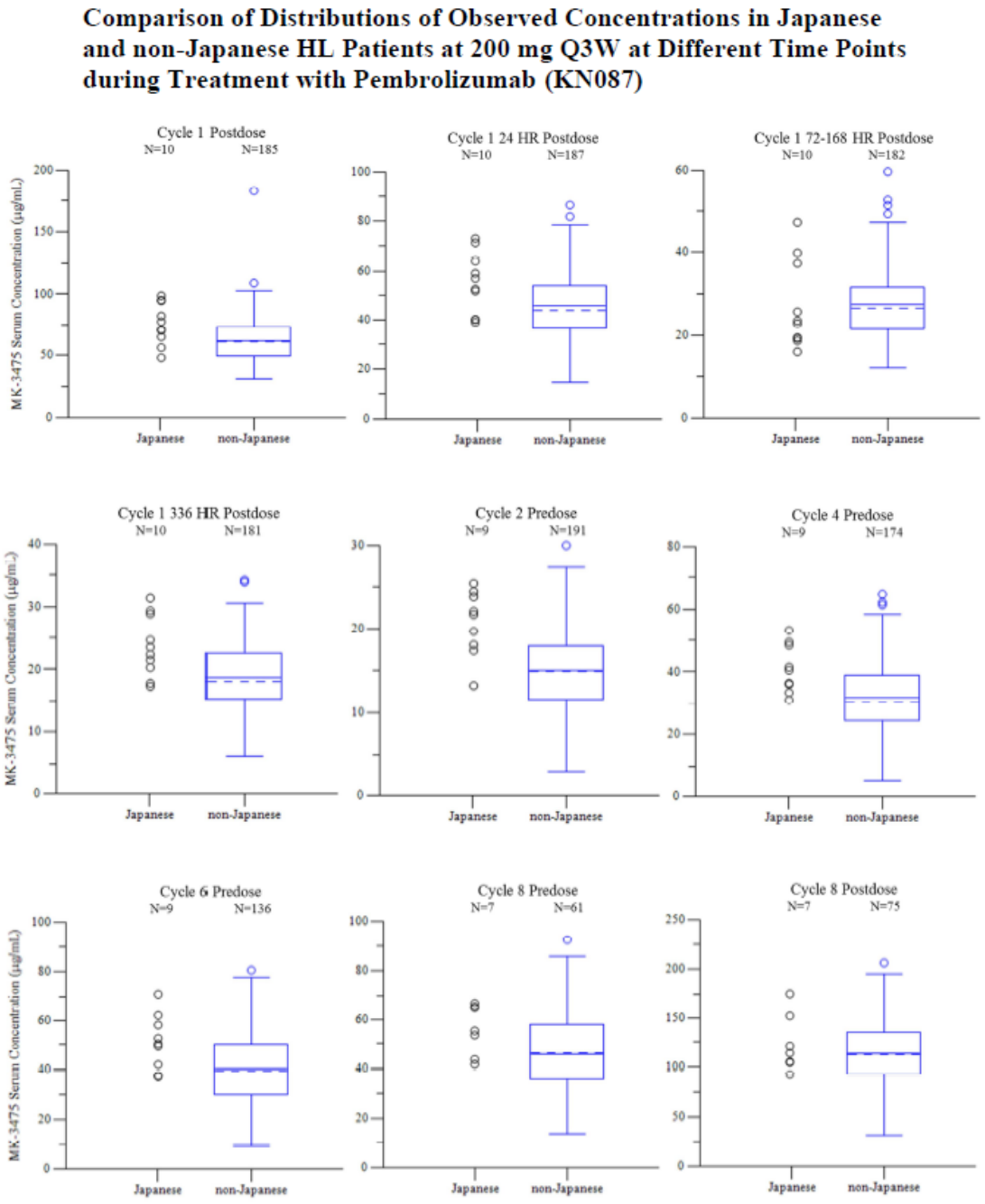


The plot includes additional concentration data at 200 mg Q3W from patients with NSCLC (KN024) and HNSCC (KN055).

The figure below summarizes the distributions of observed peak and trough concentrations of pembrolizumab in Japanese and non-Japanese HL patients at 200 mg Q3W from study KN087, both following the first administration (Cycle 1) and at Cycle 8, which represents steady state.

Overall, the peak and trough concentrations in Japanese HL patients are well contained in the distribution of observed concentrations in non-Japanese patients, indicating similarity in the pharmacokinetics of pembrolizumab across both populations.

Figure 6: concentrations in Japanese and non-Japanese HL patients



2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody which 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

An integrated immunogenicity evaluation has been performed across data from studies KN001, KN002, KN006, KN010, KN012, KN013, KN024, KN052, KN055, KN087 and KN164.

In the immunogenicity assessment, 3268 subjects were included (1535 Melanoma subjects, 1237 NSCLC subjects, 101 HNSCC subjects, 121 UC subjects, 54 MSI-H subjects and 220 HL subjects). The overall immunogenicity incidence was defined as the proportion of treatment emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

The samples were assayed for anti-pembrolizumab antibodies presence, using a validated electrochemiluminescense (ECL) immunoassay. Bioanalysis of pembrolizumab ADA was carried out using the standard 3-tiered assay approach that consisted of screening (Tier 1), confirmation (Tier 2) and antibody titer assessment (Tier 3). Only Tier 2 confirmed ADA positive samples moved to Tier 3 and were reported with a titer value. Tier 2 confirmed ADA positive samples were also assessed using a nAb assay based on the ability of ADA to block (neutralize) the critical first step in the pharmacological action of pembrolizumab, which is binding to PD-1, its *in vivo* target. Finally, Protein G depletion was used to confirm the presence pembrolizumab neutralizing antibodies.

A summary of subject immunogenicity results is reported below:

Summary of Subject Immunogenicity Results

Pooled analysis, Stratified by treatment				
Immunogenicity status	All treatments	Treatment		
		2 mg/kg	10 mg/kg	200 mg
Assessable subjects[a]	3268	706	2037	525
Inconclusive subjects[b]	1649	136	1488	25
Evaluable subjects[c]	**1619**	**570**	**549**	**500**
Negative[d]	1574 (97.2%)	555 (97.4%)	534 (97.3%)	485 (97.0%)
Non-Treatment emergent positive[d]	16 (1.0%)	7 (1.2%)	4 (0.7%)	5 (1.0%)
Treatment emergent Positive[d]	29 (1.8%)	8 (1.4%)	11 (2.0%)	10 (2.0%)

Pooled analysis, Stratified by Indication						
Immunogenicity status	Melanoma	NSCLC	HNSCC	UC[e]	MSI-H[f]	HL
Assessable subjects[a]	1535	1237	101	121	54	220
Inconclusive subjects[b]	1101	444	39	27	0	38
Evaluable subjects[c]	**434**	**793**	**62**	**94**	**54**	**182**
Negative[d]	427 (98.4%)	765 (96.5%)	59 (95.2%)	93 (98.9%)	51 (94.4%)	179 (98.4%)
Non-Treatment emergent positive[d]	4 (0.9%)	6 (0.8%)	2 (3.2%)	0	2 (3.7%)	2 (1.1%)
Treatment emergent Positive[d]	3 (0.7%)	22 (2.8%)	1 (1.6%)	1 (1.1%)	1 (1.9%)	1 (0.5%)

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..
e: One of these subjects is identified as MSI-H (AN PPD), this subject has no ADA positive samples and is classified as ADA negative.
f: All subjects except one subject (AN PPD), are identified as MSI-High

Source: [Ref. 5.3.5.3: 04GTJD: Table 5]

During the course of the study, measurement of the ADA samples was transferred from Intertek to another Vendor (PPD).

As part of the assay transfer, the ADA screening assay was further optimized to increase the DTL. Part of the samples was analyzed at Intertek, and part of the samples was analyzed at PPD. All the samples were analyzed using the same type of assay. For the evaluation of each individual ADA sample, the DTL of the corresponding assay has been used. The DTL for the ADA assay executed at Intertek is 25 µg/mL, the DTL for the ADA screening assay executed at PPD is 124 µg/mL.

In the current database, all samples were tested in the ADA screening assay,8019 samples were tested at Intertek (KN001, KN002, KN006, KN010, and KN012), and 6520 samples were tested at PPD (KN001, KN006, KN010, KN012, KN013, KN024, KN052, KN055, KN087 and KN164).

Evaluation of drug tolerance level

The immunogenicity status of a subject could only be conclusively confirmed to be negative if all pre-treatment and post-dose samples were negative in the confirmatory assay for antibodies against pembrolizumab and if the concentration of pembrolizumab in the last post-dose sample was below the drug tolerance level.

At the recommended dosing regimen of 200 mg fixed dose, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level for about 95% of the subjects.

At the recommended dosing regimen of 200 mg, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level (<DTL) for about 95% of the subjects (n=0 last post dose sample with concentration >DLT), indicating that the DLT for the ADA assay is adequate for 200 mg.

Considering the pooled analysis stratified by treatment and indication, 1 subjects out of 220 assessable subjects (0.5%) with HL had treatment emergent ADA. Overall, in all assessable subjects including 3268 subjects, the incidence rate for treatment emergent ADA was 1.8%, (29 out of 1619) similar to those observed with the previous immunogenicity database (2.0% TE ADA).

The results of the neutralizing assay of the confirmed positive ADA samples were provided. The submitted summary report includes the immunogenicity assessment of 3727 subjects (1535 melanoma, 1238 NSCLC, 101 HNSS, 54 MSI-H, 220 HL and 579 UC subjects). Out of them, 2034 subjects were evaluable, with 1.8% (36 out of 2034) incidence of treatment emergent ADA, based on a pooled analysis (melanoma, NSCLC, HNSCC, MSI-H, HL and UC). Nine of the 36 treatment emergent positive subjects (1 melanoma, 5 NSCLC, 1 HL and 2 UC) tested positive in the neutralizing assay and thus were considered as 'treatment emergent neutralizing positive', accounting for a total incidence rate of treatment emergent neutralizing positive subjects of 0.4% (9 out of 2034) in the overall population. No impact of binding or neutralizing ADA on pembrolizumab exposure was observed.

Exposure-Response analysis

An ER analysis was performed to explore the relationship between pembrolizumab dose and the anti-tumour response measured as the change from baseline of the sum of the area of index lesions in subjects with rrcHL

The dataset for this analysis include 31 subjects from KN013 (10 mg/kg Q2W) and 210 subjects from KN087 (200 mg Q3W).

Table 3: number of patients with available PK data:

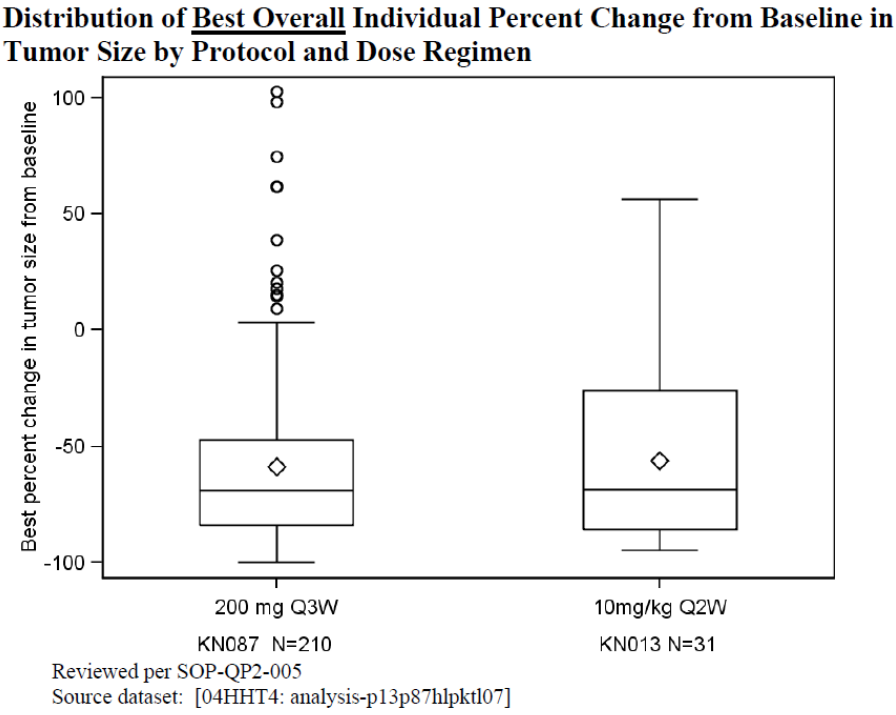
Distribution of rrcHL Treated With Pembrolizumab on KN013 and KN087

Protocol	Treatment	Allocated	Treated
KN013	10 mpk Q2W	31	31
KN087	200 mg Q3W	211	210

Source dataset: [04HHT4: analysis-p13p87hlpktl07]

A flat dose-response relationship for change in tumour size in pembrolizumab treated rrcHL subjects was demonstrated from studies KN013 and KN087.

Figure 7: Box-and-whisker plots of tumour size change, stratified by dose:



rrcHL subjects who received 10 mg/kg Q2W (KN013) exhibited similar tumour size reduction as those dosed 200 mg Q3W (KN087), demonstrating a flat dose-response relationship as already shown in other indications.

2.3.4. Discussion on clinical pharmacology

The updated clinical pharmacology results new in this submission include: PK data from KEYNOTE-013 (KN013) and KEYNOTE-087 (KN087), an integrated review of the available data to evaluate the appropriateness of the 200 mg Q3W dose for the rrcHL indication based on the response data from KN013 (10 mg/kg Q2W) and KN087 (200 mg Q3W) and other previously submitted data and an updated evaluation of immunogenicity including data from KN013 and KN087.

The starting point for the population PK analysis submitted in the current variation application was a previous population PK analysis based on dataset including 2188 subjects across the melanoma and NSCLC indications (KN001, KN002 and KN006 studies). This former analysis is considered the definitive population PK model to inform the label for pembrolizumab and no further model development was performed in the current analysis which incorporates data from HL patients recruited in studies KN013 and KN087. Thus, the final dataset consist of a total of 13771 determinations of pembrolizumab concentrations from 2417 patients.

The approach taken was to utilize the definitve population PK model to predict pembrolizumab levels in HL patients after 200 mg Q3W and 10 mg/kg Q2W. The predictions were compared with observed levels determined in studies KN087 and KN013.

Plasma drug trough concentrations in cycle 1 observed at 200 mg Q3W in HL patients are slightly higher compared to the range of concentrations at dose levels of 2 mg/kg Q3W and of 200 mg Q3W in MEL and NSCLC

patients. Descriptive statistics of all later PK sampling time points and a comprehensive PK evaluation at steady state from both studies KN087 and KN013 were provided. With the 200 mg Q3W regimen, very few simulated patients >100 kg fall below the 5th percentile of exposures from the 2 mg/kg Q3W regimen. Therefore, the 200 mg is a conservative fixed dose that maintains exposures between the established clinical bounds of 2 and 10 mg/kg for the overwhelming majority of subjects, even those >100 kg.

The observed median steady-state trough concentrations (C_{min}) in cHL is up to 40% higher than that in other tumour types; however, the range of trough concentrations are similar. There are no notable differences in median peak concentrations (C_{max}) between cHL and other tumour types. However, based on available safety data in cHL and other tumour types, (see discussion on clinical safety) these differences are not clinically meaningful. Information on the observed median steady state levels in HL patients from Keynote -013 and -087 and on possible PK differences to melanoma /NSCLC is adequately described in section 5.2 of the SmPC.

The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure.

Overall, the model proved adequate to capture pembrolizumab concentration indicating that the definitive population PK model provides an adequate representation of the pembrolizumab pharmacokinetics in HL, in addition to melanoma and NSCLC. The PK report and the evaluation of studies KN087 and KN013 presented by the MAH includes descriptive statistics for Cmin and Cmax from cycle 1 of both studies only.

The MAH performed an ER analysis to explore the relationship between pembrolizumab dose and the anti-tumour response measured as the change from baseline of the sum of the area of index lesions in subjects with rrcHL. A flat dose-response relationship for change in tumour size in pembrolizumab treated rrcHL subjects was demonstrated from studies KN013 and KN087.

In all 3268 subjects assessed, the incidence rate for treatment emergent ADA was 1.8%, (29 out of 1619) similar to that observed with the previous immunogenicity database (2.0% TE ADA).

Out of the 2034 subjects across indications who were evaluable for immunogevicity assessment, 1.8% (36 out of 2034) incidence of treatment emergent ADA, based on a pooled analysis (melanoma, NSCLC, HNSCC, MSI-H, HL and UC). Nine of the 36 treatment emergent positive subjects (1 melanoma, 5 NSCLC, 1 HL and 2 UC) tested positive in the neutralizing assay and thus were considered as 'treatment emergent neutralizing positive', accounting for a total incidence rate of treatment emergent neutralizing positive subjects of 0.4% (9 out of 2034) in the overall population. No impact of binding or neutralizing ADA on pembrolizumab exposure was observed.

2.3.5. Conclusions on clinical pharmacology

Pharmacological data submitted are considered adequate to support the proposed extension of indication in patients with classical Hodgkin's Lymphoma. Observed differences in C_{min} between cHL and other tumour types have been observed were not clinically meaningful. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Pembrolizumab has been administered at 10 mg/kg Q2W in the phase Ib study KEYNOTE-013 and at a fixed 200 mg dose Q3W in the subsequent phase II pivotal study KEYNOTE-087 as shown based on modelling and simulations performed (See discussion on clinical efficacy).

2.4.2. Main study(ies)

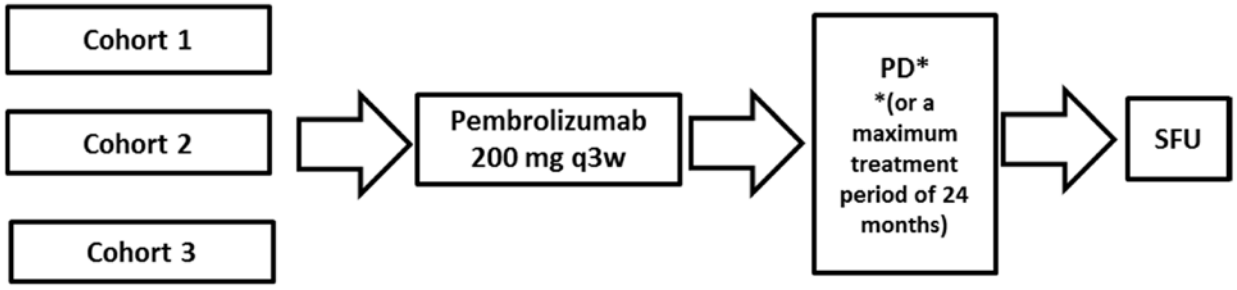
KEYNOTE-087

A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma

Methods

KEYNOTE-087 was a multi-center, single-arm, multi-cohort, non randomized Phase 2 trial.

Figure 8: Study design



N= 180; 3 Cohorts (60 subjects/cohort): read Entry Criteria in section 5.1

Cohort 1: who failed to achieve a response or progressed after auto-SCT and have relapsed after treatment with or failed to respond to brentuximab vedotin (BV)

Cohort 2: who were unable to achieve a CR or PR to salvage chemotherapy and did not receive auto-SCT and have relapsed after treatment with or failed to respond to BV

Cohort 3: who failed to respond to or progressed after auto-SCT and have not received BV post auto-SCT. These subjects may or may not have received BV as part of primary or salvage treatment.

*PD = progressive disease
SFU = survival follow-up

Study participants

Main Inclusion Criteria

- Age ≥ 18 years of age.
- Relapsed or refractory de novo classical Hodgkin lymphoma meeting one of the following cohort inclusions:
    - Relapsed: disease progression after most recent therapy
    - Refractory: failure to achieve CR or PR to most recent therapy

- Cohort 1: Have failed to achieve a response or progressed after auto-SCT. Subjects must have relapsed after treatment with or failed to respond to BV post auto-SCT.
- Cohort 2: Were unable to achieve a CR or a PR to salvage chemotherapy and did not receive auto-SCT. Subjects must have relapsed after treatment with or failed to respond to BV.
- Cohort 3: Have failed to achieve a response or progressed after auto-SCT and have not have received BV post auto-SCT. Note: These subjects may or may not have received BV as part of primary treatment, or salvage treatment.

- Measureable disease defined as at least one lesion that can be accurately measured in at least two dimensions with spiral computerized tomography (CT) scan. Minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis.
- Availability of an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy at Screening.
- Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
- Adequate organ function
  - creatinine ≤1.5 X upper limit of normal [ULN] OR CrCl ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN;
  - total bilirubin ≤ 1.5 X ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN; AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
  - absolute neutrophil count (ANC) ≥1,000 /mcL; platelets ≥75,000 / mcL; haemoglobin ≥8 g/dL

Main Exclusion Criteria

- Diagnosis of immunosuppression or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Prior allogeneic hematopoietic stem cell transplantation 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 vs. host disease.
- Known additional malignancy that is progressing or requires active treatment.
- Evidence of active, non-infectious pneumonitis.
- Active infection requiring intravenous systemic therapy.
- A known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
- A known clinically active CNS involvement.
- Pregnancy or breastfeeding, or expecting to conceive or father children within the projected duration of the trial.
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte associated antigen-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

Treatments

All subjects were to receive pembrolizumab 200 mg as a 30 minute IV infusion every 3 weeks (Q3W) on an outpatient basis on Day 1 of each cycle.

Dose interruption was planned for haematological toxicities if grade 4 and restart if toxicity resolves to grade 0-1 or baseline; treatment discontinuation was foreseen if toxicity does not resolve within 12 weeks of last infusion.

Planned dose modifications for other adverse events (AEs) associated with pembrolizumab exposure are summarised in table 4.

Table 4: Dose modifications due to toxicity

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Subjects could only receive study treatment if absence of signs and symptoms indicating disease progression, no decline in ECOG performance status, absence of rapid progression of disease. If PD was shown at the Week 12 disease response assessment, study drug could be continued, at the discretion of the PI, until the next disease response assessment, provided that the subjects' clinical condition was stable. If progression of disease was shown at a time point beyond Week 12 disease response assessment, the subject could not receive further treatment with study medication.

Subjects who experienced a complete or partial response or had stable disease were able to remain on treatment for up to 2 years (approximately 37 administrations) or until unacceptable toxicity or progression.

Subjects who attained a CR may have considered stopping pembrolizumab after receiving a minimum of six months of treatment with at least two doses since CR had been confirmed. Subjects who later experienced disease progression would have been eligible for retreatment with pembrolizumab at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, resuming therapy at the same dose and schedule as at the time of initial discontinuation.

Objectives

Primary objectives

- To determine the safety and tolerability of pembrolizumab within each of the 3 specified cohorts, and pooled.

- To evaluate the Objective Response Rate (ORR) of pembrolizumab by blinded, independent central review (BICR) according to the IWG response criteria (Cheson, 2007) within each of the 3 cohorts of subjects with r/r cHL.

Secondary objectives

Within each of the 3 cohorts of subjects with r/r cHL:

- To evaluate the ORR of pembrolizumab by investigator assessment according to the IWG response criteria and, additionally, by BICR using the 5-point scale according to the Lugano Classification.

- To evaluate Complete Remission Rate (CRR) of pembrolizumab by BICR and by investigator assessment according to the IWG response criteria and, additionally, by BICR using the 5-point scale according to the Lugano Classification.

- To evaluate Progression Free Survival (PFS) and Duration of Response (DOR) with pembrolizumab by BICR and by investigator assessment according to the IWG response criteria.

- To evaluate Overall Survival (OS) with pembrolizumab.

Exploratory objectives

Within each of the 3 cohorts, and potentially pooled:

- To evaluate ORR, CRR, PFS and DOR for subjects who continue treatment with pembrolizumab beyond documented progression.

- To explore the pharmacokinetic (PK) profile of pembrolizumab, immunogenicity and exposure of the proposed dose and dosing regimen

- To evaluate changes in health-related quality-of-life (HR-QoL) assessments from baseline using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) and European Quality of Life Five Dimensions Questionnaire (EuroQoL EQ-5D).

- To compare the extent of pre-pembrolizumab PD-L1 expression in tumour biopsies for pembrolizumab responders versus non-responders.

- To investigate the relationship between candidate efficacy biomarkers and anti-tumour activity of pembrolizumab utilizing pre and post-treatment lymph node biopsies and blood sampling.

- To explore the relationship between genetic variation across the human genome and response to the treatment administered.

Outcomes / endpoints

Response assessment

Anti-tumour activity of pembrolizumab was evaluated using the IWG response criteria by CT/PET. For lymphomas that were not FDG-avid at screening, PET was not repeated in follow-up assessments. The IWG criteria were applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy).

Initial disease assessment or tumour imaging was performed within 28 days prior to the first dose of trial treatment. CT scans were repeated every 12 weeks for subsequent assessments and PET was repeated at Week 12 and Week 24 (and as clinically indicated) to confirm CR or PD.

Assessment of lymphoma B symptoms occurred with each lymphoma disease response assessment.

When a subject assessment showed PD, study drug could be continued, at the discretion of the PI, until the next disease response assessment, provided that the subjects' clinical condition was stable. Imaging was, however, mandatory if there was clinical suspicion of progression (see also the "Treatments" section above for additional details on study drug continuation after initial evidence of PD).

Bone marrow biopsies were collected at screening and to confirm CR (in subjects who had marrow involvement), or if clinically indicated. Lymph node biopsies were collected at screening and at Week 12.

Primary endpoint

The primary efficacy endpoint was ORR, defined as the proportion of subjects in the analysis population who had a complete response (CR) or partial response (PR) using IWG criteria at any time during the study. Response for the primary analysis was determined by BICR.

Secondary endpoints

Secondary efficacy endpoints included:

- ORR according to Investigator (site) assessment using IWG criteria;

- ORR according to BICR using the Lugano 5-point classification;

- Complete response rate (CRR) by BICR, defined as the proportion of subjects in the analysis population who have CR by IWG criteria;

- PFS by BICR, defined as the time from first dose to the first documented disease progression according to IWG criteria or death due to any cause, whichever occurred first;

- Duration of response (DOR) by BICR, defined as time from first IWG response to disease progression in subjects who achieve a PR or better

- Overall survival (OS) defined as time from first dose to date of death.

Exploratory endpoints

Pre-specified exploratory efficacy endpoints included: the percentage of subjects eligible for stem cell transplant (SCT) post-study therapy, the percentage of subjects receiving SCT following post-study therapy (yes/no) and ORR, DOR, CRR, and PFS incorporating response assessments for subjects continuing pembrolizumab treatment after initial PD.

The EORTC QLQ-C30 and EuroQoL EQ-5D instruments were used to capture PRO data. The treatment effect con

PRO score change from baseline was evaluated at Week 12 to minimize loss of data due to death or disease progression and to allow for comparison in subjects still on treatment. The EQ-5D and EORTC QLQ-C30 questionnaires were administered by trained site personnel and completed electronically by the subjects themselves at the time points specified in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30.

The PRO completion rate was defined as the proportion of subjects who completed at least one PRO questionnaire to obtain a valid PRO score at each visit among the ASaT population. The PRO compliance rate was defined as the proportion of subjects who completed at least one PRO questionnaire to obtain a valid PRO score among those who were expected to complete these questionnaires at each visit according to their individual status. These rates exclude subjects from the denominator who are missing certain visits by design (e.g., due to death, discontinuation due to progression, discontinuation due to AE, other discontinuation of treatment, translations not being available or no visit being scheduled). Visits of “treatment discontinuation” and “safety follow-up” were mapped to different time points according to the actual visit time window.

Sample size

The planned sample size was 60 subjects in each Cohort for the Objective Response Rate (ORR) analysis. A target of 190 subjects is needed to be enrolled in the study assuming that approximately 5% of enrolled subjects will not be treated. For the three cohorts, there is at least 93% statistical power (1-sided nominal 2.5% alpha) to detect a 40% or higher ORR for the MK-3475 arm compared to a fixed control rate of 20% using the exact binomial test. Success for this hypothesis requires at least 16/60 responses. The selection of 20% as a fixed control rate was based on historical data in previously conducted studies in R/R HL prior to the approval of brentuximab vedotin, where response rates ranged between 18%-53% (Johnston et al, 2010, Fehniger et al, 2011, Younes et al, 2012, and Moskowitz et al, 2012). However, this study is being conducted in brentuximab vedotin failures and to date, there is no published data on the ORR in this particular patient population. Thus, a 20% ORR was chosen as a conservative control rate considering that all subjects to be enrolled in this study have failed an additional line of therapy (brentuximab vedotin) than seen previously.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

The analysis of primary efficacy endpoints was based on the All-Subjects-as-Treated (ASaT) population, i.e., subjects were included if they received at least one dose of study medication. Supportive analyses were conducted in the Full-Analysis-Set (FAS) population, which consisted of all subjects who 1) received at least one dose of study medication; 2) had a baseline disease assessment, and 3) had a post baseline disease assessment OR discontinued the trial due to progressive disease/drug-related AE.

Unless specified otherwise, analyses were conducted separately by Cohort.

The primary efficacy endpoint for this study was the Objective Response Rate (ORR). The 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 for each cohort versus a fixed control rate for each cohort. Secondary analyses for ORR were performed based on investigator's (i.e. study site) assessment and by central review based on the Lugano Classification (JCO, 2014).

Regarding the secondary endpoints, the complete remission rate (CRR), was analyzed by point estimates and 95% 2-sided exact CIs. Additional analyses were based on site assessment and by central review using the Lugano (JCO, 2014) criteria.

The non-parametric Kaplan-Meier method was used to estimate the PFS curve. Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression is approximated by the date of the first assessment at which PD is objectively documented per IWG criteria, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. A secondary analysis was performed for PFS based on investigator's assessment. In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses were performed with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers initiation of new anticancer treatment to be a PD event for subjects without documented PD or death and lost to follow-up to be a PD event for subjects without documented PD or death and lost to follow-up after ≥ 2 missed disease assessments. In the sensitivity analysis 2, the SCT after starting study treatment is not considered a sign of progression of disease but rather the benefit of treatment as hence censored at the date of SCT for the PFS analysis.

The analysis of Duration Of Response (DOR) consisted of Kaplan-Meier estimates. Duration of response data are censored on the date of the last disease assessment documenting absence of progressive disease for subjects who 1) do not have tumour progression and are still on study at the time of an analysis, 2) are given antitumour treatment (including stem cell transplant) other than the study treatment, or 3) are removed from study prior to documentation of tumour progression.

Duration of Response was based upon central review according to the IWG criteria; a secondary analysis of DOR was conducted using investigator assessment.

Regarding the Overall Survival endpoint, medians were estimated in the given analysis population, separately by cohort. In addition, the Kaplan-Meier method was used to estimate the survival curves, separately by Cohort. The survival rate at 6 and 12 months using the Kaplan-Meier estimates were provided.

EORTC QLQ-C30 and EuroQoL EQ-5D data were summarized, as part of the pre-specified exploratory analysis, and presented up to and including Week 36 assessment time point (corresponding to just beyond the median duration of follow-up), in the ASaT population, for all cohorts combined. Changes from baseline to Week 12 in the QLQ-C30 global health status/QoL domain and the EQ-5D VAS scale and Utility dimension were assessed, without imputation for missing data. Constrained longitudinal data analysis models were used to evaluate the change of PRO score from baseline to Week 12, overall, and in different subgroups of patients, by their response status. Descriptive analyses yielded the number and proportion of patients who “improved”, “deteriorated”, or remained “stable” in their QLQ-C30 global health status/QoL at Week 12, according to a 10-point or greater score change text from baseline.

Consistency of ORR is across various subgroups was determined by the point estimate of the ORR (with an exact 95% CI) plotted within each category of the following classification variables within each Cohort: Age category (≤65 vs. >65 years), Sex (female vs. male), Race (white vs. non-white), Region (US, ex-US),Number of prior therapies (< 4 vs ≥4). For Cohorts 1 and 3 only: Time elapsed since transplant failure (<12 months vs. ≥12 months). No multiplicity adjustment was planned as there is a single comparison of MK-3475 using 1 endpoint in the primary hypothesis within each Cohort. Other efficacy analyses will be considered supportive

and/or explanatory.

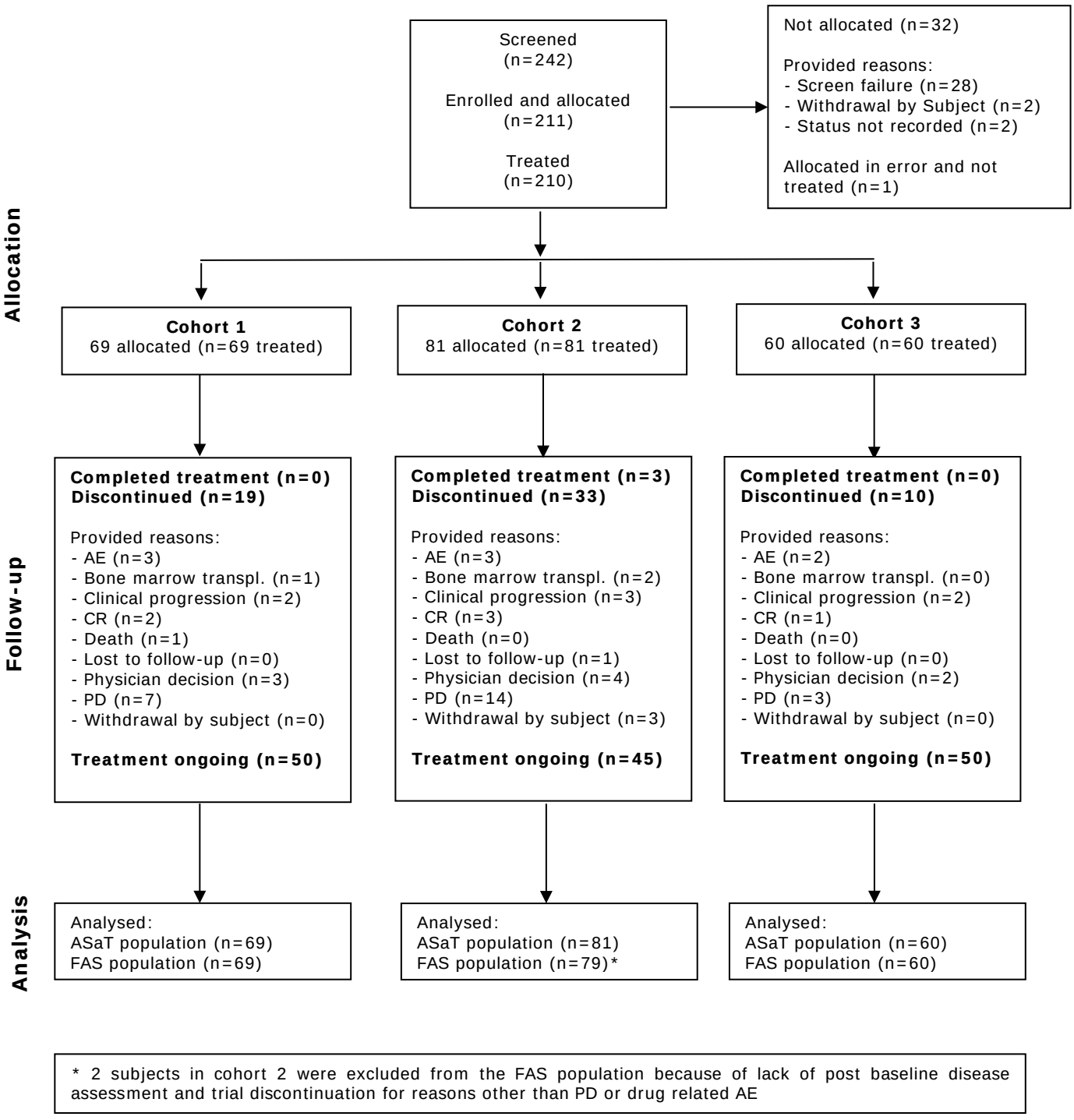
An interim analysis was planned for futility alone. The interim analysis would be conducted when 50% of the subjects within a cohort have been evaluated for response.

Additional efficacy analyses, that were not pre-specified in the SAP, based on refractory (PD or stable disease [SD] to a prior regimen) status and/or relapsed after ≥ 3 lines of prior anticancer therapy, including prior SCT, are also included in the present CSR.

Results

Participant flow

Figure 9: Participant flow in study KN-087



Based on a review of baseline data entered by the Investigator, including prior therapies received, 5 subjects were analysed in a cohort different than originally assigned.

Recruitment

Study KEYNOTE-087 was conducted at 51 centers: 11 in the US; 7 in Japan; 4 each in France, Israel, and Spain; 3 each in Italy, Russia, and the United Kingdom; 2 each in Australia, Germany, Greece, Hungary, and Sweden; and 1 each in Canada and Norway.

The first subject was enrolled in study Cohort 1 on 24-Jun-2015, and the last subject on 8-Feb-2016. The first subject was enrolled in study Cohort 2 on 24-Jun-2015, and the last subject on 16-Dec-2015. The first subject was enrolled in study Cohort 3 on 16-Jun-2015 and the last subject on 2-Mar-2016.

Conduct of the study

Protocol amendments

Table 5: Summary of protocol amendments**.**

Protocol Version Number (Date)	Description	Amendment Provided:	Countries in Scope
3475-087-00 (27-Feb-2015)	Original MK3475-087 protocol	N/A	Australia, Austria, Canada, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Netherlands, Norway, Russia, Spain, United Kingdom, United States
3475-087-02 (26-May-2015)	Sweden-specific protocol, corresponding to study protocol 00	• a list of required contraception • additions to the list of chemotherapeutic agents that may harm the fetus • changed the duration for using birth control from 120 days to 180 days after the last dose of study therapy • provided safety and adverse event profile from KEYNOTE-013, as well as beneficial language from KEYNOTE-001 and KEYNOTE-013	Sweden
3475-087-03 (21-Dec-2015)	MK3475-087 protocol amendment	• an update to the definitions for Cohorts 1, 2, and 3 • added guidelines for grade 2 Infusion Reactions • Removed the allowance for radiotherapy during study • revised the interim analysis instructions • updated the power calculation language • modified the progression-free survival analyses	Australia, Austria, Canada, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Netherlands, Norway, Russia, Spain, United Kingdom, United States
3475-087-05 (25-Feb-2016)	Sweden-specific protocol, corresponding to study protocol 03	• protocol changes as noted in version 03 • country-specific changes for Sweden as noted in version 02	Sweden
3475-087-01	Cancelled document	N/A. Draft document. Not finalized, used, or distributed.	N/A
3475-087-04	Cancelled document	N/A. Draft document. Not finalized, used, or distributed.	N/A

There were 104 major protocol deviations, and the most commonly occurring was regarding informed consent (65 incidents) and missed AEs report. No subject was excluded from analyses due to protocol deviations.

Baseline data

Table 6: Demographic and baseline characteristics for all subjects (ASaT population, n=210)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	69		81		60		210	
Gender								
Male	36	(52.2)	43	(53.1)	34	(56.7)	113	(53.8)
Female	33	(47.8)	38	(46.9)	26	(43.3)	97	(46.2)
Age (Years)								
<65	69	(100.0)	66	(81.5)	57	(95.0)	192	(91.4)
>=65	0	(0.0)	15	(18.5)	3	(5.0)	18	(8.6)
Mean	37.0		42.3		36.8		39.0	
SD	10.9		17.4		13.4		14.5	
Median	34.0		40.0		32.0		35.0	
Range	19 to 64		20 to 76		18 to 73		18 to 76	
Race								
American Indian Or Alaska Native	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.5)
Asian	7	(10.1)	4	(4.9)	1	(1.7)	12	(5.7)
Black Or African American	2	(2.9)	2	(2.5)	3	(5.0)	7	(3.3)
Missing	1	(1.4)	1	(1.2)	1	(1.7)	3	(1.4)
Multi-Racial	2	(2.9)	0	(0.0)	0	(0.0)	2	(1.0)
White	57	(82.6)	73	(90.1)	55	(91.7)	185	(88.1)
Ethnicity								
Hispanic Or Latino	6	(8.7)	5	(6.2)	3	(5.0)	14	(6.7)
Not Hispanic Or Latino	48	(69.6)	65	(80.2)	48	(80.0)	161	(76.7)
Not Reported	4	(5.8)	7	(8.6)	4	(6.7)	15	(7.1)
Unknown	11	(15.9)	4	(4.9)	5	(8.3)	20	(9.5)
Race Group								
White	57	(82.6)	73	(90.1)	55	(91.7)	185	(88.1)
Non-White	11	(15.9)	7	(8.6)	4	(6.7)	22	(10.5)
Missing	1	(1.4)	1	(1.2)	1	(1.7)	3	(1.4)
US Region								
US	13	(18.8)	20	(24.7)	19	(31.7)	52	(24.8)
Ex-US	56	(81.2)	61	(75.3)	41	(68.3)	158	(75.2)
Disease Subtype								
Classical Hodgkin Lymphoma- Nodular Sclerosis	55	(79.7)	65	(80.2)	49	(81.7)	169	(80.5)
Classical Hodgkin Lymphoma- Mixed Cellularity	9	(13.0)	10	(12.3)	5	(8.3)	24	(11.4)
Classical Hodgkin Lymphoma- Lymphocyte Rich	4	(5.8)	1	(1.2)	3	(5.0)	8	(3.8)
Classical Hodgkin Lymphoma- Lymphocyte Depleted	0	(0.0)	4	(4.9)	1	(1.7)	5	(2.4)
Missing	1	(1.4)	1	(1.2)	2	(3.3)	4	(1.9)
ECOG Performance Status								
0	29	(42.0)	44	(54.3)	29	(48.3)	102	(48.6)
1	39	(56.5)	37	(45.7)	31	(51.7)	107	(51.0)
2	1	(1.4)	0	(0.0)	0	(0.0)	1	(0.5)
Prior Lines of Therapy Group								
>=3	68	(98.6)	78	(96.3)	36	(60.0)	182	(86.7)

Subject Characteristics By Cohort
(ASaT Population)

	COHORT 1		COHORT 2		COHORT 3		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Prior Lines of Therapy Group								
< 3	1	(1.4)	3	(3.7)	24	(40.0)	28	(13.3)
Prior Lines of Therapy								
Subjects with data	69		81		60		210	
Mean	4.5		4.0		3.5		4.0	
SD	1.7		1.7		1.8		1.7	
Median	4.0		4.0		3.0		4.0	
Range	2.0 to 12.0		1.0 to 11.0		2.0 to 10.0		1.0 to 12.0	
Refractory or Relapsed After 3 or More Lines								
Yes	69	(100.0)	81	(100.0)	60	(100.0)	210	(100.0)
Time of relapse since SCT failure Group								
>=12 months	37	(53.6)	0	(0.0)	7	(11.7)	44	(21.0)
<12 months	32	(46.4)	0	(0.0)	53	(88.3)	85	(40.5)
Missing	0	(0.0)	81	(100.0)	0	(0.0)	81	(38.6)
Time of relapse since SCT failure (Months)								
Subjects with data	69		0		60		129	
Mean	30.2				6.3		19.1	
SD	39.6				11.8		32.3	
Median	12.6				1.9		7.9	
Range	2.5 to 247.9				0.4 to 76.0		0.4 to 247.9	
Brentuximab Use								
Yes	69	(100.0)	81	(100.0)	25	(41.7)	175	(83.3)
No	0	(0.0)	0	(0.0)	35	(58.3)	35	(16.7)
Prior Radiation								
Yes	31	(44.9)	21	(25.9)	24	(40.0)	76	(36.2)
No	38	(55.1)	60	(74.1)	36	(60.0)	134	(63.8)
Bulky Lymphadenopathy								
Yes	5	(7.2)	12	(14.8)	3	(5.0)	20	(9.5)
No	64	(92.8)	69	(85.2)	57	(95.0)	190	(90.5)
Baseline B Symptoms								
Yes	22	(31.9)	26	(32.1)	19	(31.7)	67	(31.9)
No	47	(68.1)	55	(67.9)	41	(68.3)	143	(68.1)
Baseline Bone Marrow Involvement								
Yes	3	(4.3)	5	(6.2)	3	(5.0)	11	(5.2)
No	66	(95.7)	75	(92.6)	57	(95.0)	198	(94.3)
Missing	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.5)

(Database Cutoff Date: 27JUN2016).

Source: [P087V01MK3475: analysis-adsl]

All subjects (N=210) were refractory to a previous therapy or had relapsed after ≥ 3 lines of therapy. Subjects in Cohorts 1 and 3 were post-auto-SCT (n = 129 total), and subjects in Cohort 2 (n = 81) had not received an auto-SCT. A total of 175 (83.3%) subjects had also previously failed to respond to or relapsed after treatment with BV. Seventy-six (36.2%) subjects had prior radiation therapy. The median number of prior lines of therapy was 4.0 (range: 1 to 12).

Numbers analysed

See above section.

Outcomes and estimation

Primary endpoint: Response rates

All subjects

The primary endpoint ORR per BICR in the ASaT population was 68.1% (143/210; 95% confidence interval [CI]: 61.3%, 74.3%). CR rate (CRR) per BICR in the ASaT population was 21.9% (46/210, 95% CI 16.5%, 28.1%)

Table 7: Summary of best overall response based on central review per IWG (ASaT)

Response Evaluation	MK-3475 200 mg (N=210)	
	n (%)	95% CI†
Complete Remission (CR)	46 (21.9)	(16.5, 28.1)
Partial Remission (PR)	97 (46.2)	(39.3, 53.2)
Objective Response (CR+PR)	**143 (68.1)**	**(61.3, 74.3)**
Stable Disease (SD)	35 (16.7)	(11.9, 22.4)
Progressive Disease (PD)	27 (12.9)	(8.6, 18.2)
Non-Evaluable (NE)	5 (2.4)	(0.8, 5.5)
† Based on binomial exact confidence interval method. (Database Cutoff Date: 27JUN2016)		

Source: [P087V01MK3475: analysis-adsl; adorr]

Five subjects "not evaluable" for response by BICR were considered non-responders. Four of these subjects discontinued the study without their first efficacy assessment at Week 12, and the fifth subject was considered PD at Day 16 by site review, leading to discontinuation, but not read by central review as an on-study scan.

Table 8: Response rates based on IWG criteria - by site review.

Response Evaluation	MK-3475 200 mg (N=210)	
	n (%)	95% CI†
Complete Remission (CR)	53 (25.2)	(19.5, 31.7)
Partial Remission (PR)	87 (41.4)	(34.7, 48.4)
Objective Response (CR+PR)	**140 (66.7)**	**(59.9, 73.0)**
Stable Disease (SD)	43 (20.5)	(15.2, 26.6)
Progressive Disease (PD)	23 (11.0)	(7.1, 16.0)
No Assessment (NA)	4 (1.9)	(0.5, 4.8)
† Based on binomial exact confidence interval method. (Database Cutoff Date: 27JUN2016)		

Source: [P087V01MK3475: analysis-adsl; adorr]

Cohort 1

The primary endpoint ORR was 72.5% (50/69; 95% CI: 60.4%, 82.5%) per BICR in the ASaT population of Cohort 1 (N=69) which was significantly greater than the expected 20% (p-value < 0.001)**;** CRR is 21.7% (15/69, 95% CI 12.7%, 33.3%).

Table 9: Summary of best overall response based on central review per IWG (Cohort 1)

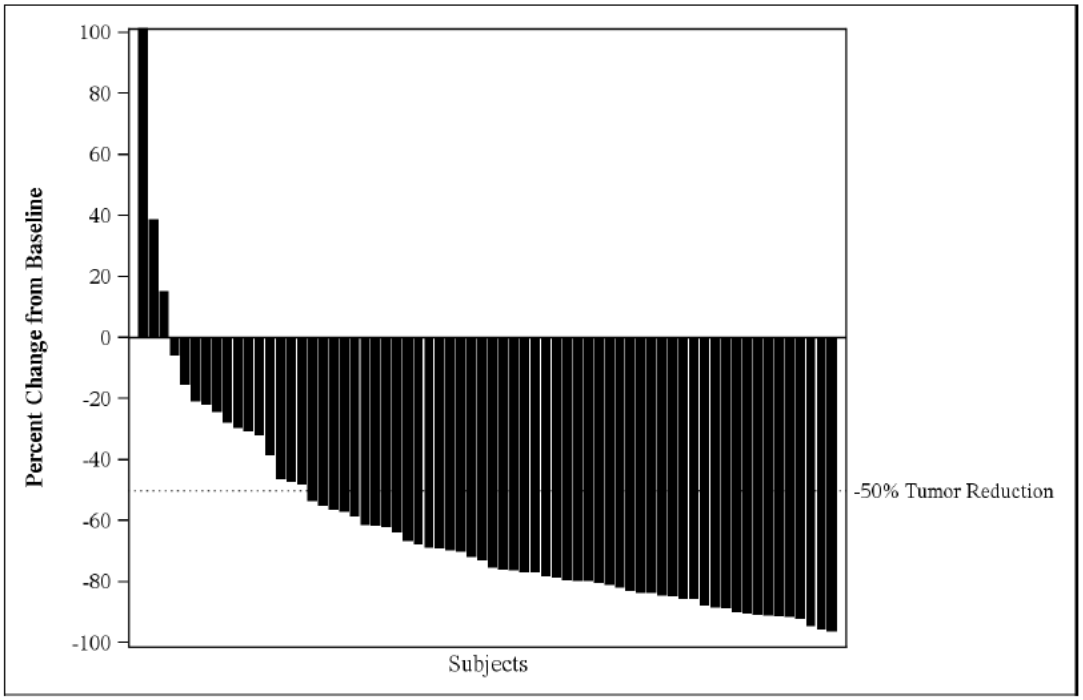
Response Evaluation	MK-3475 200 mg COHORT 1 (N=69)			
	n	%	95% CI[†]	p-Value[‡]
Complete Remission (CR)	15	21.7	(12.7, 33.3)	
Partial Remission (PR)	35	50.7	(38.4, 63.0)	
Objective Response (CR+PR)	**50**	**72.5**	**(60.4, 82.5)**	**< 0.001**
Stable Disease (SD)	13	18.8	(10.4, 30.1)	
Progressive Disease (PD)	3	4.3	(0.9, 12.2)	
Non-Evaluable (NE)	3	4.3	(0.9, 12.2)	

[†] Based on binomial exact confidence interval method.
[‡] One-sided p-value based on exact binomial distribution for testing. H_0: $p \leq 0.20$ versus H_1: $p > 0.20$
Database Cutoff Date: 27JUN2016

Source: [P087V01MK3475: analysis-adsl; adorr]

ORR based on IWG criteria by site review in Cohort 1 was 66.7% (46/69; 95% CI: 54.3%, 77.6%). CRR by site review in Cohort 1 was 29% (20/69, 95% CI 18.7%, 41.2%); 66 of 69 subjects had some degree of tumour reduction.

Figure 10: Tumour change from baseline by BICR in the ASaT Cohort 1



Tumour change from baseline by site review was overall consistent with the BICR assessment.

Cohort 2

The ORR per BICR in the ASaT population of Cohort 2 (n=81) was 65.4% (53/81; 95% CI: 54.0%, 75.7%) (N=69) which was significantly greater than the expected 20% (p-value < 0.001) (see Table below). CRR was 22.2% (18/81, 95% CI 13.7%, 32.8%).

Table 10: Summary of best overall response based on central review per IWG (Cohort 2)

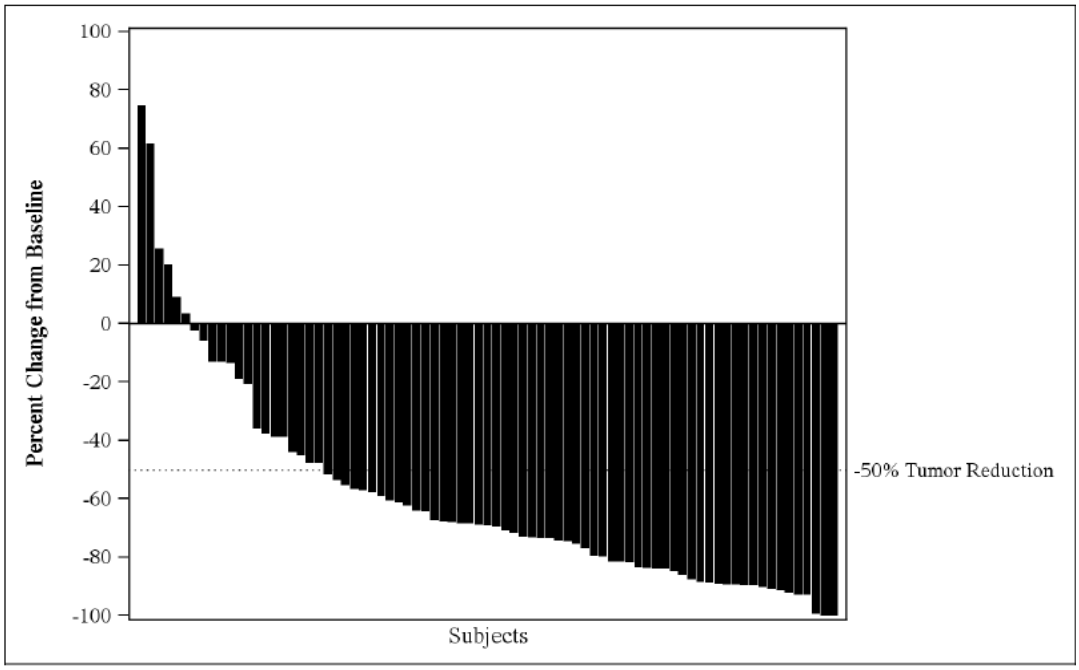
Response Evaluation	MK-3475 200 mg COHORT 2 (N=81)			
	n	%	95% CI[†]	p-Value[‡]
Complete Remission (CR)	18	22.2	(13.7, 32.8)	
Partial Remission (PR)	35	43.2	(32.2, 54.7)	
Objective Response (CR+PR)	**53**	**65.4**	**(54.0, 75.7)**	**< 0.001**
Stable Disease (SD)	9	11.1	(5.2, 20.0)	
Progressive Disease (PD)	17	21.0	(12.7, 31.5)	
Non-Evaluable (NE)	2	2.5	(0.3, 8.6)	

[†] Based on binomial exact confidence interval method.
[‡] One-sided p-value based on exact binomial distribution for testing. H_0: $p \leq 0.20$ versus H_1: $p > 0.20$
Database Cutoff Date: 27JUN2016

Source: [P087V01MK3475: analysis-adsl; adorr]

ORR based on IWG criteria by site review in Cohort 2 was 65.4% (53/81; 95% CI: 54.0%, 75.7%), and CRR 24.7% (20/81; 95% CI 15.8%, 35.5%); 75 of 81 subjects had some degree of tumour reduction (fig. 10).

Figure 11: Tumour change from baseline by site review in the overall ASaT population of Cohort 2



Tumour change from baseline by site review was overall consistent with the BICR assessment.

Cohort 3

The ORR per BICR in the ASaT population of Cohort 3 (n=60) was 66.7% (40/60; 95% CI: 53.3%, 78.3%) (N=69) which was significantly greater than the expected 20% (p-value < 0.001) (see Table below). CRR was 21.7% (13/60, 95% CI 12.1%, 34.2%).

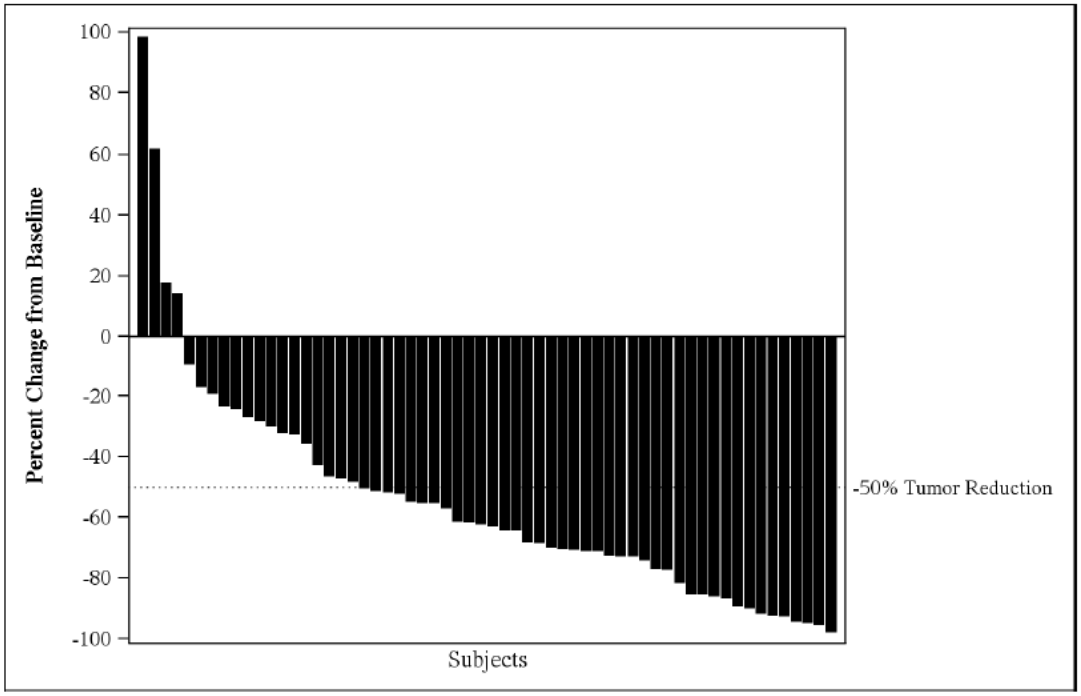
Table 11: Summary of best overall response based on central review per IWG (Cohort 3)

Response Evaluation	MK-3475 200 mg COHORT 3 (N=60)			
	n	%	95% CI[†]	p-Value[‡]
Complete Remission (CR)	13	21.7	(12.1, 34.2)	
Partial Remission (PR)	27	45.0	(32.1, 58.4)	
Objective Response (CR+PR)	**40**	**66.7**	**(53.3, 78.3)**	**< 0.001**
Stable Disease (SD)	13	21.7	(12.1, 34.2)	
Progressive Disease (PD)	7	11.7	(4.8, 22.6)	

[†] Based on binomial exact confidence interval method.
[‡] One-sided p-value based on exact binomial distribution for testing. H_0: $p \leq 0.20$ versus H_1: $p > 0.20$
Database Cutoff Date: 27JUN2016

ORR based on IWG criteria by site review in Cohort 3 was 68.3% (41/60; 95% CI: 55.0%, 79.7%). CRR by site review in Cohort 3 was 21.7% (13/60, 95% CI 12.1%, 34.2%); 56 of 60 subjects had some degree of tumour reduction.

Figure 12: Tumour change from baseline by BICR in the ASaT Cohort 3 population



Tumour change from baseline by site review was overall consistent with the BICR assessment.

Secondary endpoints

Duration of Response (DOR)

All subjects

Subjects were followed for a median of 7.1 months (range 1.0 to 12.1 months). The median time to response by BICR was 2.8 months (range 2.0 to 8.1 months), and median DOR was not reached (range 0.0+ to 8.3+

months). Among the 143 subjects with response, a response of at least 3 months in duration was observed in 45 subjects (86.9% by Kaplan-Meier method), and a response of at least 6 months in duration was observed in 4 subjects (65.3% by Kaplan-Meier method). At the time of the data cutoff, 115 (80.4%) responders had ongoing response.

Median time to response by site review was 2.8 months (range 2.0 to 5.7 months) and median DOR was 8.3 months (range 0.0+ to 8.3 months). Among the 140 subjects with a response, a response of at least 3 months in duration was observed in 49 subjects (88.2% by Kaplan-Meier method), and a response of at least 6 months in duration was observed in 6 subjects (63.6% by Kaplan-Meier method). At the time of the data cutoff, 113 (80.7%) responders had ongoing response.

Cohort 1

The median time to response by BICR for Cohort 1 was 2.7 months (range 2.0 to 5.7 months) and median DOR was not reached (range 0.0+ to 8.3+ months). Among the 50 subjects with response, a response of at least 3 months in duration was observed in 18 subjects (84.1% by Kaplan-Meier method), and a response of at least 6 months in duration was observed in 1 subject (63.1% by Kaplan-Meier method). At the time of the data cutoff, 39 (78.0%) responders had ongoing response.

DOR results by site review in Cohort 1 were consistent with the BICR analysis.

Cohort 2

The median time to response by BICR was 2.8 months (range 2.2 to 5.6 months) and median duration of response was not reached (range 0.0+ to 6.3+ months). Among the 53 subjects with response, a response of at least 3 months in duration was observed in 17 subjects(87.2% by Kaplan-Meier method), and a response of at least 6 months in duration was observed in 2 subjects (80.5% by Kaplan-Meier method) had an ongoing response ≥ 6 months [Figure 11-10]. At the time of the data cutoff, 40 (75.5%) responders had ongoing response.

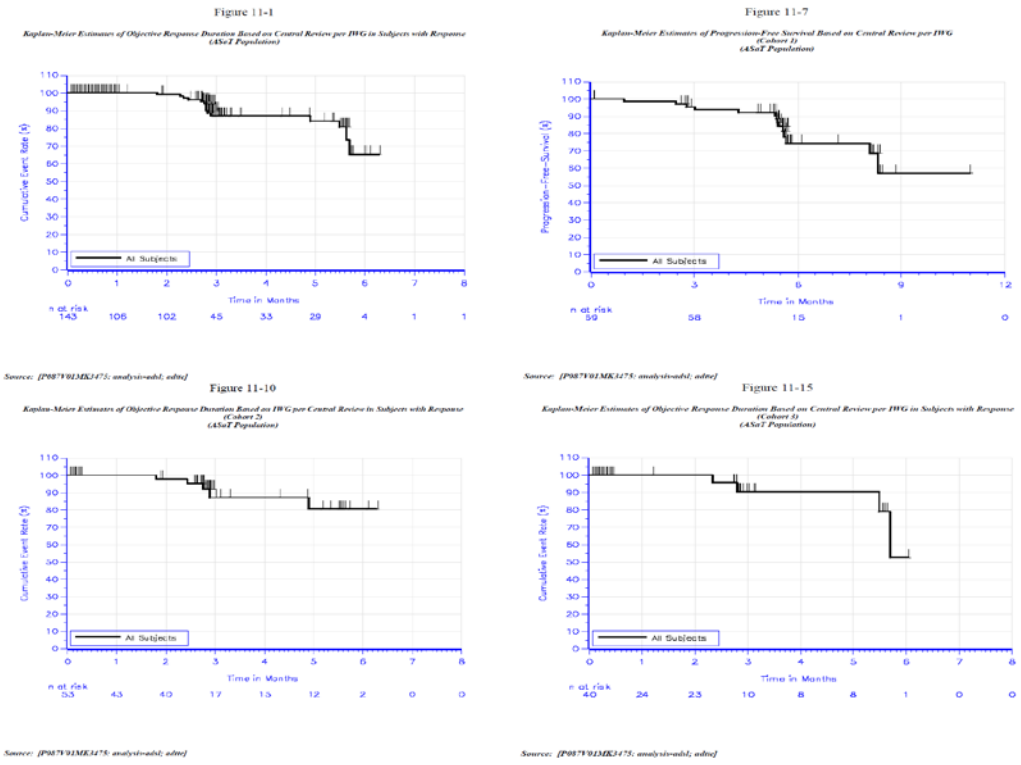
DOR results by site review in Cohort 2 were consistent with the BICR analysis.

Cohort 3

The median time to response by BICR was 2.8 months (range 2.6 to 8.1 months) and median DOR was not reached (range 0.0+ to 6.0+ months). Among the 40 subjects with response, a response of at least 3 months in duration was observed in 10 subjects (90.3% by Kaplan-Meier method), and a response of at least 6 months in duration was observed in 1 subject (52.7% by Kaplan-Meier method). At the time of the data cutoff, 36 (90.0%) responders had ongoing response.

DOR results by site review in Cohort 3 were consistent with the BICR analysis.

Figure 13: Kaplan-Meier plots for DOR per BICR in the overall population and in Cohorts 1-3



Progression Free Survival (PFS)

All subjects

The median PFS in all subjects per BICR was 10.8 months (95% CI: 8.3 months, NR).

Table 12: PFS Central review (ASaT)

	MK-3475 200 mg (N=210)
Number (%) of PFS Events	51 (24.3)
Person-Months	1078
Event Rate/100 Person-Months (%)	4.7
Median PFS (Months)[†]	10.8
95% CI for Median PFS[†]	(8.3, Not reached)
PFS rate at 3 Months in % [†]	86.3
PFS rate at 6 Months in % [†]	71.7

Progression-free survival is defined as time from first dose to disease progression, or death, whichever occurs first.
[†] From product-limit (Kaplan-Meier) method for censored data.
(Database Cutoff Date: 27JUN2016).

Source: [P087V01MK3475: analysis-adsl; adtte]

The median PFS per site review in the ASaT population in all subjects was 11.1 months (95% CI: 8.1 months, NR). The site-assessed PFS rate at 3 and 6 months was 89.9% and 73.1%, respectively.

Two sensitivity analyses were performed for PFS, as prespecified in the statistical analysis plan of the protocol (see also the "statistical methods" section above). The results observed using the first approach (Sensitivity Analysis 1) were similar to the primary analyses (median PFS in all subjects by BICR 10.8 months [95% CI 8.3 months, NR]). PFS estimates under the second, more conservative, approach (Sensitivity Analysis 2) were reduced (median PFS in all subjects by BICR 8.5 months [95% CI 8.0 months, NR].

Cohort 1

Table 13: PFS data per BICR in the ASaT population - Cohort 1

	MK-3475 200 mg (N=69)
Number (%) of PFS Events	14 (20.3)
Person-Months	377
Event Rate/100 Person-Months (%)	3.7
Median PFS (Months)[†]	Not reached
95% CI for Median PFS[†]	(8.1, Not reached)
PFS rate at 3 Months in % [†]	95.4
PFS rate at 6 Months in % [†]	74.2
Progression-free survival is defined as time from first dose to disease progression, or death, whichever occurs first. [†] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 27JUN2016).	

Source: [P087V01MK3475: analysis-adsl; adtte]

The median PFS in the ASaT population of Cohort 1 per site review was not reached (95% CI: 8.1 months, not reached). The site-assessed PFS rate in Cohort 1 at 6 and 12 months was 90.6% and 79.0%, respectively. Results from sensitivity analyses were overall consistent with the primary analysis for Cohort 1.

Cohort 2

Table 14: PFS data per BICR in the ASaT population - Cohort 2

	MK-3475 200 mg (N=81)
Number (%) of PFS Events	23 (28.4)
Person-Months	404
Event Rate/100 Person-Months (%)	5.7
Median PFS (Months)[†]	Not reached
95% CI for Median PFS[†]	(7.3, Not reached)
PFS rate at 3 Months in % [†]	78.0
PFS rate at 6 Months in % [†]	68.6
Progression-free survival is defined as time from first dose to disease progression, or death, whichever occurs first. [†] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 27JUN2016).	

Source: [P087V01MK3475: analysis-adsl; adtte]

The median PFS in the ASaT population of Cohort 2 per site review was 8.1 months (95% CI: 6.9 months, not reached). The site-assessed PFS rate in Cohort 2 at 3 and 6 months was 89.2% and 65.9%, respectively. Results from sensitivity analysis 1 were overall consistent with the primary analysis for Cohort 2. PFS estimates under sensitivity analysis 2 were reduced: the median PFS by BICR for cohort 2 was 8 months (95% CI 5.7 months, NR).

Cohort 3

Table 15: PFS data per BICR in the ASaT population - Cohort 3

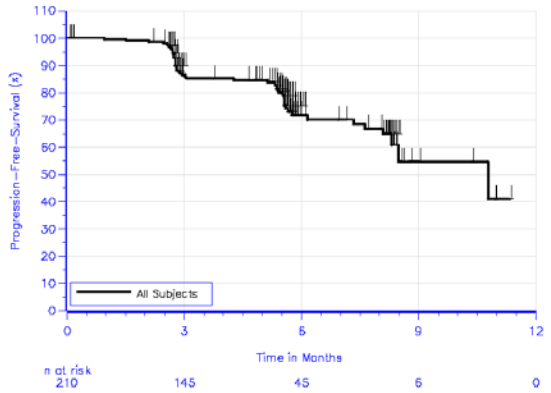
	MK-3475 200 mg (N=60)
Number (%) of PFS Events	14 (23.3)
Person-Months	298
Event Rate/100 Person-Months (%)	4.7
Median PFS (Months)[†]	10.8
95% CI for Median PFS[†]	(6.1, Not reached)
PFS rate at 3 Months in % [†]	86.5
PFS rate at 6 Months in % [†]	73.3
Progression-free survival is defined as time from first dose to disease progression, or death, whichever occurs first. [†] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 27JUN2016).	

The median PFS in the ASaT population of Cohort 3 per site review was 8.5 months (95% CI: 7.5, 11.1 months). The site-assessed PFS rate in Cohort 3 at 3 and 6 months was 89.3% and 76.2%, respectively. Results from sensitivity analysis 1 were overall consistent with the primary analysis for Cohort 3. PFS estimates under sensitivity analysis 2 were reduced: the median PFS by BICR for Cohort 3 was 8.5 months (95% CI 6.1 months, NR).

Figure 14: Kaplan-Meier plots for PFS per BICR in the overall population and in Cohorts 1-3

Figure 11-2

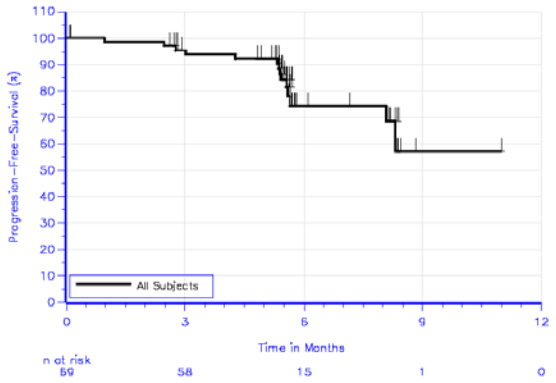
Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG (ASaT Population)



Source: [P087V01MK3475: analysis-adsl; adtte]

Figure 11-7

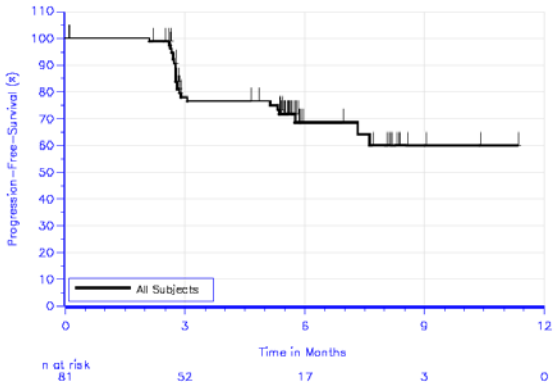
Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG (Cohort 1) (ASaT Population)



Source: [P087V01MK3475: analysis-adsl; adtte]

Figure 11-12

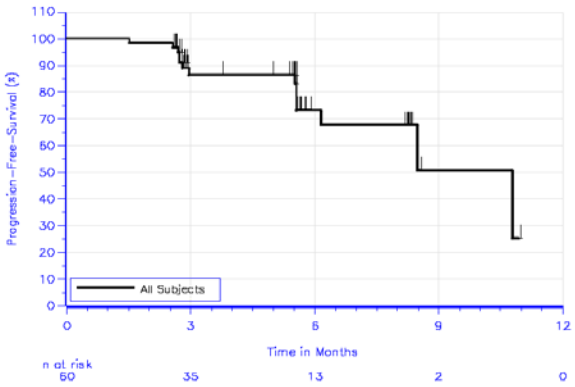
Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG (Cohort 2) (ASaT Population)



Source: [P087V01MK3475: analysis-adsl; adtte]

Figure 11-17

Kaplan-Meier Estimates of Progression-Free Survival Based on Central Review per IWG (Cohort 3) (ASaT Population)



Source: [P087V01MK3475: analysis-adsl; adtte]

Overall survival (OS)

Median OS was not reached in the overall ASaT population and in all cohorts (see Table below). Only 3 events were observed in the overall population, 1 in each cohort.

Table 16: Summary of OS (ASaT)

	MK-3475 200 mg (N=210)
Death (%)	3 (1.4)
Median Survival (Months)[†]	Not reached
95% CI for Median Survival[†]	(Not reached, Not reached)
OS rate at 6 Months in % [†]	99.5
OS rate at 12 Months in % [†]	Not reached
OS: Overall survival. [†] From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 27JUN2016	

Source: [P087V01MK3475: analysis-adsl; adtte]

Exploratory endpoints

PROs

Compliance rates for both the EORTC QLQ-C30 and EQ-5D were ~90% or above at baseline, and over 96% at Week 12. Completion rates remained above 90% at each time point after baseline, until Week 24, when they dropped as patients discontinued the study due to disease progression, physician decision, AEs, or death (compliance rates were 78.8% and 78.2% at Week 24 and 52.9% and 52.9% at Week 36 for the EORTC QLQ-C30 and EQ-5D questionnaires, respectively).

EORTC QLQ-C30

The proportion of subjects with "improved", "stable", or "deteriorated" global health status/QoL at Week 12 according to a 10 point or greater change from baseline is summarised in Table below.

Table 17: Summary of EORTC QLQ-C30 Scores at week 12

	Week 12			
EORTC QLQ-C30	Subjects who responded (CR+PR)	Subjects with SD	Subjects with PD	Total
	n (%)	n (%)	n (%)	n (%)
Global Health Status/Quality of Life				
Total	109	48	25	182
Improved	46 (42.2)	19 (39.6)	8 (32.0)	73 (40.1)
Stable	52 (47.7)	21 (43.8)	12 (48.0)	85 (46.7)
Deteriorated	11 (10.1)	8 (16.7)	5 (20.0)	24 (13.2)
[†]: Improved: change from baseline ≥ 10; Deteriorated : change from baseline ≤ -10; Stable: change from baseline between > -10 and < 10.				

Source: [P087V01MK3475: analysis-adplda]

Global health status/QoL deteriorated by 10 or more points at Week 12 in approximately 6% to 10% fewer subjects with CR/PR than in subjects with SD or PD. Conversely, global health status/QoL improved by 10 or more points at Week 12 in about 2% to 10% more CR/PR subjects than in SD and PD subjects. The longitudinal changes from baseline to Week 12 in the EORTC QLQ-C30 global health status/QoL scores are summarised in Table below, together with the least squares (LS) mean (95% CI) of the score change from baseline to Week 12.

Table 18: Analysis of change from baseline in EORTC QLQ-C30 at week 12 (ASaT)

Treatment	Baseline		Week 12		Change from Baseline at Week 12	
	N[†]	Mean (SD)	N[†]	Mean (SD)	N[††]	Mean (SE)
All Cohorts	189	64.2 (21.4)	199	72.4 (19.4)	182	8.5 (1.6)
Subjects who responded (CR+PR)	111	64.1 (20.7)	121	74.0 (19.4)	109	9.9 (2.1)
Subjects with SD	49	66.2 (22.9)	50	73.7 (18.6)	48	7.3 (3.2)
Subjects with PD	29	61.5 (21.9)	28	63.4 (18.7)	25	5.0 (3.9)

Comparison	Difference in LS Means[†††] (95% CI)	p-Value
Responder vs. Non-Responder[††††]	4.5 (-0.44, 9.44)	0.0739

[†] N = Number of subjects in All Subjects as Treated population with each time point observation;
[††] N = Number of subjects in All Subjects as Treated population with Baseline and Week 12 observations;
[†††] Based on cLDA model with the PRO score as the response variable, study visit and ECOG (0 vs. 1 or 2) as covariates;
[††††] Response by investigator review at week 12; subjects with PD include subjects without week 12 assessment.
SD: Standard deviation; LS Mean: Least square mean; CI: Confidence interval

Source: [P087V01MK3475: analysis-adplda]

The baseline global health status/QoL score was similar across all response subgroups, and at week 12 there was an overall improvement of 8.5 points (standard error: 1.6) compared to baseline. The difference in LS means between responders and non-responders at Week 12 was 4.5 points (95% CI: -0.44, 9.44; two-sided nominal p=0.0739).

EQ-5D

The EQ-5D VAS score at baseline was similar across CR/PR, SD, and PD subgroups.

Table 19: Analysis of change from baseline in EQ-5D VAS at week 12 (ASaT)

Treatment	Baseline		Week 12		Change from Baseline at Week 12	
	N[†]	Mean (SD)	N[†]	Mean (SD)	N[††]	Mean (SE)
All Cohorts	199	70.6 (18.1)	199	78.3 (16.9)	189	8.2 (1.4)
Subjects who responded (CR+PR)	118	69.3 (18.0)	121	79.3 (17.0)	115	10.7 (1.8)
Subjects with SD	49	73.2 (20.1)	51	79.1 (16.5)	49	5.2 (2.9)
Subjects with PD	32	71.3 (15.2)	27	72.5 (16.2)	25	3.2 (2.8)

Comparison	Difference in LS Means[†††] (95% CI)	p-Value
Responder vs. Non-Responder[††††]	4.2 (-0.10, 8.41)	0.0558

[†] N = Number of subjects in All Subjects as Treated population with each time point observation;
[††] N = Number of subjects in All Subjects as Treated population with Baseline and Week 12 observations;
[†††] Based on cLDA model with the PRO score as the response variable, study visit and ECOG (0 vs. 1 or 2) as covariates;
[††††] Response by investigator review at week 12; subjects with PD include subjects without week 12 assessment.
SD: Standard deviation; LS Mean: Least square mean; CI: Confidence interval

Source: [P087V01MK3475: analysis-adplda]

At week 12 there was an overall improvement of 8.2 points (standard error: 1.4) from baseline (a change in VAS score of 7 or more points has been reported to be clinically meaningful in cancer patients). Improvement was greatest for those with CR/PR (+10.7 points), followed by SD (+5.2 points), and PD (+3.2 points). The difference in LS means of the score change between responders and non-responders was 4.2 points (95% CI: -0.10, 8.41; two-sided nominal p=0.0558).

The EQ-5D Utility scores showed consistency of results, with similarity of scores at baseline across all response sub-groups, and subjects with CR/PR having a comparatively better improvement in their Utility scores from baseline to Week 12, than subjects with SD or PD (respectively, +0.09 points vs. +0.03 points vs. -0.02 points). The difference in LS means of the score change between responders and non-responders was 0.08 points (95%

CI: 0.023, 0.134; two-sided nominal p=0.0057).

Stem Cell Transplant Post-Study Therapy

There were 1/210 subjects (0.5%) who underwent autologous stem cell transplant at some point after treatment with pembrolizumab. A total of 6/210 subjects (2.9%) underwent allogeneic transplant at some point after treatment with pembrolizumab.

At the time of the update analysis (data cut-off date 25/09/2016), with an additional 3.0 months of safety follow-up, there were a total of 4 subjects who underwent autologous SCT following pembrolizumab therapy. All 4 subjects were known to be alive as of the last survival follow-up date. With respect to allogeneic SCT, 10 subjects in KEYNOTE-087 had a transplant at some point after the study, an increase of 4 subjects. One subject of the 10 died due to graft versus host disease (GvHD); the remaining 9 subjects were alive as of the most recent follow-up. The median follow-up duration from date of allogeneic transplant to death or last date the subject was known to be alive for these 10 subjects was 3.5 months (range: 0.03-10.3 months). However, 1 subject who received allogeneic SCT within 1 month of the data cutoff date had not yet been contacted after transplant.

Ancillary analyses

Subgroup analyses were conducted to investigate pembrolizumab activity in cHL according to: refractory vs. relapsed after ≥ 3 lines of therapy; number of prior therapies, age, race, region, gender and time since transplant failure.

Refractory vs. relapsed after ≥ 3 Lines of therapy

Response rates

Table 20: Summary of response rates (IWG) by status of refractory or relapsed after ≥ 3 lines of therapy:

	Refractory to Any Therapy Received (N=170)		Relapsed ≥3 lines of therapy (N=40)	
Response Evaluation	n (%)	95% CI†	n (%)	95% CI†
Complete Remission (CR)	36 (21.2)	(15.3, 28.1)	10 (25.0)	(12.7, 41.2)
Partial Remission (PR)	83 (48.8)	(41.1, 56.6)	14 (35.0)	(20.6, 51.7)
Objective Response (CR+PR)	**119 (70.0)**	**(62.5, 76.8)**	**24 (60.0)**	**(43.3, 75.1)**
Stable Disease (SD)	26 (15.3)	(10.2, 21.6)	9 (22.5)	(10.8, 38.5)
Progressive Disease (PD)	21 (12.4)	(7.8, 18.3)	6 (15.0)	(5.7, 29.8)
Non-Evaluable (NE)	4 (2.4)	(0.6, 5.9)	1 (2.5)	(0.1, 13.2)

† Based on binomial exact confidence interval method.
Note: Columns are mutually exclusive (hierarchical) starting with subjects refractory to any prior therapy, then subjects relapsed after 3 or more lines but not refractory to any prior therapy received.
(Database Cutoff Date: 27JUN2016)

Source: [P087V01MK3475: analysis-adsl; adorr]

Note: Subjects were categorized as refractory or relapsed in a hierarchical manner (mutually exclusive categories), where refractory included subjects who were refractory to any one or more lines of therapy and relapsed included subjects who had relapsed disease after ≥ 3 prior lines of therapy, but who were not refractory at any point.

Refractory subjects were further analyzed by whether they were refractory to the first therapy received (N=74), last therapy received (N=74), or any other therapy received (N=22). An additional analysis was conducted in primary refractory subjects, i.e. patients who were refractory to first line therapy and never achieved a response

(CR or PR) to subsequent therapies (N=36). The ORR based on IWG criteria by BICR in these subjects was 80.6% (29/36; 95% CI: 64.0%, 91.8%), and the CRR was 25% (9/36; 95% CI: 12.1%, 42.2%).

The ORR based on IWG criteria by BICR in subjects who relapsed after 3 or more lines of therapy regardless of refractory status (N= 145) was 66.2% (96/145; 95% CI: 57.9%, 73.8%). CRR was 22.1% (32/145; 95% CI: 15.6%; 29.7%).

An analysis was also conducted to include responses post-PD per IWG criteria by site review. The ORR in this analysis was consistent with the overall analysis (66.7%; 140/210; 95% CI: 59.9%, 73.0%). CRR was 25.2% (53/210; 95% CI: 19.5%, 31.7%).

DOR

Differences in DOR per BICR between subjects refractory versus those relapsed after ≥ 3 lines of therapy were minor. Among the 170 subjects refractory to any therapy received, 119 had a response with 37 responses ongoing at ≥3 months and 3 responses ongoing at ≥ 6 months; median DOR was not reached (95% CI: 5.6 months, NR).

Among the 145 subjects relapsed after ≥ 3 lines of therapy, 96 had a response with 31 responses ongoing at ≥ 3 months and 2 responses ongoing at ≥ 6 months. The median DOR by BICR in subjects who relapsed after 3 or more lines of therapy regardless of refractory status (N = 145) was not reached (range 0.0+, 8.3+ months).

Median DOR by site review for subjects who were refractory to therapy was 8.3 months (range 0.0+, 8.3+ months). Median DOR by site review for subjects who had relapsed after ≥ 3 lines of therapy was not reached (range 0.0+, -5.6+ months).

Number of prior therapies

The ORR by BICR in subjects with < 3 prior therapies was 64.3% (18/28; 95% CI: 44.1%, 81.4%), while among subjects with ≥ 3 prior therapies, ORR was 68.7% (125/182; 95% CI: 61.4%, 75.3%).

The differences in ORR by site review by number of prior therapies were minimal (< 3: ORR 67.9%, 19/28; 95% CI: 47.6%, 84.1%; ≥ 3: ORR 66.5%, 121/182; 95% CI: 59.1%, 73.3%).

In Cohort 1 and Cohort 2, differences in ORR by number of prior therapies were unable to be assessed because almost all of the subjects had at least 3 prior therapies (68/69). In Cohort 3, differences in ORR by BICR by number of prior therapies (< 3: n=24 versus ≥ 3: n=36) were consistent with the overall population.

Time Since Transplant Failure

Differences in ORR by BICR by time since transplant failure (< 12 months: n=85 vs. ≥ 12 months: n=44) were minimal. The ORR in subjects with less than 12 months since transplant failure was 65.9% (95% CI: 54.8%, 75.8%), while among subjects with 12 months or more since transplant failure, ORR was 77.3% (95% CI: 62.2%, 88.5%).

The differences in ORR by site review by time since transplant failure were similar (< 12 months: ORR 67.1%; 95% CI: 56.0%, 76.9%; ≥ 12 months: ORR 68.2%; 95% CI: 52.4%, 81.4%).

In Cohort 1, differences in ORR by BICR by time since transplant failure were consistent with the overall population. In Cohort 3, differences in ORR by time since transplant failure were difficult to discern because the majority of subjects were < 12 months since transplant failure (53/60).

Age

The ORR by BICR by subjects < 65 years of age (n=192) was higher compared to subjects ≥ 65 years of age (n=18). The ORR in subjects < 65 years of age was 69.8% (95% CI: 62.8%, 76.2%), while among subjects ≥ 65 years of age, ORR was 50.0% (95% CI: 26.0%, 74.0%).

A similar difference between age groups in ORR by site review was observed (< 65 years: ORR 68.2%; 95% CI: 61.1%, 74.7%; ≥ 65 years: ORR 50.0%; 95% CI: 26.0%, 74.0%).

In Cohort 1 and 3, differences in ORR by age were unable to be assessed because most of the subjects were < 65 years. In Cohort 2, the ORR by BICR by age class was consistent with the overall population.

The MAH performed an exploratory analysis to possibly assess the concomitant effects of baseline conditions, such as ECOG status or co-morbidity.

Updated ORR results with a cut –off of 25 September 2016 were provided and are presented in the following table.

As seen below, the numbers in the ECOG subgroup in the ≥ 65 year old population are small, but do not suggest that ECOG status adversely affects ORR in the elderly subpopulation.

Table 21: ORR (25-Sep-2016 cut-off); overall population and in the ECOG subgroups (0 vs 1).

Summary of ORR in KEYNOTE-087 by Age and ECOG status

ORR (number CR+PR/number subjects in analysis)	< 65 years (n=192)	≥ 65 years (n=18)
Overall [95% CI]	71% (136/192) [64%, 77%]	50% (9/18) [26%, 74%]
ECOG=0	72% (68/95)	29% (2/7)
ECOG=1*	70% (68/97)	64% (7/11)
*Includes one subject with ECOG=2 at baseline (achieved PR in <65 years group)		

Race

ORR by BICR was consistent across race categories (white: n=185 versus non-white n=22). The ORR in white subjects was 68.6% (95% CI: 61.4%, 75.3%) and in non-white subjects was 63.6% (95% CI: 40.7%, 82.8%). There were no notable differences in ORR by site review across race categories (white: ORR 65.9%; 95% CI: 58.6%, 72.7%; non-white: ORR 68.2%; 95% CI: 45.1%, 86.1%). ORR by race in Cohorts 1-3 was consistent with the overall population.

Gender

Differences in ORR by BICR by gender (males: n=113 versus females: n=97) were minimal. The ORR in male subjects was 68.1% (95% CI: 58.7%, 76.6%), while among female subjects the ORR was 68.0% (95% CI: 57.8%, 77.1%).

The ORR by site review in females was slightly higher than in males (male: ORR 60.2%; 95% CI: 50.5%, 69.3%; female: ORR 74.2%; 95% CI: 64.3%, 82.6%).

In Cohort 1, the ORR by BICR in females (81.8%, 27/33; 95% CI: 64.5%, 93.0%) was somewhat higher compared to males (63.9%, 23/36; 95% CI: 46.2%, 79.2%).

In Cohort 2, ORR by BICR in males (76.7%, 33/43; 95% CI: 61.4%, 88.2%) was somewhat higher compared to females (52.6%, 20/38; 95% CI: 35.8%, 69.0%), but this difference was not confirmed by the analysis

according to site review (male: ORR 67.4%, 29/43; 95% CI: 51.5%, 80.9%; female: ORR 63.2%, 24/38; 95% CI: 46.0%, 78.2%).

In Cohort 3, the ORR by BICR in females (73.1%, 19/26; 95% CI: 52.2%, 88.4%) was somewhat higher compared to males (61.8%, 21/34; 95% CI: 43.6%, 77.8%); this difference was even greater in the analysis by site review (female: ORR 84.6%, 22/26; 95% CI: 65.1%, 95.6%; male: ORR 55.9%, 19/34; 95% CI: 37.9%, 72.8%).

Region

The ORR by BICR by region (US: n=52 versus ex-US: n=158) was 73.1% (95% CI: 59.0%, 84.4%) in US subjects and 66.5% (95% CI: 58.5%, 73.8%) in ex-US subjects. The differences in ORR by site review by region were similar to the BICR assessment (US: ORR 73.1%; 95% CI: 59.0%, 84.4%; ex-US: ORR 64.6%; 95% CI: 56.6%, 72.0%). The differences in ORR by BICR by region in Cohorts 1-3 were consistent with the overall population. The efficacy according to region EU or ex-EU is generally consistent with the primary analyses in the global population.

Table 22: Summary of Efficacy by Region – (25-Sep-2016 cut-off)

	KEYNOTE-087	
	EU (n=107)	Ex-EU (n=103)
ORR (95% CI)	65.4% (55.6%, 74.4%)	72.8% (63.2%, 81.1%)
Median DOR (95% CI)	8.5 m (8.5, NR)	11.1 m (8.7 m, 11.1 m)
Median PFS (95% CI)	11.3 m (8.2 m, NR)	13.7 m (10.8 m, NR)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)

NR= not reached; m=months

Pembrolizumab efficacy in BV-exposed / naïve patients (post-hoc analysis requested by the CHMP)

Updated efficacy results from pivotal study KEYNOTE-087 limited to BV-exposed patients were provided and are summarised in Table below.

Table 23– Summary of efficacy results from study KN-087 excluding BV naïve patients.

Study KEYNOTE-087		
Data cut-off date	25/09/2016	
Median follow-up (months)	10.1	(range 1.0 – 15.0)
CR rate	24%	(95% CI 17.9 - 31.0)
ORR	**68.6%**	(95% CI 61.1 – 75.4)
Median DoR (months)	11.1	(95% CI 8.5 - 11.1)
Median PFS (months)	11.3	(95% CI 10.8 – NR)

Median OS	NR	(95% CI NR – NR)

Overall, the provided results in BV-exposed patients are consistent with those observed in the overall study population, and are considered supportive of the revised indication.

A summary of efficacy (ORR, DOR, PFS and OS), based on the updated data cutoff (25 September 2016) is provided in Table below for KEYNOTE-087 Cohort 3 subjects who received prior BV and those who were BV-naive. The efficacy results for the subgroups were generally similar.

Table 24: Summary of efficacy by BV status (cohort 3)

	Cohort 3	
	Prior BV (n=25)	BV-naïve (n=35)
ORR (95% CI)	68.0% (46.5%, 85.1%)	71.4% (53.7%, 85.4%)
Median DOR (95% CI)	8.5 m (5.5, 8.5)	NR (NR, NR)
Median PFS (95% CI)	11.3 m (8.5 m, NR)	10.3 m (6.1 m, NR)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)
NR= not reached; m=months		

Pseudoprogression

Based on investigator assessment using an updated database cutoff date (25-Sep-2016), there were 13 subjects in KEYNOTE-087 who progressed and continued to receive pembrolizumab, of which 2 subsequently achieved remission. Among these 13 subjects, 2 achieved remission following PD per investigator assessment. Among these 13 subjects, there was one reported death; 4 deaths in 210 subjects overall in the KEYNOTE-087 population.

Pembrolizumab discontinuation due to CR

There were 47 subjects with best response of CR (central review) in the updated database (25-Sep-2016 cutoff)..

Table 25: Summary Statistics by Discontinuation Reason in CR pts in KN-087

Reason for Discontinuation	Median PFS* (95% CI)	Median DOR* (95% CI)	Median Treatment Duration** (range)	Median Follow-up** (range)
Complete Response (n=13)	NR (5.6, NR)	8.7 m (2.8 m, 8.7 m)	5.8 m (2.1 m, 10.8 m)	12.1 m (8.9 m, 14.2 m)
Other/Still on-treatment (n=34)	13.7 m (11.2 m, 13.7 m)	11.1m (NR, NR)	9.2 m (3.0 m, 13.7 m)	10.0 m (6.4 m, 14.7 m)
*Kaplan-Meier estimate; **arithmetic				

As of the 25-Sep-2016 data cutoff date, no subjects in KEYNOTE-087 who stopped treatment due to CR began re-treatment, i.e. “second course” of pembrolizumab treatment, per protocol.

Post –hoc Analysis of Baseline prognostic factors for r/r cHL patients

Time-to-relapse following completion of first-line therapy, Ann Arbor stage at relapse and anaemia at relapse were identified in Josting et al (2002) as independent risk factors in r/r cHL in previous studies. For KEYNOTE-087, the MAH has conducted an exploratory analysis to assess these risk factors based on the updated efficacy data (25-Sep-2016).

Hemoglobin

An analysis, performed based on the specified gender-specific “low” thresholds (<10.5 gm/dL for females and <12.0 gm/dL for males), did not show any difference in the primary endpoint of ORR per central review between subjects with low hemoglobin (69.0% [49/71]) and subjects with adequate hemoglobin (68.6% [94/137)]; 2 subjects were missing this information at baseline.

Stage

The ORR per central review was similar in subjects with “locally advanced” disease (70.9% [78/110] and in subjects with “metastatic” disease 66.0% [64/97]); 3 subjects were missing this information at baseline.

Early vs Late Relapse

The categories of refractory, early relapse and late relapse had 103, 31, and 43 subjects, respectively, and the key efficacy endpoints for KEYNOTE-087 are presented in Table below. Of the 210 subjects in KEYNOTE-087, 33 subjects were excluded: 12 subjects had missing or non-evaluable response to first-line therapy and 21 subjects with remission were missing either date of treatment completion or date of progression.

Table 26: Summary of Efficacy by Refractory or Time to Relapse After Completion of First-Line Therapy in KEYNOTE-087

	KEYNOTE-087		
	Refractory (N=103)	Early Relapse (N=31)	Late Relapse (N=43)
ORR (95% CI)	73.8% (64.2%, 82.0%)	61.3% (42.2%, 78.2%)	65.1% (49.1%, 79.0%)
Median DOR (95% CI)	11.1 m (8.5 m, 11.1 m)	NR (5.6 m, NR)	8.7 m (5.6 m, 8.7 m)
Median PFS (95% CI)	13.7 m (10.8 m, NR)	10.3 m (8.3 m, NR)	11.2 m (8.1 m, 11.2 m)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
NR= not reached; m=months			

Subjects with < 3 lines of therapy (post-hoc analysis)

Table 27: Subgroup analysis by response status, - updated database (25 September 2016 cut-off), for those subjects in KEYNOTE-087 who received < 3 versus ⩾ 3 prior lines of therapy

	Number of Prior Lines < 3 (N=28)		Number of Prior Lines ≥ 3 (N=182)	
Response Evaluation	n (%)	95% CI†	n (%)	95% CI†
Complete Remission (CR)	8 (28.6)	(13.2, 48.7)	39 (21.4)	(15.7, 28.1)
Partial Remission (PR)	12 (42.9)	(24.5, 62.8)	86 (47.3)	(39.8, 54.8)
Objective Response (CR+PR)	**20 (71.4)**	**(51.3, 86.8)**	**125 (68.7)**	**(61.4, 75.3)**
Stable Disease (SD)	5 (17.9)	(6.1, 36.9)	26 (14.3)	(9.5, 20.2)
Progressive Disease (PD)	3 (10.7)	(2.3, 28.2)	27 (14.8)	(10.0, 20.8)
No Assessment (NA)	0 (0.0)	(0.0, 12.3)	4 (2.2)	(0.6, 5.5)
† Based on binomial exact confidence interval method. (Database Cutoff Date: 25SEP2016)				

Outcome on prior BV for the 25 subjects who had therapy with BV prior to auto-SCT (post-hoc analysis)

Of the 25 subjects who had therapy with BV prior to auto-SCT in Cohort 3, 48% had a best response of CR/PR, 36% had a best response of PD/SD, and 16% were non-evaluable.

ECOG score (PS 0 vs. PS 1) (post-hoc analysis)

Table 28: summary of efficacy (ORR, DOR, PFS and OS) by ECOG PS 0 vs PS ≥ 1

	ECOG PS 0	ECOG PS ≥ 1
ORR (95% CI)	68.6% (58.7%, 77.5%)	69.4% (59.8%, 77.9%)
Median DOR (95% CI)	11.1 m (8.5 m, 11.1)	8.7 m (8.7 m, NR)
Median PFS (95% CI)	13.7 m (11.3 m, NR)	11.2 m (8.3 m, NR)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)
NR= not reached; m=months		

Histological cHL subtypes (post-hoc analysis)

The subgroups presented are "Nodular Sclerosis" (n=169), "Mixed Cellularity" (n=24), and "Other" (n=13, 8 subjects with "Lymphocyte Rich" and 5 subjects with "Lymphocyte Depleted"). There were 4 subjects with missing histology at baseline who are excluded from the analysis.

Table 29: Summary of Efficacy by Histological Subtype in KEYNOTE-087

	KEYNOTE-087			
	Nodular Sclerosis (N=169)	Mixed Cellularity (N=24)	Lymphocyte Rich (N=8)	Lymphocyte Depleted (N=5)
ORR (95% CI)	70.4% (62.9%, 77.2%)	62.5% (40.6%, 81.2%)	62.5% (24.5%, 91.5%)	80.0% (28.4%, 99.5%)
Median DOR (95% CI)	11.1 m (8.5, 11.1)	NR (2.7, NR)	NR (2.8, NR)	5.6 m (NR, NR)
Median PFS (95% CI)	11.3 m (10.8 m, NR)	8.2 m (3.1 m, NR)	NR (2.5 m, NR)	NR (8.1 m, NR)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
NR= not reached; m=months				

PD-L1 expression (post-hoc analysis requested by the CHMP)

In KEYNOTE-087, a total of 177 patients across all cohorts (out of 210 treated subjects) had evaluable pre-treatment tumour tissue. The analysis below is based on the "membrane staining score" for the categories of "< 1%" versus "≥ 1%".

For KEYNOTE-013, only the categorization of "positive" versus "negative" PD-L1 status is available for analysis, defined as positive if at least 1% of the Hodgkin Reed Sternberg (HRS) cells were positive for PD-L1 membrane staining with staining intensity of 2+ or higher. In KEYNOTE-013 there were 12 subjects with pre-treatment samples available out of the 31 subjects treated (see Table below).

Since the numbers are limited and due to the high expression of PD-L1 in these patients, only the descriptive statistics are presented, i.e., best response according to central review and interpretation is limited due to the small numbers with low PD-L1 expression. Analyses are based on the updated databases (Data cut-off of

25-Sep-2016 for KEYNOTE-087 and 27-Sep-2016 for KEYNOTE-013).

Table 30: Summary of efficacy by PD-L1 expression

Response Evaluation	KEYNOTE-087 (n=177)		KEYNOTE-013 (n=12)	
	<1% (n=1)	**≥1% (n=176)**	**Negative (n=2)**	**Positive (n=10)**
Complete Remission (CR)	0	22% (39)	0	10% (1)
Partial Remission (PR)	0	47% (82)	50% (1)	40% (4)
Objective Response (CR+PR)	**0**	**69% (121)**	**50% (1)**	**50% (5)**
Stable Disease (SD)	0	15% (26)	30% (3)	30% (3)
Progressive Disease (PD)	100% (1)	14% (25)	20% (2)	20% (2)
No Assessment (NA)	0	2% (4)	0	0

Summary of main study

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

Table 31: Summary of Efficacy for trial KEYNOTE-087

Title: A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma		
Study identifier	KEYNOTE-087; NCT02453594	
Design	KEYNOTE-087 is multicenter, single arm, multi-cohort, nonrandomized trial of pembrolizumab in subjects with r/r cHL: - who have failed to achieve a response or progressed after autologous stem cell transplant (ASCT) and have relapsed after treatment with, or failed to respond to, brentuximab vedotin (BV) post ASCT (**Cohort 1**); - who were unable to achieve a CR or PR to salvage chemotherapy and did not receive ASCT, but have relapsed after treatment with, or failed to respond to, BV (**Cohort 2**); and subjects who have failed to respond to, or progressed after, ASCT and have not received BV post auto-SCT. These subjects may or may not have received BV as part of primary or salvage treatment (**Cohort 3**). The primary objectives were to evaluate the objective response rate (ORR) of pembrolizumab by blinded independent central review (BICR) according to the Revised Response Criteria for Malignant Lymphoma (2007) from the International Working Group (IWG); and (2) determine the safety and tolerability of pembrolizumab.	
	Duration of main phase: Duration of Run-in phase:	Up to 2 years not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Exploratory: ORR of > 20% in each of the 3 cohorts using IWG response criteria by BICR.		
Treatments groups	All subjects (ASaT)		Pembrolizumab 200 mg IV Q3W for up to 2 years or until PD or unacceptable toxicity.
	Cohort 1		
	Cohort 2		
	Cohort 3		
Endpoints and definitions	Primary endpoint	ORR	All patients with CR or PR as assessed by BICR per IWG response criteria.
	Secondary endpoints	CRR	CRR as assessed by BICR per IWG response criteria.
		DOR	DOR, defined as time from first response to disease progression in subjects who achieve a PR or better, as assessed by BICR per IWG response criteria.
		PFS	PFS, defined as time from first treatment to disease progression or death, as assessed by BICR per IWG response criteria.
		OS	OS, defined as time from first treatment until the date of death.
Database lock	27-Jul-2016: trial is ongoing; this is an interim analysis report.		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	All Subjects as Treated (ASaT) population (N=210) defined as all subjects who received at least one dose of study medication. Report date: 22-Sep-2016.				
Descriptive statistics and estimate variability	Treatment group	All subjects	Cohort 1	Cohort 2	Cohort 3
	Number of subject	N=210	N=69	N=81	N=60
	ORR (%)	142/210 (68.1%)	50/69 (72.5%)	53/81 (65.4%)	40/60 (66.7%)
	95% CI	(61.3, 74.3)	(60.4, 82.5)	(54.0, 75.7)	(53.3, 78.3)
	CRR (%)	46/210 (21.9%)	15/69 (21.7%)	18/81 (22.2%)	13/60 (21.7%)
	95% CI	(16.5, 28.1)	(12.7, 33.3)	(13.7, 32.8)	(12.1, 34.2)
	Median DOR Months	NR	NR	NR	NR
	95% CI	(5.7, NR)	(5.6, NR)	(NR, NR)	(5.5, NR)
	Median PFS Months	10.8	NR	NR	10.8
	95% CI	(8.3, NR)	(8.1, NR)	(7.3, NR)	(6.1, NR)
	Median OS Months	NR	NR	NR	NR
	95% CI	(NR, NR)	(NR, NR)	(NR, NR)	(NR, NR)
Notes	ORR in each cohort was compared vs. fixed control (20% ORR); all comparisons were significant with P<.001.				

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

A systematic literature review of response to standard of care therapies for heavily pretreated patients with classical Hodgkin Lymphoma

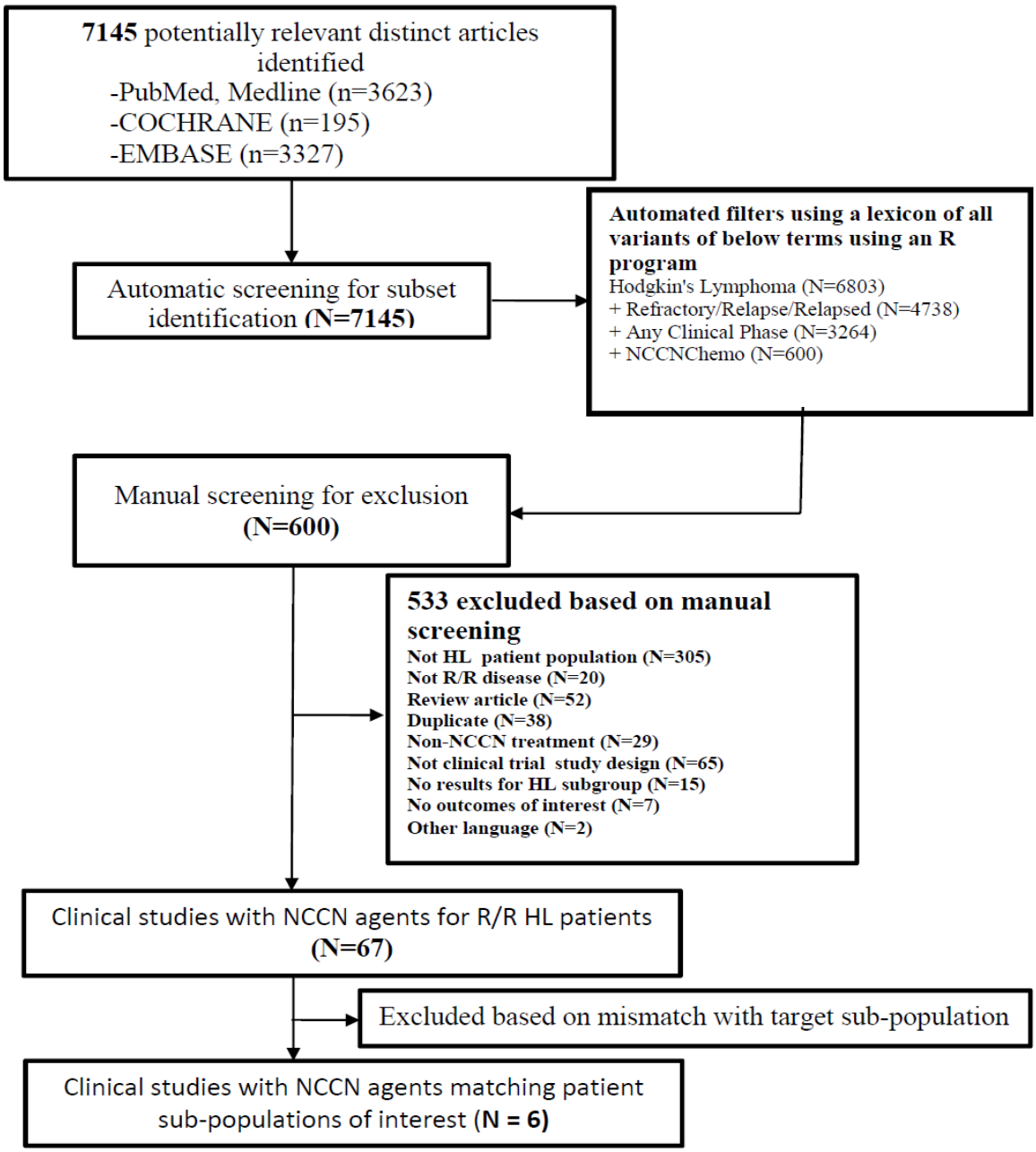
The purpose of this systematic literature review was to synthesize the response in cHL patients ineligible for ASCT or relapsed/refractory after ≥ 3 treatments (including ASCT, if eligible) with the treatments recommended by National Comprehensive Cancer Network (NCCN).

Methods

PUBMED (Medline), Cochrane, and EMBASE databases were searched to identify prospective clinical trials published in English language since January 1, 1985. Both, randomized controlled trials (RCT) as well as single arm trials were included in this review. For the purpose of this review, SOC was defined as any agent recommended in the NCCN guidelines (Version 2.2015) as a treatment option for r/r cHL.

The complete search queries, as implemented in PUBMED, Cochrane and EMBASE, were reported in section 6.0 of the Systematic Literature Review Report included in the dossier.

Figure 15: Summary of study selection process



Results

A total of 7145 records were identified in the literature search, of which 67 were trials in the r/r cHL population using a NCCN therapy. Most of the 67 studies in the r/r setting enrolled patients with only 1 or 2 prior treatments. No dedicated prospective clinical study was found in the patient population who is ineligible for transplant.

Table 32: Studies in cHL patients who are refractory/relapsed after ≥ 3 treatments (similar to the population studied in KEYNOTE-013 and KEYNOTE-087):

Therapy	N	ORR (95% CI)	Median DOR (95% CI)	Median PFS (95% CI)	Adverse Events	
					AEs Grade ≥ 3 (% of Patients)	Discontinuation (Due to AEs)
Brentuximab vedotin* [Ref. 5.4: 04HBMT]	102	75% (65-83%)	6.7 months (3.6-14.8 months)	5.6 months (5-9 months)	55%	20%
Lenalidomide [Ref. 5.4: 040ZKW]	38	18% (8-34%)	6 months (not reported)	4 months (2-6 months)	≥ 47%**	16%
Lenalidomide [Ref. 5.4: 04HTFM]	37	30% (not reported)	not reported	not reported	≥ 48%**	22%
Bendamustine [Ref. 5.4: 040ZKX]	36	53% (not reported)	5 months (not reported)	5.2 months (not reported)	≥ 20%**	not reported
Everolimus [Ref. 5.4: 040ZJD]	19	47% (24-71%)	7.1 months (3.9–14.8 months)	6.2 months (5.9-9.5 months)	74%	1 patient died of infection
Lenalidomide + Cyclophosphamide [Ref. 5.4: 04HBND]	16	38% (15-64%)	not reported	not reported	≥ 32%**	1 patient died of toxicity

AE = adverse event; CI = confidence interval; DOR = duration of response; N = number; ORR = objective response rate; PFS = progression-free survival.

*The brentuximab vedotin study excluded patients ineligible for auto-SCT.

** Percentage of patients with the single maximum toxicity is included because % of subjects who experienced any grade ≥ 3 AE is not reported. Hence, this % represents an underestimate of true % of patients who experienced any AEs Grade ≥ 3.

The responses in the subgroup of heavily pretreated refractory patients were not separately reported. Additionally, the benefit/risk in most of these studies was poorly characterized considering the small study sizes (only one study with 102 patients; the remaining studies with 16 to 38 patients). These studies represent therapies with different mechanisms of action, which is likely driving differences in response. Hence, a meta-analysis was not performed to obtain an overall average response across studies/therapies.

The study with BV stands out in terms of ORR (75% in 102 patients). However, median DOR (6.7 months) and PFS (5.6 months) were modest and within the range of chemotherapy treatments. Furthermore, 55% of the patients experienced AEs of grade 3 or higher, and 20% discontinued due to adverse events (AEs), suggesting benefit/risk with BV may not be favourable for some patients because of tolerability issues. It should also be noted that the study with BV excluded patients ineligible for auto-SCT, and a lower ORR of 30% was reported with BV in a retrospective analysis of two Phase 1 studies in the subgroup of patients who were not candidates for ASCT (Forero-Torres A et al, Oncologist 2012).

Everolimus and bendamustine had ORRs around 50% but PFS was modest: 6.2 months with everolimus and 5.2 months with bendamustine. Additionally, with everolimus, the majority (74%) of patients experienced grade ≥ 3 AEs. The use of lenalidomide in this setting has yielded modest ORRs of < 38%.

Several studies were noted during this systematic literature review investigation with good responses in rrcHL patients but were considered unsuitable for comparison with KEYNOTE-013 and KEYNOTE-087 due to the reasons outlined below.

- A retrospective study with bendamustine reported an ORR of 56% in patients who had previously failed BV (Zinzani PL et al., Clin Lymphoma Myeloma Leuk 2015). Considering this systematic literature review focused on prospective studies, this study did not meet the criterion of a suitable comparator.

- A study of retreatment with BV in patients who previously responded (CR/PR) to the same BV treatment, discontinued treatment while in remission, and subsequently experienced disease progression or relapse. This study reported an ORR of 60% (Bartlett NL, J Hematol Oncol 2014). Considering this study enrolled only the subgroup of patients who have previously responded to BV, the patient population was more restrictive compared to KEYNOTE-013 and KEYNOTE-087. Adverse events that were ≥ Grade 3 occurred in 48% of patients and led to discontinuation in 31% of the patients (including HL and systemic anaplastic large cell lymphoma patients).

- A recent follow-up to the pivotal BV study (Younes et al. JCO 2012) reported updated response but it was based on investigator assessment, instead of independent review by central facility. Furthermore, patients who received allogeneic stem cell transplant following BV treatment were also included in the efficacy assessments making it difficult to characterize the clinical benefit of BV.

- A conference abstract (Johnston PB et al, Blood 2012) reported an ORR of 42% with everolimus. However, the abstract did not provide sufficient details about how heavily pretreated patient population was enrolled, e.g., median and/or range of prior lines of therapy were not reported. Also, grade 3/4 adverse events were observed in 58% of the patients.

Supportive studies

A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Haematologic Malignancies (KEYNOTE-013)

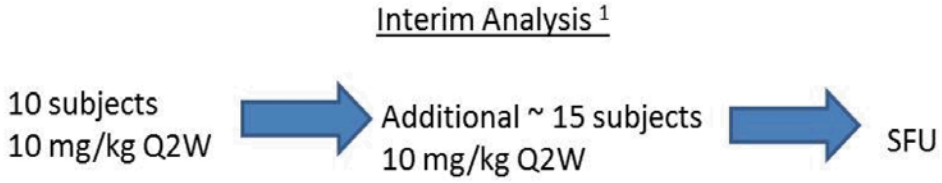
Study KEYNOTE-013 was a multicenter, multi-cohort trial of pembrolizumab in subjects with haematological malignancies to determine the safety and efficacy of pembrolizumab. This study was conducted at 5 centres: 2 in the United States, 1 each in Canada, France, and Italy.

With respect to the present application, data in cHL come from Cohort 3, which included subjects with relapsed/refractory nodular sclerosing or mixed cellularity cHL that had failed, were ineligible for, or refused a stem cell transplant and had relapsed after treatment with or failed to respond to brentuximab vedotin.

Figure 16: Study design

Figure 2.7.3-hl: 2

Trial Design



Q2W = every 2 weeks; SFU = survival follow-up.

[1] An interim analysis may have been performed depending on the rate of enrollment or other factors determined during the course of the trial. This interim analysis would only be performed when ≥ 10 subjects had 12-week assessments completed.

Methods

The primary objectives of study KEYNOTE-013 were to determine the safety and tolerability of pembrolizumab

and to evaluate complete remission rate (CRR) based on the Revised Response Criteria for Malignant Lymphoma (2007) from the International Working Group (IWG) in subjects with r/r nodular sclerosing or mixed cellularity cHL that have failed, are ineligible for, or refused a stem cell transplant.

Secondary efficacy endpoints included PFS, OS, ORR and DOR.

Patients with r/r nodular sclerosing or mixed cellularity cHL, aged ≥ 18 years, with a 0/1 ECOG performance status and with measurable disease were considered eligible. All subjects must have failed/were ineligible for/refused a stem cell transplant (where stem cell transplant is standard of care) and must have relapsed after treatment with (or failed to) respond to brentuximab vedotin (BV). Patients with active infections, autoimmune diseases or who had received prior allogeneic haematopoietic stem cell transplantation within the last 5 years were excluded.

Pembrolizumab was administered at the 10 mg/kg dose iv every 2 weeks until unacceptable toxicity or disease progression, or up to 52 doses (approximately 2 years).

The full analysis set (FAS) population (defined as all subjects who had at least one dose of pembrolizumab, had a baseline efficacy evaluation, and at least one post-baseline efficacy evaluation or discontinued treatment due to pembrolizumab-related AE or PD) was to serve as the primary population for the analyses of efficacy data in this trial. Supportive analyses of efficacy were to be conducted in the intention-to-treat population.

The primary efficacy endpoint for the HL cohort was to be CRR, defined as the proportion of subjects meeting the IWG response criteria for a CR at any time during the study. Response for the primary analysis was to be assessed by the investigator using the IWG response criteria by computed tomography/positron emission tomography (PET) at Week 12 and then every 8 weeks. Assessment of lymphoma B symptoms occurred with each lymphoma disease response assessment. Bone marrow biopsies were collected at screening, and to confirm CR (in subjects who had marrow involvement), or if clinically indicated. Lymph node biopsies were collected at Screening and at Week 12. Blood for correlative biomarkers studies was collected at Screening, Week 12, and upon PD.

A 90% confidence interval (CI) (two-sided) along with a one-sided p-value for testing the null hypothesis (CRR $\leqslant$ 0.10) based on the binomial distribution was to be provided. The HL cohort was considered to have reached the efficacy objective if the corresponding one-sided p-value for testing the respective null hypothesis was less than 5%.

Secondary endpoints in the HL cohort included: PFS, OS, ORR, DOR, PD-L1 expression at baseline among responders/non-responders.

Results

The first r/r cHL subject was enrolled in the study on 03-Dec-2013 and the last on 23-Jul-2014. At the time of data cutoff date (03-June-2016) a total of 31 subjects were enrolled and 23 subjects had discontinued study treatment. The primary reason for discontinuation for 14 (45.2%) subjects was disease progression. Discontinuations due to AEs were reported for 3 (9.7%) of subjects. Treatment was ongoing in 3 (9.7%) subjects (see Table below). The median duration of follow-up, defined as the time from first dose to the date of death or the database cutoff if the subject was still alive, was 24.9 months (range 7.0 to 29.7 months).

Table 33: Subjects' Disposition

	MK-3475 10 mg/kg	
	n	(%)
Subjects in population	31	
Subject Study Medication Disposition		
Completed	5	(16.1)
Discontinued	23	(74.2)
Adverse Event	3	(9.7)
Clinical Progression	1	(3.2)
Complete Response	1	(3.2)
Physician Decision	3	(9.7)
Progressive Disease	14	(45.2)
Withdrawal By Subject	1	(3.2)
On Study Treatment	3	(9.7)
Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record. (Database Cutoff Date: 03JUN2016).		

Source: [P013V01MK3475: analysis-adsl] [P013V01MK3475: tabulations-dsplus; explus; seplus]

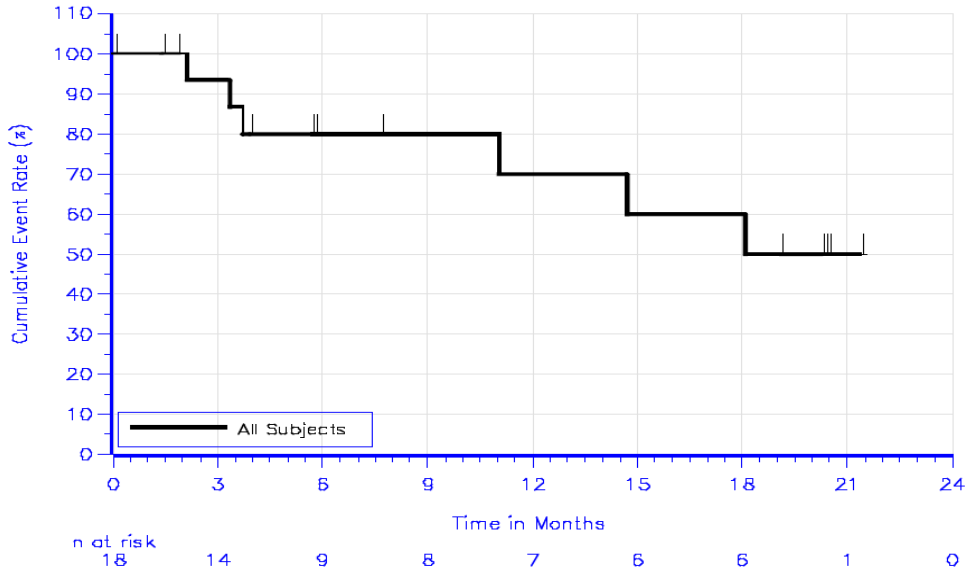
Subjects were 58.1% male and 93.5% white. Median age was 32 years. Enrollment was approximately equal between US (51.6%) and ex-US (48.4%) subjects. All subjects had cHL according to the following subgroups: 30 (96.8%) subjects had nodular sclerosing HL, and 1 (3.2%) had mixed cellularity HL. All subjects (n = 31) were refractory to a previous therapy (100%), or had relapsed after ≥ 3 lines of therapy (96.8%). Twenty-three (74.2%) subjects had failed to respond to or relapsed after a previous auto-SCT, and 8 (25.8%) were ineligible for auto-SCT. All subjects had also previously failed to respond to or relapsed after treatment with BV. Thirteen (41.9%) subjects had prior radiation therapy. The median number of prior lines of therapy was 5 (range 2 to 15). Twenty-nine percent of patients had documented bulky disease, and B symptoms were present in 32.3% of patients.

The primary population for efficacy analyses was the All-Subjects-as-Treated (ASaT) population. Subjects who received at least one dose of study medication were included.

Complete response was defined as having no evidence of disease, including being PET-negative. CRR, the study primary endpoint, per both BICR and site review in all subjects was 19.4% (6/31; 90% CI: 8.8%, 34.7%; p = 0.0834). ORR, defined as the percentage of subjects achieving CR or PR, was 58.1% (18/31; 95% CI: 39.1%, 75.5%) per blinded, independent central review (BICR) and 64.5% (20/31; 95% CI: 45.4%, 80.8%) per site review.

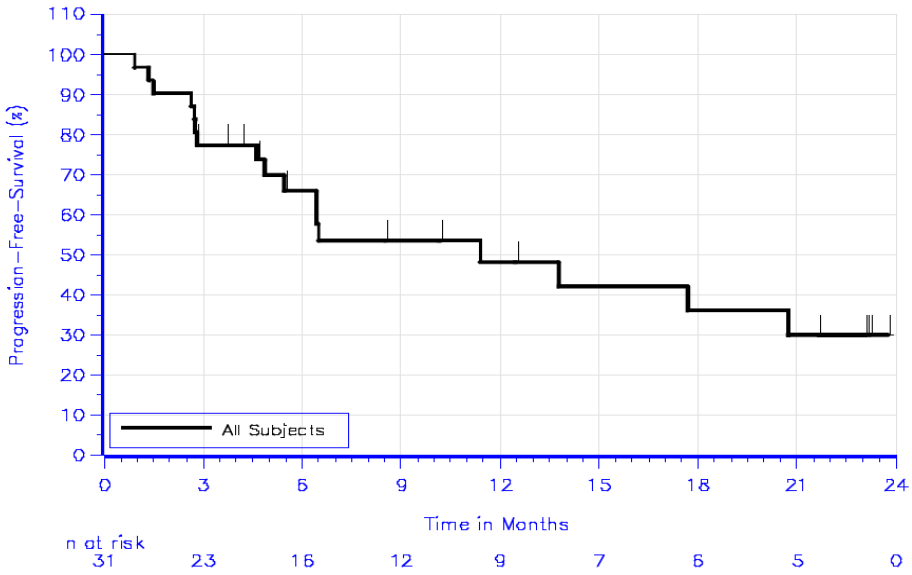
The median time to response (TTR) per BICR was 2.8 months (range 2.4 to 8.6 months) and median DOR was not reached (range 0.0+ to 21.4+ months) (95% CI: 3.7 months, not reached). Among the 18 subjects with response, a response of at least 6 months in duration was observed in 9 subjects (80.0% by Kaplan-Meier method), and a response of at least 12 months in duration was observed in 7 subjects (70.0% by Kaplan-Meier method). At the time of data cutoff, 4 (22.2%) responders were ongoing.

Figure 17: Kaplan - Meier estimates of DOR (ASaT)



The median PFS per BICR was 11.4 months (95% CI: 4.9 months, not reached). PFS rate at 6 months was 66%, and at 12 months 48.2%.

Figure 18: Kaplan – Meier estimates of PFS (ASaT)



Median OS was not reached (95% CI: not reached, not reached). OS rate at 6 months was 100% and at 12 months was 87%.

Subjects were also analysed by transplant status (i.e. corresponding to KEYNOTE-087 cohorts):

- subjects who failed auto-SCT, then failed BV (N = 16);

- subjects who were transplant ineligible, then failed BV (N = 8);

- subjects who progressed after BV, then progressed after auto-SCT (N = 7).

In subjects who failed auto-SCT and BV, the ORR was 68.8% (11/16) per BICR. CRR was 18.8% (3/16). The median time to response by BICR was 2.8 months (range 2.4 to 8.6 months). Median DOR by BICR was not reached (range 2.1 to 21.4+ months). Among the 16 subjects with response, 7 (81.8% by Kaplan-Meier method) subjects had a response duration of ≥ 6 months and 5 (68.2% by Kaplan-Meier method) subject had a response duration of ≥ 12 months. At the database cut-off date, there were 3 (27.3%) subjects who had ongoing response for ≥ 12 months.

In subjects who were ineligible for auto-SCT and failed BV, the ORR was 37.5% (3/8) per BICR. CRR was 25% (2/8). The median time to response by BICR was 2.8 months (range 2.6 to 3.1 months). Median DOR was not reached (range 0.0+ to 19.1+ months). Among the 3 subjects with response, 1 (50.0% by Kaplan-Meier method) subject had a response duration of ≥ 6 months and 1 (50.0% by Kaplan-Meier method) subject had a response duration of ≥ 12 months. At the database cut-off date, 1 (33.3%) subject had ongoing response by BICR.

In subjects who failed BV and then failed auto-SCT, the ORR was 57.1% (4/7) per BICR. CRR was 14.3% (1/7). The median time to response by BICR was 2.9 months (range 2.8 to 4.5 months). Median DOR was 14.7 months (range 1.4+ to 14.7 months; 95% CI: not reached, not reached). Among the 4 subjects with response, 1 (100% by Kaplan-Meier method) subject had a response duration of ≥ 6 months and ≥ 12 months. At the database cut-off date, no subjects had ongoing response by BICR.

Subgroup analyses according to number of lines of prior therapies and refractoriness status were also reported.

The ORR by BICR among subjects who relapsed after ≥ 3 lines of therapy was 60.0%, the CRR was 16.0% (4/25; 95% CI: 4.5%, 36.1%) and the median DOR was 18.1 months (range 1.4+ to 21.4+ months).

The ORR by BICR among subjects who were refractory to any prior therapy was 55.6% (15/27), 58.3% (7/12) among subjects refractory to first therapy received, 54.5% (6/11) among subjects refractory to last therapy received, 50.0% (2/4) among subjects refractory to any other therapy received and 50.0% (2/4) among subjects who were primary refractory (i.e. refractory to their firstline therapy who never achieved CR or PR in subsequent therapies). The CRR by BICR for subjects with refractory disease was 22.2% (6/27), and the median DOR was 18.1 months (range 0.0+, 21.4+).

2.4.3. Discussion on clinical efficacy

To support the Keytruda extension of indication in the treatment of adult patients with cHL who have refractory disease, or have relapsed after greater than 3 prior lines of therapy, the MAH submitted the results from one single pivotal study (phase 2 trial KEYNOTE-087) and from the cHL cohort of phase 1b study KEYNOTE-013.

Design and conduct of clinical studies

Study KEYNOTE-087

In the pivotal study KEYNOTE-087 pembrolizumab activity was investigated in three different r/r cHL populations, including patients refractory to /relapsed after auto-SCT and BV received after transplantation

(Cohort 1); patients refractory to salvage chemotherapy, auto-SCT naïve, refractory to /relapsed after BV (Cohort 2); patients refractory to /relapsed after auto-SCT, naïve to BV post-transplantation but who could have received BV as part of primary treatment, or salvage treatment (Cohort 3).

The provided eligibility criteria are considered overall adequate to define the target population in each of the three cHL cohorts. The high unmet need in Cohorts 1 and 2 is not questioned, and the lack of standard alternatives when ASCT and BV are no longer an option justifies the lack of comparator. As mentioned in the CHMP scientific advice (EMEA/H/SA2437/9/2015/II), an approval based on data from a single, uncontrolled pivotal trial would not be refused in principle, in a clinical setting where no effective alternatives can be identified. Conversely, it is noted that a subset of the patients enrolled in Cohort 3 are still eligible for treatment with BV (i.e. BV naïve patients). The lack of comparator in this setting is hardly acceptable. This is reflected in the revised indication proposed by the MAH ("KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed/refractory classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV"), that specifically excludes subjects who are BV naïve and for whom treatment with BV could still be a treatment option.

The study primary efficacy objective was to evaluate the activity of pembrolizumab within each of the 3 study cohorts. ORR according to the IWG response criteria (Cheson, 2007), as assessed by blinded independent central review (BICR), was the primary efficacy endpoint. Even though, PFS/DFS or OS are usually preferred in trials investigating new treatments in haematologic malignancies (see the EMA/CHMP/205/95/Rev.4 guideline) their interpretation in the absence of a randomised control would be problematic. In this context, ORR can be considered an acceptable primary endpoint.

Subjects who experienced a CR /PR or had stable disease could remain on treatment for up to 2 years, or until unacceptable toxicity or progression. In the case CR were maintained for a minimum of 6 months, discontinuation of pembrolizumab was permitted with restart only at the time of disease progression. The possibility to discontinue pembrolizumab in presence of a stable CR is considered of great clinical value in cHL, especially if the young median age of the patients is taken into account. Unfortunately, the currently available data (only 13 patients had discontinued pembrolizumab due to CR at the time of the most recent data cutoff date) are not considered sufficient to issue specific recommendation on treatment discontinuation.

In accordance to current clinical practice, tumour response was assessed by CT/PET (CT scans were repeated every 12 weeks and PET was repeated at Week 12, Week 24 and as clinically indicated to confirm CR or PD). In order to account for pseudoprogression patients with a first assessment of PD at week 12 could continue pembrolizumab until the next disease response assessment, based on physician discretion. This is considered acceptable, however, the impact of the unique histological structure of cHL (unlike most other neoplasms, in cHL the vast majority of tumour mass consists of non-clonal inflammatory cells) on pseudoprogression is currently poorly characterized (only 13 patients in pivotal study KEYNOTE-087 continued pembrolizumab after an initial assessment of PD, and only 2/13 reached a subsequent clinical response) and would deserve further investigation.

Study KEYNOTE-013

Supportive data from cohort 3 of study KEYNOTE-013, including only patients with nodular sclerosis or mixed cellularity cHL refractory to /relapsed after both ASCT and BV, were submitted.

A different pembrolizumab regimen was administered across the two studies, the fixed 200 mg Q3W dose in study KEYNOTE-087 and the weight-based 10 mg/Kg Q2W in study KEYNOTE-013.

The study primary efficacy objective was to evaluate CRR with pembrolizumab based on the 2007 IWG Revised Criteria. Response was assessed by CT/PET at Week 12 and then every 8 weeks. Secondary efficacy endpoints included PFS, OS, ORR and DOR.

Systematic Literature Review

To further contextualize the efficacy data observed in the provided single arm studies, the MAH also provided a systematic literature review to summarize the available information on response rates with NCCN-recommended treatments in cHL patients ineligible for ASCT or relapsed/refractory after ≥ 3 treatments. PUBMED (Medline), Cochrane, and EMBASE databases were searched to identify prospective clinical trials since January 1, 1985, and a total of 7145 records were identified. At the end of the selection process, however, only 6 publications were retained. These studies represent therapies with different mechanisms of action, with large heterogeneity in terms of response rates (reported ORRs ranged from 18% to 53%, median DOR from 5 to 7 months, and median PFS between 4 and 6 months). As a consequence, no meta-analysis was eventually performed, and the main information that emerged from this review was that robust clinical data in such advanced cHL setting are currently lacking

Efficacy data and additional analyses

The study population in KN-087 is considered representative of patients with advanced r/r cHL. The majority of patients had nodular sclerosis cHL (80.5%), with mixed cellularity representing approximately 10% of the overall study population, and the rarer lymphocyte-rich and lymphocyte-depleted subtypes less than 5%. Nearly 10% of subjects had bulky disease and 30% presented B symptoms at the time of enrolment.

The patient population enrolled in KN-013 is representative of a more advanced clinical setting, with a median number of 5 prior lines of therapy including BV and is not fully comparable to the pivotal study.

In the pivotal KN-087, the analysis by central review in the overall population at the time of the most recent data cut-off date (25/09/2016) showed a clinically relevant activity of pembrolizumab, with ORR 69% (CRR 22.4%). The lower limit of the 95% confidence interval for ORR was above 60%, and the analysis by site review (ORR 66%, CRR 25%) was also consistent with the primary analysis. Similar outcomes were observed across all cohorts (ORR by central review was 73.9%, 64.2% and 70% and CRR 21.7%, 24.7% and 20% in Cohorts 1, 2 and 3 respectively) and the provided waterfall plots showed some level of tumour reduction in the vast majority of patients. Overall, subgroup analyses show consistency among subgroups and support the primary results.

Results observed in the supportive study KN-013 at the time of the most recent data cut-off date (27/09/2016) were broadly consistent. Compared to KN-087, a lower ORR (58.1%) by BICR was reported. This slightly reduced activity can be related to the differences in study population across the two studies. However, it is also noted that the analysis by site review (ORR 20/31; 64.5%) and the CRR by BICR (19.4%) are in accordance with the magnitude of effect observed in the pivotal study.

Results in terms of time-to-event endpoints are difficult to put into context in the framework of an uncontrolled study. Overall, DOR (median not reached in both studies) and median PFS by BICR (11.3 months in KN-087 and 11.4 months in KN-013) suggest that durable responses can be achieved with pembrolizumab, even in this advanced setting of disease. OS results were still immature in both KN-087 (only 4 events) and KN-013 (87% of subjects were still alive at 12 months). At the time of the most recent data cut-off date, the median follow-up was quite short for KN-087 (10.1 months), but was significantly longer for the supportive KN-013 (28.7 months). Results of further secondary/exploratory endpoints (i.e, ORR/CRR by BICR using the 5-point scale

according to the Lugano Classification, correlation of PD-L1 level expression in tumour biopsies and response to pembrolizumab) were not yet available.

The secondary/exploratory analyses will be included in the final CSR for study KN-087, which is planned to be submitted by 3Q2021 (see Annex II).

The MAH also provided several additional analyses by response status (refractory or relapsed after ≥3 lines of therapy) and by number of previous therapy (<3 vs. ≥3 lines of therapy). Prior SCT was counted as one line of therapy. The term refractory was defined as best response of stable disease or PD to any prior line of therapy. Subjects who were refractory were further analysed by whether they were refractory to the first therapy received, last therapy received, or any other therapy received. The ORRs in these subgroups range roughly between 50 and 80%; in some cases with wide confidence intervals due to small sample sizes. No clear correlations can be seen between response rates and possible assumptions based on biological rationales (for example possible lower response rates for more intensively pre-treated patients or for subjects who were refractory to all lines of prior treatment). These analyses were not pre-specified in the SAP and were likely performed after review of the characteristics of the study population and support the currently proposed wording of the indication.

In study KN-087, HR-QoL PROs (EORTC QLQ-C30 and EQ-5D) were analysed in 182 subjects who received at least one dose of study medication and completed at least one PRO instrument. Overall, compliance rates were high (i.e. above 90% until week 24), and both PROs instruments consistently pointed toward an improvement in global health status for responders. However, the added value of this analysis in the assessment of clinical benefit with pembrolizumab is considered limited. In fact, all comparisons referred to subgroups in the same treatment arm (responders and non-responders) that are intuitively associated to health status, even in absence of a significant treatment effect. Moreover, no formal hypothesis was formulated in the study protocol regarding the extent of the expected changes, and no strategy to control multiplicity was employed.

Overall, the analyses by central and site review in patients already exposed to BV in Cohorts 1 and 2 (i.e. patients with few or none recognized alternatives, since BV and ASCT were not an option) showed an ORR ranging between 65% and 74%, that is considered remarkable in this advanced setting. Indeed, although results from specific studies in patients who have failed (or are not eligible to) ASCT and have already received BV are not currently available, the ORR with experimental treatments in advanced cHL rarely exceeds 50% (see i.e. Rueda et al, Acta Oncol 2015 or Zinzani PL et al, Clin Lymphoma Myeloma Leuk 2015). In this regard, the 24.7% CRR observed in Cohort 2 (i.e. patients ineligible to ASCT) is also of particular clinical relevance. Transplant eligibility also relies, in fact, on the ability to achieve pre-transplant remission, since DFS and OS after transplant are significantly longer in patients who underwent transplant in CR (see e.g. Sureda A. et al., JCO 2001). Therefore, patients previously transplant-ineligible due to the persistence of residual disease could eventually become eligible following treatment with pembrolizumab, with all the implications on long-term disease control.

The outcomes in Cohort 3 are difficult to interpret as approximately 60% of subjects in Cohort 3 were BV-naïve. Since ORRs as high as 60%-75% (CR rate 34%) have been reported with BV in patients for whom ASCT was no longer an option or as “rechallenge” in patients who had responded (CR or PR) to their last BV-including treatment (see e.g. Younes A. et al. JCO 2012; Chen R. et al. Blood 2016, Gopal AK et al. Blood 2015, Bartlett et al. J Haematol Oncol 2014), only a direct comparison could assess the actual clinical benefit of pembrolizumab vs. BV in this clinical setting. The indication was revised to exclude BV-naïve patients.

Further, all 81 subjects in Cohort 2 of KN-087 and 8 subjects in KN-013 were ineligible for auto-SCT. The inclusion criteria for Cohort 2 required that subjects “were unable to achieve a CR or a PR to salvage

chemotherapy" as the reason for not being eligible for auto-SCT. Apart from 4 subjects who were not candidates for auto-SCT because of advanced age and comorbidities, and one subject who refused the procedure, all other subjects in both studies were ineligible for auto-SCT due to chemo-refractory disease to salvage therapy. Therefore only insufficient efficacy or safety data are available to support the treatment with pembrolizumab for subjects who are considered ineligible for auto-SCT due to other reasons than chemo-refractory disease such as advanced disease or comorbidities.

Apart from chemoresistance, transplant ineligibility is usually determined by age and comorbidities. In this regard, only 18 patients were aged ≥ 65 years in pivotal study KN-087 and, as reported by the MAH, the activity of pembrolizumab in this subpopulation (ORR 50%) seems to be somehow reduced compared to younger subjects (ORR 71%). Similarly, with all the limits of considering performance status as a surrogate measure of comorbidity, median DOR and PFS appear to be slightly reduced in patients with ECOG score ≥1 vs. ECOG score 0. In addition, subjects in KN-087 and KN-013 with ECOG status of 1 had higher rates of drug-related AEs, Grade 3-5 AEs, serious AEs and AEs leading to discontinuation compared to subjects with ECOG PS of 0. The results observed in the small subset of patients in KN-087 (n=5) who have received pembrolizumab albeit transplant-ineligible due to reasons other than failure of salvage chemotherapy (2 CR, 1 PR), even if encouraging, are nonetheless too limited to draw definitive conclusions. However, taking into account the high unmet need and the absence of effective alternatives for patients with r/r cHL who have failed BV and are ineligible to ASCT due to reasons other than failure of salvage chemotherapy (Linch DC et al, Lancet 1993 and Schmitz N et al, Lancet 2002) all patients who are transplant-ineligible regardless of the reasons for ineligibility, should be covered by the indication. Uncertainties on the extent of clinical benefit in subjects ineligible to transplant due to reasons other than chemoresistance are reflected in the SmPC (sections 4.4 and 5.1).

The submitted data support the efficacy of Keytruda as monotherapy in the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. The efficacy of Keytruda in patients who are eligible for BV cannot be evaluated; A phase III study (study KEYNOTE-204) of pembrolizumab vs. BV in BV-naïve subjects with r/r cHL who have failed to achieve a response to (or progressed after) ASCT, or who are not eligible to ASCT and have received at least 2 prior chemotherapy regimens, is currently ongoing, and might eventually provide the additional evidence required to support the use of pembrolizumab in an earlier setting of disease.

Additional information about the long term efficacy of pembrolizumab in CR subjects (including subjects who have discontinued pembrolizumab) will be included in the final CSRs for KEYNOTE-087 and KEYNOTE-204 (see RMP and Annex II). Additional data on efficacy in subjects who have transplantation following treatment with pembrolizumab will be provided with the CSR for KEYNOTE-204. Subjects in both treatments arms who achieve CR or PR and discontinue study treatment to receive SCT will continue to be followed in the trial. Disease assessments will be conducted every 12 week until disease progression.

2.4.4. Conclusions on the clinical efficacy

Based on data from studies KEYNOTE-087 and KEYNOTE-013, the efficacy of pembrolizumab in r/r cHL patients for whom ASCT and BV are not an option is considered demonstrated.

In the absence of direct comparison, the clinical benefit of pembrolizumab in r/r cHL patents still eligible to BV cannot be evaluated; data on comparison to BV from the Phase 3 study KN-204 are expected early 2021.

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

- The MAH will submit the final study report for study P087, A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL)
- The MAH will submit the final study report for study P013, A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Haematologic Malignancies
- The MAH should submit the final study report for study P204: A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma.

2.5. Clinical safety

Introduction

With the recent extension of the indication to the treatment of 2nd line NSCLC (II/07) the known pembrolizumab safety profile is presently based on 2799 patients (on 1232 NSCLC patients from studies KEYNOTE-001 and KEYNOTE-010 and on 1567 melanoma patients from studies KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006).

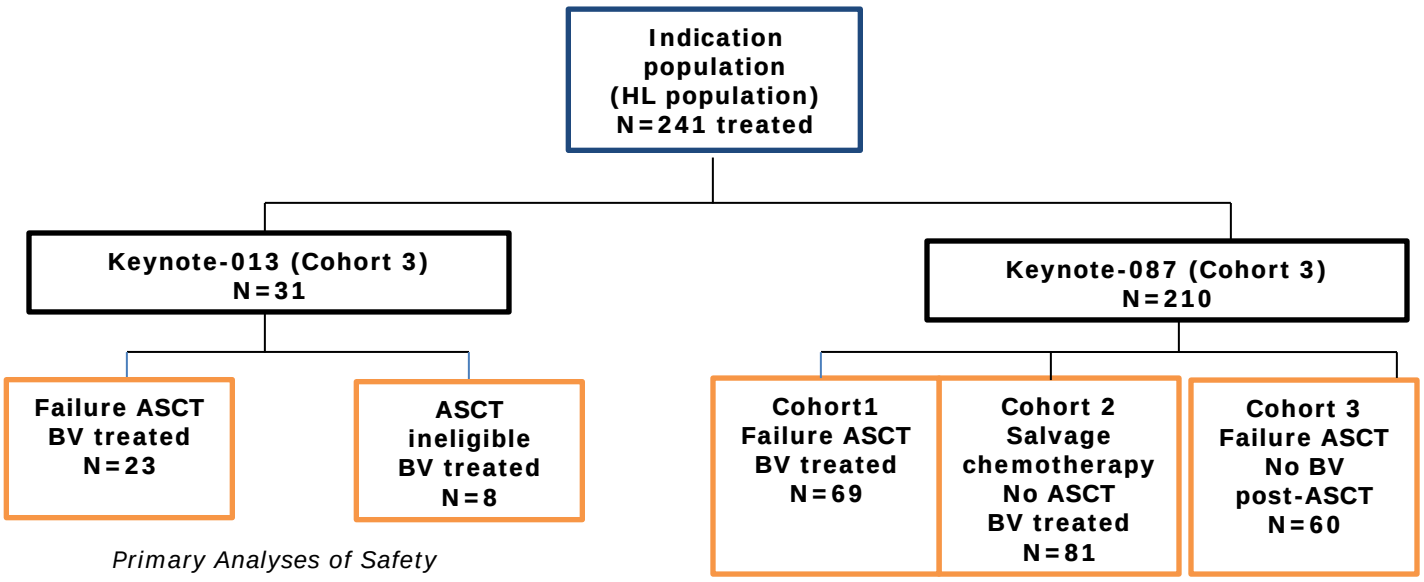
The now submitted safety database includes results from KEYNOTE-013 and KEYNOTE-087, which comprises a total number of 241 subjects with relapsed/refractory classical Hodgkin Lymphoma (cHL).

Table 34: Study Populations for the analysis of clinical safety data

Population	Studies	N
Indication population (HL Population)	Subjects in KN013 (Cohort 3: HL) and in KN087	241
Reference Safety Dataset for MK-3475	Subjects with NSCLC in KN001 and 010; subjects with melanoma in KN001, 002, and 006	2799
Cumulative Running Safety Dataset for MK-3475	Subjects in KN013, 087, 001, 002, 006, 010, 012 (Cohorts B, and B2), 013 (Cohort 3 [HL]), 016 (Cohort A [Colorectal Cancer]), 024, 087, and 164	3475
HL = Hodgkin Lymphoma; HNSCC = head and neck squamous cell carcinoma; KN = KEYNOTE; N = number; NSCLC = non-small cell lung cancer		

The Indication population (HL Population) (n=241) comprises subjects who participated in Study KEYNOTE-013 and Study KEYNOTE-087. All subjects had relapsed or refractory cHL with a median age of 35.0 years (range 18 to 76 years). The majority of subjects were male (54.4 %) and white (88.8%). Subjects were heavily pre-treated, and majority of subjects had relapsed after ASCT (63.4%). The median number of prior systemic therapies was 4 (range 1 to 15). In the HL Population, 36.9% had radiation therapy prior to participation in KEYNOTE-013 or KEYNOTE-087.

Figure 19: Summary of Safety Data of Pembrolizumab Monotherapy in cHL



Primary Analyses of Safety

The primary analyses of AEs, SAEs, and AEs leading to discontinuation are based on all treated subjects using a safety window of 30 days after last dose. The safety data cut of was 03-Jun-2016 for Keynote-013 and 27-Jun-2016 Keynote-087. Adverse events are summarized as counts and frequencies and include events from the first dose of pembrolizumab, up to 30 days after the last dose. Counts and listings tables for SAEs and ECIs, include events from the first dose, up to 90 days after the last dose of pembrolizumab, to account for the extended safety follow-up period per protocol.

The primary analysis populations are the All-Subjects-as-Treated (ASaT) populations in study KN-013 and KN-087, which refer to the population of all subjects who were enrolled per study and received at least 1 dose of treatment. For the pooled analysis of Keynote 013 and Keynote 087, the APaT population is referred to as the primary analysis population. Adverse events observed from subjects who received pembrolizumab as part of the in study crossover have not been presented.

Patient exposure

Subjects in the HL Population were exposed to pembrolizumab for a median of 5.82 months (range: 0.03 to 24.05) with a median of 9 administrations (range: 1 to 52), compared with a median of 4.17 months (range: 0.03 to 30.39) and a median of 7 administrations (range: 1 to 59) in the Reference Population. Of the 241 subjects in the HL Population, 214 (88.8%) remained on pembrolizumab for ≥ 3 months and 117 (48.5%) remained on pembrolizumab for ≥ 6 months; 11 (4.6%) were exposed to pembrolizumab for ≥ 12 months. In comparison, 1656 of 2799 (59.2%) subjects in the Reference Population remained on pembrolizumab for ≥ 3 months and 1153 (41.2%) remained on pembrolizumab for ≥ 6 months; 600 (21.4%) remained on pembrolizumab for ≥ 12 months.

Table 35: Summary of Drug Exposure (APaT Population) vs Reference Safety Dataset

	KN013[1] and KN087 for MK-3475	Reference Safety Dataset for MK-3475[††]	Cumulative Running Safety Dataset for MK-3475[‡‡]
	N=241	N=2799	N=3475
Time on Therapy (months)			
Mean	6.60	6.51	6.48
Median	5.82	4.17	4.83
SD	4.04	5.93	5.79
Range	0.03 to 24.05	0.03 to 30.39	0.03 to 30.39
Number of Administrations			
Mean	11.09	11.11	11.03
Median	9.00	7.00	8.00
SD	8.13	9.64	9.55
Range	1.00 to 52.00	1.00 to 59.00	1.00 to 59.00

Duration of Exposure is calculated as last dose date - first dose date +1.
[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, [2] KN012 Cohort B and B2 (Head and Neck Cancer), [1] KN013 Cohort 3 (Hodgkin´s Lymphoma), [3] KN016 Cohort A (Colorectal Cancer), KN024, KN087, and KN164.
(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).
(KN012 Database Cutoff Date for Head and Neck: 19FEB2016).
(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 03JUN2016).
(KN016 Database Cutoff Date for Colorectal Cancer: 19FEB2016).
(KN024 Database Cutoff Date: 09MAY2016).
(KN087 Database Cutoff Date: 27JUN2016).
(KN164 Database Cutoff Date: 03JUN2016).

Source: [ISS: analysis-adsl; explus]

Table 36: Exposure by Duration (APaT Population)

Duration of Exposure	KN013[1] and KN087 for MK-3475 (N=241)		Reference Safety Dataset for MK-3475[††] (N=2799)		Cumulative Running Safety Dataset for MK-3475[‡‡] (N=3475)	
	n	Patient Years	n	Patient Years	n	Patient Years
≥ 0 m	241	132.6	2,799	1517.7	3,475	1876.6
≥ 1 m	235	132.5	2,394	1503.6	2,996	1860.4
≥ 3 m	214	128.4	1,656	1379.5	2,150	1718.9
≥ 6 m	117	89.9	1,153	1197.8	1,449	1461.1
≥ 12 m	11	19.3	600	800.3	676	912.0

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date +1.
[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, [2] KN012 Cohort B and B2 (Head and Neck Cancer), [1] KN013 Cohort 3 (Hodgkin´s Lymphoma), [3] KN016 Cohort A (Colorectal Cancer), KN024, KN087, and KN164.
(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).
(KN012 Database Cutoff Date for Head and Neck: 19FEB2016).
(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 03JUN2016).
(KN016 Database Cutoff Date for Colorectal Cancer: 19FEB2016).
(KN024 Database Cutoff Date: 09MAY2016).
(KN087 Database Cutoff Date: 27JUN2016).
(KN164 Database Cutoff Date: 03JUN2016).

Source: [ISS: analysis-adsl; explus]

In the Indication cHL Population, the most common reason for discontinuation of pembrolizumab treatment was disease progression. 4 % of subjects discontinued treatment because of study drug toxicity. At the time of database lock, 69% of subjects remained on treatment in KN087and 25.9 of subjects in KN013.

Adverse events

Summary of adverse events

Table 2.4.3 summarizes AEs in the APaT population.

In general, pembrolizumab was well tolerated among subjects with HL. Most AEs were of low-grade toxicity as evidenced by the lower rate of subjects with AEs categorized as Grade 3, 4, or 5, regardless of causality in the

241-subject HL Population (56 [23.2%]) compared with the reference population [Table 2.7.4: 7]. Among subjects with HL, 231 (95.9%) reported at least 1 AE regardless of causality, compared to 2727 of 2799 (97.4%) subjects in the Reference Population. Regardless of AE category (eg, drug-related AEs, AEs categorized as Grade 3, 4, or 5, drug-related AEs categorized as Grade 3, 4, or 5, SAEs, drug-related SAEs, deaths, and discontinuations due to drug-related AEs or drug-related SAEs), the results reported among subjects with HL remained consistent with the Reference Population. Based on the AE summary, there was no change in the safety profile of pembrolizumab with the addition of new AE data from subjects with HL.

Table 37. Adverse Event Summary Subjects Treated with MK-3475 from KN0131, KN087, KN001, KN002, KN006, KN010, KN0122, KN0163, KN024, and KN164

	KN013[1] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	241		2,799		3,475	
with one or more adverse events	231	(95.9)	2,727	(97.4)	3,382	(97.3)
with no adverse event	10	(4.1)	72	(2.6)	93	(2.7)
with drug-related[†] adverse events	158	(65.6)	2,062	(73.7)	2,509	(72.2)
with toxicity grade 3-5 adverse events	56	(23.2)	1,273	(45.5)	1,566	(45.1)
with toxicity grade 3-5 drug-related adverse events	24	(10.0)	386	(13.8)	488	(14.0)
with non-serious adverse events	231	(95.9)	2,671	(95.4)	3,314	(95.4)
with serious adverse events	37	(15.4)	1,041	(37.2)	1,267	(36.5)
with serious drug-related adverse events	13	(5.4)	281	(10.0)	348	(10.0)
with dose modification[§] due to an adverse event	67	(27.8)	884	(31.6)	1,120	(32.2)
who died	2	(0.8)	110	(3.9)	146	(4.2)
who died due to a drug-related adverse event	0	(0.0)	10	(0.4)	11	(0.3)
discontinued[‡] due to an adverse event	11	(4.6)	334	(11.9)	397	(11.4)
discontinued due to a drug-related adverse event	10	(4.1)	146	(5.2)	179	(5.2)
discontinued due to a serious adverse event	7	(2.9)	253	(9.0)	303	(8.7)

	KN013[1] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
discontinued due to a serious drug-related adverse event	6	(2.5)	101	(3.6)	126	(3.6)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

[§] Defined as overall action taken of dose reduced, drug interrupted or drug withdrawn.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

MedDRA version used is 19.0

[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.

[§§] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, [2] KN012 Cohort B and B2 (Head and Neck Cancer), [1] KN013 Cohort 3 (Hodgkin´s Lymphoma), [3] KN016 Cohort A (Colorectal Cancer), KN024, KN087, and KN164.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

(KN012 Database Cutoff Date for Head and Neck: 19FEB2016).

(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 03JUN2016).

(KN016 Database Cutoff Date for Colorectal Cancer: 19FEB2016).

(KN024 Database Cutoff Date: 09MAY2016).

(KN087 Database Cutoff Date: 27JUN2016).

(KN164 Database Cutoff Date: 03JUN2016).

Common adverse events

The most frequent reported AEs (incidence >15%) by decreasing incidence were pyrexia (23.2%), cough (22.8%), diarrhea (17.8%) and fatigue (15.8%). In comparison, in the Reference Population the most commonly reported of which were fatigue (37.3%), nausea (24.5%), diarrhea (22.3%), and cough (22.0%).

Table 38 Subjects With Adverse Events (Incidence ⩾ 10% in One or More Treatment Groups)

Adverse Events ≥ 10%	KN013 and KN087 n (%) N=241	Reference safety dataset n (%) N=2799
Pyrexia	56 (23.2)	357 (12.8)
Cough	55 (22.8)	615 (22.0)
Diarrhea	43 (17.8)	625 (22.3)
Fatigue	38 (15.8)	1044 (37.3)
Nausea	34 (14.1)	685 (24.5)
Hypothyroidism	31 (12.9)	236 (8.4)
Vomiting	30 (12.4)	387 (13.8)
Constipation	28 (11.6)	497 (17.8)

Dyspnea	28 (11.6)	534 (19.1)
Pruritis	28 (11.6)	562 (20.1)
Upper respiratory tract infection	25 (10.4)	182 (6.5)
Rash	24 (10.0)	499 (17.8)

Drug-related adverse events

158 of 241 (65.6%) subjects had a drug-related AE. The most frequently reported drug-related AEs by decreasing incidence were hypothyroidism (26 [10.8%]), pyrexia (23 [9.5%]), diarrhoea (20 [8.3%]), fatigue (17 [7.1%]), nausea (16 [6.6%]), headache (14 [5.8%]), and rash (13 [5.4%]).

In comparison, 2062 of 2799 (73.7%) subjects in the Reference Population had a drug-related AE, the most common of which included fatigue (678 [24.2%]), pruritus (467 [16.7%]), rash (386 [13.8%]),diarrhoea (343 [12.3%]), and hypothyroidism (213 [7.6%]).

Table 39: Subjects With Drug-Related Adverse Events by Decreasing Incidence in one or More Treatment Groups) (ApaT Population)

Most common drug-related adverse events	**KN013 and KN087 n (%) N=241**	**Reference safety dataset n (%) N=2799**
Hypothyroidism	26 (10.8)	213 (7.6)
Pyrexia	23 (9.5)	126 (4.5)
Diarrhea	20 (8.3)	343 (12.3)
Fatigue	17 (7.1)	678 (24.2)
Nausea	16 (6.6)	304 (10.9)
Headache	14 (5.8)	111 (4.0)
Rash	13 (5.4)	386 (13.8)
Cough	12 (5.0)	112 (4.0)
Dyspnea	11 (4.6)	109 (3.9)

Neutropenia	10 (4.1)	8 (0.3)
Pneumonitis	10 (4.1)	80 (2.9)
Vomiting	10 (4.1)	107 (3.8)

Grade 3 to 5 Adverse Events

There were 56 (23.2%) who had Grade 3 to 5 AEs in the APaT population. The most frequently reported Grade 3 to 5 AEs by decreasing incidence were: anaemia (2.9%), pneumonia (1.7%), Colitis (1.2%), diarrhoea (1.2%), herpes zoster (1.2%), neutropenia (1.2%) and thrombocytopenia (1.2%).

Table 40: Subjects With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ⩾1% in One or More Treatment Groups) (APaT Population)

Most common Grade 3-5 adverse events	**KN013 and KN087 n (%) N=241**	**Reference safety dataset n (%) N=2799**
Anemia	7 (2.9)	90 (3.2)
Pneumonia	4 (1.7)	75 (2.7)
Colitis	3 (1.2)	32 (1.1)
Diarrhea	3 (1.2)	36 (1.3)
Dyspnea	3 (1.2)	78 (2.8)
Herpes zoster	3 (1.2)	1 (0.0)
Neutropenia	3 (1.2)	5 (0.2)
Thrombocytopenia	3 (1.2)	10 (0.4)

Drug-related Grade 3 to 5 Adverse Events

The incidence of drug-related AEs categorized as Grade 3, 4, or 5 among subjects in the HL Population was consistent with the Reference Population. Drug-related AEs categorized as Grade 3, 4, or 5 occurred in 24 of 241 (10.0%) subjects compared to 386 of 2799 (13.8%) subjects in the Reference Population.

Table 41: Subjects with drug – related grade 3-5 adverse events

Most common drug- related Grade 3-5 adverse events	**KN013 and KN087 n (%) N=241**	**Reference safety dataset n (%) N=2799**
Colitis	2 (0.8)	27 (1.0)
Diarrhea	2 (0.8)	25 (0,9)
Dyspnea	2 (0.8)	12(0.4)
Thrombocytopenia	2 (0.8)	3 (0.1)

Serious adverse event / deaths / other significant events

In the HL Population, 37 of 241 (15.4%) subjects had an SAE, the most frequent (incidence >1%) of which included: pneumonia (5 [2.1%]), pneumonitis (4 [1.7%]), and pyrexia (4 [1.7%]). In comparison, 1041 of 2799 (37.2%) subjects in the Reference Population had an SAE, of which the most commonly reported was pneumonia (85 [3.0%]), pleural effusion (48 [1.7%]), dyspnea (45 [1.6%]), and pneumonitis (46 [1.6%]).

Table 42 Subjects With SAEs Up to 90 Days of Last Dose (Incidence ⩾ 1% in One or More Treatment Groups)

	KN013[1] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	241		2,799		3,475	
with one or more adverse events	37	(15.4)	1,041	(37.2)	1,267	(36.5)
with no adverse events	204	(84.6)	1,758	(62.8)	2,208	(63.5)
Pneumonia	5	(2.1)	85	(3.0)	100	(2.9)
Pneumonitis	4	(1.7)	46	(1.6)	59	(1.7)
Pyrexia	4	(1.7)	35	(1.3)	45	(1.3)
Anaemia	2	(0.8)	31	(1.1)	39	(1.1)
Colitis	2	(0.8)	31	(1.1)	36	(1.0)
Dyspnoea	2	(0.8)	45	(1.6)	54	(1.6)
Pleural effusion	0	(0.0)	48	(1.7)	57	(1.6)
Pulmonary embolism	0	(0.0)	41	(1.5)	49	(1.4)

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.

MedDRA version used is 19.0

[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, and KN010.

[§§] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, [2] KN012 Cohort B and B2 (Head and Neck Cancer), [1] KN013 Cohort 3 (Hodgkin´s Lymphoma), [3] KN016 Cohort A (Colorectal Cancer), KN024, KN087, and KN164.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

(KN012 Database Cutoff Date for Head and Neck: 19FEB2016).

(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 03JUN2016).

(KN016 Database Cutoff Date for Colorectal Cancer: 19FEB2016).

(KN024 Database Cutoff Date: 09MAY2016).

(KN087 Database Cutoff Date: 27JUN2016).

(KN164 Database Cutoff Date: 03JUN2016).

Drug-related Serious Adverse Events

The incidence of drug-related SAEs that occurred up to 90 days after the last dose of pembrolizumab was generally comparable between subjects in the HL and Reference Population. In the HL Population, drug-related SAEs occurred in 13 of 241 (5.4%) subjects, the most common of which was pneumonitis (4 [1.7%]). In comparison, 281 of 2799 (10.0%) subjects in the Reference Population had a drug-related SAE, the most common of which was also pneumonitis (44 [1.6%]).

Deaths due to adverse events

The incidence of deaths in the HL Population was low and comparable to that of the Reference Population]. In the HL population, deaths occurred in 2 of 241 (0.8%) subjects, neither of which was classified as drug related by the investigator; both deaths occurred in KEYNOTE-087. One (0.4%) subject died as a result of graft-versus-host disease (GVHD) after a donor (allogeneic) stem-cell transplant and 1 (0.4%) subject died as a result of septic shock. In comparison, 110 of 2799 (3.9%) subjects died in the Reference Population, and 10

(0.4%) of these deaths were drug related

Adverse Events of Special Interest (AEOSI)

The analysis of AEOSI was the primary method of assessing immune-related AEs (irAEs) for this study and was based on a compiled list of preferred AE terms potentially associated with an immune etiology. The Sponsor developed this pre-specified list of terms representing potentially irAEs to consistently evaluate potential irAEs across several System Organ Classes. The AEOSI are presented regardless of Investigator-assessed causality and generally include all AE grades (with the exception of severe skin reactions). In an attempt to capture all informative data, the list of terms is intentionally broad; consequently, some reported terms may not have an obvious immune mechanism. The list of terms is updated periodically based on emerging pembrolizumab safety data.

Summary of Adverse Event of Special Interest

Table 2.4.9 displays the summary of AEOSI in the APaT population. The incidence of AEOSI among subjects in the HL Population was comparable to the Reference Population regardless of AEOSI category (eg, drug-related AEs, AEs categorized as Grade 3, 4, or 5, drug-related AEs categorized as Grade 3, 4, or 5, SAEs, drug-related SAEs, deaths, and discontinuations due to drug-related AEs or drug-related SAEs)A majority of these events were Grade 1 or 2 in severity, as only 2,5% of pembrolizumab-treated subjects experienced Grade 3 to 5 AEOSI. There were no deaths reported due to AEOSI in either treatment group. Seven (2.9%) subjects discontinued due to drug-related AEOSI.

Table 43: Adverse Event Summary Important AEOSI (APaT Population)

	KN013[†] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	241		2,799		3,475	
with one or more adverse events	54	(22.4)	536	(19.1)	695	(20.0)
with no adverse event	187	(77.6)	2,263	(80.9)	2,780	(80.0)
with drug-related[¶] adverse events	47	(19.5)	465	(16.6)	595	(17.1)
with toxicity grade 3-5 adverse events	6	(2.5)	152	(5.4)	189	(5.4)
with toxicity grade 3-5 drug-related adverse events	5	(2.1)	125	(4.5)	154	(4.4)
with non-serious adverse events	49	(20.3)	427	(15.3)	566	(16.3)
with serious adverse events	7	(2.9)	153	(5.5)	183	(5.3)
with serious drug-related adverse events	6	(2.5)	132	(4.7)	160	(4.6)
with dose modification[§] due to an adverse event	16	(6.6)	189	(6.8)	239	(6.9)
who died	0	(0.0)	4	(0.1)	4	(0.1)
who died due to a drug-related adverse event	0	(0.0)	4	(0.1)	4	(0.1)
discontinued[‡] due to an adverse event	7	(2.9)	81	(2.9)	99	(2.8)
discontinued due to a drug-related adverse event	7	(2.9)	79	(2.8)	97	(2.8)
discontinued due to a serious adverse event	3	(1.2)	63	(2.3)	75	(2.2)
discontinued due to a serious drug-related adverse event	3	(1.2)	62	(2.2)	74	(2.1)

Overall Adverse Event of Special Interest (AEOSI)

Table 44: Adverse Event Summary for Important Identified AEOSI (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN013[1] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	241		2,799		3,475	
with one or more adverse events	54	(22.4)	536	(19.1)	695	(20.0)
with no adverse events	187	(77.6)	2,263	(80.9)	2,780	(80.0)
Adrenal Insufficiency	**0**	**(0.0)**	**22**	**(0.8)**	**24**	**(0.7)**
Adrenal insufficiency	0	(0.0)	20	(0.7)	22	(0.6)
Adrenocortical insufficiency acute	0	(0.0)	1	(0.0)	1	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	1	(0.0)	1	(0.0)
Colitis	**4**	**(1.7)**	**49**	**(1.8)**	**58**	**(1.7)**
Colitis	4	(1.7)	46	(1.6)	54	(1.6)
Colitis microscopic	0	(0.0)	2	(0.1)	2	(0.1)
Enterocolitis	0	(0.0)	1	(0.0)	2	(0.1)
Guillain-Barre Syndrome	**0**	**(0.0)**	**2**	**(0.1)**	**2**	**(0.1)**
Axonal neuropathy	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	1	(0.0)	1	(0.0)
Hepatitis	**1**	**(0.4)**	**19**	**(0.7)**	**21**	**(0.6)**
Autoimmune hepatitis	0	(0.0)	12	(0.4)	12	(0.3)
Drug-induced liver injury	0	(0.0)	2	(0.1)	3	(0.1)
Hepatitis	1	(0.4)	6	(0.2)	7	(0.2)
Hyperthyroidism	**7**	**(2.9)**	**96**	**(3.4)**	**119**	**(3.4)**
Hyperthyroidism	7	(2.9)	96	(3.4)	119	(3.4)
Hypophysitis	**0**	**(0.0)**	**17**	**(0.6)**	**18**	**(0.5)**
Hypophysitis	0	(0.0)	9	(0.3)	10	(0.3)
Hypopituitarism	0	(0.0)	8	(0.3)	8	(0.2)
Hypothyroidism	**31**	**(12.9)**	**237**	**(8.5)**	**316**	**(9.1)**
Hypothyroidism	31	(12.9)	236	(8.4)	315	(9.1)
Myxoedema	0	(0.0)	1	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	1	(0.0)	1	(0.0)
Myositis	**2**	**(0.8)**	**11**	**(0.4)**	**17**	**(0.5)**
Myopathy	0	(0.0)	3	(0.1)	4	(0.1)

	KN013[‡] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Myositis	**2**	**(0.8)**	**11**	**(0.4)**	**17**	**(0.5)**
Myositis	2	(0.8)	7	(0.3)	12	(0.3)
Rhabdomyolysis	0	(0.0)	1	(0.0)	1	(0.0)
Nephritis	**1**	**(0.4)**	**4**	**(0.1)**	**6**	**(0.2)**
Nephrotic syndrome	1	(0.4)	0	(0.0)	1	(0.0)
Tubulointerstitial nephritis	0	(0.0)	4	(0.1)	5	(0.1)
Pancreatitis	**0**	**(0.0)**	**9**	**(0.3)**	**17**	**(0.5)**
Autoimmune pancreatitis	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	7	(0.3)	14	(0.4)
Pancreatitis acute	0	(0.0)	1	(0.0)	2	(0.1)
Pneumonitis	**10**	**(4.1)**	**94**	**(3.4)**	**119**	**(3.4)**
Interstitial lung disease	1	(0.4)	7	(0.3)	10	(0.3)
Pneumonitis	10	(4.1)	87	(3.1)	110	(3.2)
Skin	**1**	**(0.4)**	**46**	**(1.6)**	**58**	**(1.7)**
Jaundice	0	(0.0)	1	(0.0)	1	(0.0)
Rash pustular	0	(0.0)	1	(0.0)	1	(0.0)
Contusion	0	(0.0)	1	(0.0)	1	(0.0)
Pruritus genital	0	(0.0)	1	(0.0)	1	(0.0)
Decubitus ulcer	0	(0.0)	0	(0.0)	1	(0.0)
Dermatitis	0	(0.0)	1	(0.0)	1	(0.0)
Dermatitis bullous	0	(0.0)	2	(0.1)	2	(0.1)
Dermatitis exfoliative	0	(0.0)	2	(0.1)	2	(0.1)
Dermatitis psoriasiform	1	(0.4)	0	(0.0)	1	(0.0)
Drug eruption	0	(0.0)	1	(0.0)	1	(0.0)
Erythema	0	(0.0)	1	(0.0)	1	(0.0)
Erythema multiforme	0	(0.0)	3	(0.1)	3	(0.1)
Exfoliative rash	0	(0.0)	2	(0.1)	2	(0.1)
Lichen planus	0	(0.0)	2	(0.1)	2	(0.1)
Papule	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigoid	0	(0.0)	2	(0.1)	3	(0.1)
Pruritus	0	(0.0)	4	(0.1)	4	(0.1)
Psoriasis	0	(0.0)	2	(0.1)	3	(0.1)
Rash	0	(0.0)	9	(0.3)	12	(0.3)
Rash erythematous	0	(0.0)	1	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	2	(0.1)	3	(0.1)
Rash macular	0	(0.0)	0	(0.0)	1	(0.0)

	KN013[1] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Skin	**1**	**(0.4)**	**46**	**(1.6)**	**58**	**(1.7)**
Rash maculo-papular	0	(0.0)	7	(0.3)	8	(0.2)
Rash pruritic	0	(0.0)	1	(0.0)	2	(0.1)
Skin lesion	0	(0.0)	1	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	1	(0.0)	1	(0.0)
Toxic skin eruption	0	(0.0)	1	(0.0)	2	(0.1)
Thyroiditis	**2**	**(0.8)**	**16**	**(0.6)**	**29**	**(0.8)**
Autoimmune thyroiditis	0	(0.0)	5	(0.2)	6	(0.2)
Thyroiditis	2	(0.8)	11	(0.4)	23	(0.7)
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**6**	**(0.2)**	**8**	**(0.2)**
Diabetic ketoacidosis	0	(0.0)	2	(0.1)	4	(0.1)
Type 1 diabetes mellitus	0	(0.0)	5	(0.2)	6	(0.2)
Uveitis	**1**	**(0.4)**	**14**	**(0.5)**	**15**	**(0.4)**
Iridocyclitis	0	(0.0)	2	(0.1)	2	(0.1)
Iritis	1	(0.4)	2	(0.1)	3	(0.1)

Hypothyroidism was the most commonly reported AEOSI among subjects in the HL Population across KEYNOTE-013 and KEYNOTE-087 (12.9%). All events were low grade (Grade 1 or 2) [Table 5.3.5.3.3-hl: 92], and no subject received corticosteroid treatment. In comparison, 237 of 2799 (8.5%) of subjects in the Reference Population experienced at least 1 episode of hypothyroidism, 5 (0.2%) of which were considered SAEs.

Grade 1 to 4 pneumonitis was observed in 10 (4.1%) subjects.

Table 45: patients treated with pembrolizumab in KN013 and KN087 with identified AEOSI (incidence in %)

	KN 013 (%)	KN087
AEOSI	45.2	26.7
AEOSI Grade ⩾3	9.7	1.9
Discontinuation due to AEOSI	9.7	2.4
Pneumonitis	12.9	2.9
Pneumonitis Grade ≥3	0	0
Colitis	6.5	1
Colitis Grade ⩾3	6.5	0.5
AEOSI skin Grade ⩾3	0	1
AEOSI hypothyroidism	16.1	12.4
AEOSI hyperthyroidism	3.2	4.7
Infusion reactions	0	7.6
Infusion reactions Grade ⩾3	0	6.2
Nephrotic syndrome Grade ⩾3	3.2	0
Myositis	0	1

Myositis Grade ⩾3	0	0.5

Infusion reactions

Sixteen of 241 (6.6%) subjects in the HL Population had at least 1 infusion reaction. Of the 16 subjects who experienced an infusion reaction, 15 (6.2%) subjects experienced infusion reactions considered drug related all subjects with infusion reactions were in KEYNOTE-087. Of the infusion reactions reported, 1 (0.4%) was categorized as Grade 3and considered serious and drug- related, resulting in discontinuation of pembrolizumab. The median time to onset of an infusion reaction episode was 1 day (range: 1 to 240) The majority of infusion reactions were low grade (Grade 1 or 2); no one died of an infusion reaction Few infusion reactions were managed with corticosteroids among subjects with HL and all infusion reactions resolved.

Table 46: Adverse Event Summary AEOSI- Infusion Reactions

	KN013[†] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[‡‡]	
	n	(%)	n	(%)	n	(%)
Subjects in population	241		2,799		3,475	
with one or more adverse events	16	(6.6)	70	(2.5)	95	(2.7)
with no adverse event	225	(93.4)	2,729	(97.5)	3,380	(97.3)
with drug-related[†] adverse events	15	(6.2)	46	(1.6)	65	(1.9)
with toxicity grade 3-5 adverse events	1	(0.4)	6	(0.2)	7	(0.2)
with toxicity grade 3-5 drug-related adverse events	1	(0.4)	3	(0.1)	4	(0.1)
with non-serious adverse events	15	(6.2)	65	(2.3)	87	(2.5)
with serious adverse events	1	(0.4)	5	(0.2)	8	(0.2)
with serious drug-related adverse events	1	(0.4)	2	(0.1)	4	(0.1)
with dose modification[§] due to an adverse event	2	(0.8)	26	(0.9)	28	(0.8)
who died	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)
discontinued[‡] due to an adverse event	1	(0.4)	2	(0.1)	3	(0.1)
discontinued due to a drug-related adverse event	1	(0.4)	2	(0.1)	3	(0.1)
discontinued due to a serious adverse event	1	(0.4)	1	(0.0)	2	(0.1)

Laboratory findings

To assess whether laboratory abnormalities represented clinically meaningful changes from baseline, an analysis of the shifts from baseline in the CTCAE grades of laboratory abnormalities (based on the highest CTCAE grade for a given laboratory test during the study) was performed. A clinically meaningful worsening in CTCAE Grade was defined as a shift from less than Grade 3 to Grade 3, 4, or 5; or a shift from Grade 0 to Grade 2.

Clinically meaningful worsening in laboratory CTCAE grades was comparable between subjects in the HL Population and the Reference Population. In the HL Population, the laboratory abnormalities with the most frequent (incidence > 10%), clinically meaningful worsening in CTCAE grade, included phosphate decreased (46 [19.1%]), lymphocytes decreased (31 [12.9%]), and neutrophils decreased (31 [12.9%])

Safety in special populations

Age

Table 47. Adverse Event Summary by Age Subjects Treated with MK-3475 from KN013[1] and KN087 (APaT Population)

	Age (years)					
	<65		65-74		75-84	
	n	(%)	n	(%)	n	(%)
Subjects in population	221	(100.0)	19	(100.0)	1	(100.0)
with one or more adverse events	212	(95.9)	18	(94.7)	1	(100.0)
who died	1	(0.5)	1	(5.3)	0	(0.0)
with serious adverse events	29	(13.1)	8	(42.1)	0	(0.0)
discontinued‡ due to an adverse event	9	(4.1)	2	(10.5)	0	(0.0)
CNS (confusion/extrapyramidal)	14	(6.3)	1	(5.3)	0	(0.0)
AE related to falling	5	(2.3)	2	(10.5)	0	(0.0)
CV events	26	(11.8)	6	(31.6)	0	(0.0)
Cerebrovascular events	0	(0.0)	1	(5.3)	0	(0.0)
Infections	102	(46.2)	14	(73.7)	0	(0.0)

‡ Study medication withdrawn.
MedDRA preferred terms 'Malignant neoplasm progression' ,'Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
AEs were followed up to 30 days after last dose of study treatment, SAEs were followed up to 90 days after last dose of study treatment
[1]KN013 Cohort 3 (Hodgkin´s Lymphoma).
(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 03JUN2016).
(KN087 Database Cutoff Date: 27JUN2016).

Gender

Table 48: Adverse Event Summary by Gender (Male, Female)

	KN013[1] and KN087 for MK-3475				Reference Safety Dataset for MK-3475[††]				Cumulative Running Safety Dataset for MK-3475[‡‡]			
	M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	131		110		1,659		1,140		2,092		1,383	
with one or more adverse events	125	(95.4)	106	(96.4)	1,616	(97.4)	1,111	(97.5)	2,036	(97.3)	1,346	(97.3)
with no adverse event	6	(4.6)	4	(3.6)	43	(2.6)	29	(2.5)	56	(2.7)	37	(2.7)
with drug-related[†] adverse events	81	(61.8)	77	(70.0)	1,239	(74.7)	823	(72.2)	1,515	(72.4)	994	(71.9)
with toxicity grade 3-5 adverse events	25	(19.1)	31	(28.2)	759	(45.8)	514	(45.1)	953	(45.6)	613	(44.3)
with toxicity grade 3-5 drug-related adverse events	11	(8.4)	13	(11.8)	251	(15.1)	135	(11.8)	314	(15.0)	174	(12.6)
with serious adverse events	19	(14.5)	18	(16.4)	636	(38.3)	405	(35.5)	785	(37.5)	482	(34.9)
with serious drug-related adverse events	8	(6.1)	5	(4.5)	184	(11.1)	97	(8.5)	226	(10.8)	122	(8.8)
who died	2	(1.5)	0	(0.0)	69	(4.2)	41	(3.6)	96	(4.6)	50	(3.6)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	9	(0.5)	1	(0.1)	9	(0.4)	2	(0.1)
discontinued[‡] due to an adverse event	9	(6.9)	2	(1.8)	197	(11.9)	137	(12.0)	241	(11.5)	156	(11.3)
discontinued due to a drug-related adverse event	8	(6.1)	2	(1.8)	98	(5.9)	48	(4.2)	118	(5.6)	61	(4.4)
discontinued due to a serious adverse event	6	(4.6)	1	(0.9)	155	(9.3)	98	(8.6)	188	(9.0)	115	(8.3)
discontinued due to a serious drug-related adverse event	5	(3.8)	1	(0.9)	72	(4.3)	29	(2.5)	86	(4.1)	40	(2.9)

ECOG PS

The incidences of AEs was similar between subjects with an ECOG performance status of 1 and ECOG performance status of 0 , nevertheless drug-related AEs, Grade 3-5 AEs, deaths, SAEs, and discontinuations due to AEs were higher in subjects with ECOG PS 1.

Table 49 Adverse Event Summary by ECOG Status Category (0, 1) Subjects Treated with MK-3475(APaT Population)

	KN013[1] and KN087 for MK-3475						Reference Safety Dataset for MK-3475[††]					
	[0] Normal Activity		[1] Symptoms, but ambulatory		Other/Missing		[0] Normal Activity		[1] Symptoms, but ambulatory		Other/Missing	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	116		124		1		1,446		1,347		6	
with one or more adverse events	111	(95.7)	119	(96.0)	1	(100.0)	1,417	(98.0)	1,305	(96.9)	5	(83.3)
with no adverse event	5	(4.3)	5	(4.0)	0	(0.0)	29	(2.0)	42	(3.1)	1	(16.7)
with drug-related[†] adverse events	70	(60.3)	87	(70.2)	1	(100.0)	1,149	(79.5)	911	(67.6)	2	(33.3)
with toxicity grade 3-5 adverse events	14	(12.1)	42	(33.9)	0	(0.0)	588	(40.7)	682	(50.6)	3	(50.0)
with toxicity grade 3-5 drug-related adverse events	8	(6.9)	16	(12.9)	0	(0.0)	201	(13.9)	184	(13.7)	1	(16.7)
with serious adverse events	10	(8.6)	27	(21.8)	0	(0.0)	466	(32.2)	572	(42.5)	3	(50.0)
with serious drug-related adverse events	3	(2.6)	10	(8.1)	0	(0.0)	148	(10.2)	133	(9.9)	0	(0.0)
who died	0	(0.0)	2	(1.6)	0	(0.0)	38	(2.6)	71	(5.3)	1	(16.7)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.3)	6	(0.4)	0	(0.0)
discontinued[‡] due to an adverse event	1	(0.9)	10	(8.1)	0	(0.0)	148	(10.2)	185	(13.7)	1	(16.7)
discontinued due to a drug-related adverse event	1	(0.9)	9	(7.3)	0	(0.0)	82	(5.7)	64	(4.8)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	7	(5.6)	0	(0.0)	104	(7.2)	148	(11.0)	1	(16.7)
discontinued due to a serious drug-related adverse event	0	(0.0)	6	(4.8)	0	(0.0)	52	(3.6)	49	(3.6)	0	(0.0)

Complications Following Post-allogeneic Stem Cell Transplantation (SCT)

Of the 31 subjects in KEYNOTE-013, 11 (35%) were reported as having received an allogeneic SCT at some point after stopping treatment with pembrolizumab. Of these 11 subjects, 2 subjects experienced a drug-related SAE of veno-occlusive disease (VOD) of the liver following transplant; in 1 subject the event was fatal, and the other subject recovered. No hyperacute GVHD has been reported. As of the database cutoff date of 03-Jun-2016, 9 of the 11 subjects were known to be alive; 1 died due to VOD and 1 was lost to follow-up. The median follow-up duration from date of allogeneic SCT to death or last date the subject was known to be alive for these 11 subjects was 13.4 months (range: 0.7 to 20.2 months).

Of the 210 subjects in KEYNOTE-087, 6 (3%) were reported as having received allogeneic SCT at some point after stopping treatment with pembrolizumab.

ASCT-naive Subjects

In KN-087 Cohort 2, 81 patients were ASCT naive. Drug-related AEs were reported in a total of 47 (58%) subjects, and Drug-Related Grade 3-5 Adverse Events were reported in 7 (8.6%) of the ASCT naïve subjects. This is comparable to the Indication Population.

Safety related to drug-drug interactions and other interactions

Data on safety of DDIs or other interactions were not submitted in support of this application.

Discontinuation due to adverse events

Adverse Events Leading to Treatment Interruption

The most common AEs leading to pembrolizumab interruption were pneumonitis (5 [2.1%]), diarrhea (4 [1.7%]), and alanine aminotransferase increased (3 [1.2%])

Adverse Events Leading to Treatment Discontinuation

An analysis of subjects with drug-related AEs resulting in treatment discontinuation is presented in Table 2.4.17. The incidence of drug-related AEs that resulted in discontinuation of pembrolizumab was comparable between the HL and Reference Population. Among subject with HL, 10 of 241 (4.1%) discontinued pembrolizumab due to a drug-related AE. The most common drug-related AE leading to pembrolizumab discontinuation was pneumonitis (2.1%).

Table 50: Subjects With Drug-Related Adverse Events Resulting in Treatment Discontinuation by Decreasing Incidence (Incidence >0% in One or More Treatment Groups) (APaT Population)

	KN013[1] and KN087 for MK-3475		Reference Safety Dataset for MK-3475[††]		Cumulative Running Safety Dataset for MK-3475[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	241		2,799		3,475	
with one or more adverse events	10	(4.1)	146	(5.2)	179	(5.2)
with no adverse events	231	(95.9)	2,653	(94.8)	3,296	(94.8)
Pneumonitis	5	(2.1)	34	(1.2)	47	(1.4)
Cytokine release syndrome	1	(0.4)	0	(0.0)	1	(0.0)
Infusion related reaction	1	(0.4)	0	(0.0)	1	(0.0)
Interstitial lung disease	1	(0.4)	2	(0.1)	4	(0.1)
Myelitis	1	(0.4)	0	(0.0)	1	(0.0)
Myocarditis	1	(0.4)	0	(0.0)	1	(0.0)
Nephrotic syndrome	1	(0.4)	0	(0.0)	1	(0.0)
Acute kidney injury	0	(0.0)	2	(0.1)	2	(0.1)
Adrenal insufficiency	0	(0.0)	1	(0.0)	1	(0.0)
Alanine aminotransferase increased	0	(0.0)	2	(0.1)	6	(0.2)
Anaphylactoid reaction	0	(0.0)	1	(0.0)	1	(0.0)
Arterial thrombosis	0	(0.0)	1	(0.0)	1	(0.0)
Arthralgia	0	(0.0)	3	(0.1)	3	(0.1)
Arthritis	0	(0.0)	2	(0.1)	2	(0.1)
Aspartate aminotransferase increased	0	(0.0)	2	(0.1)	5	(0.1)
Ataxia	0	(0.0)	1	(0.0)	1	(0.0)
Atrial fibrillation	0	(0.0)	0	(0.0)	1	(0.0)
Atrioventricular block complete	0	(0.0)	1	(0.0)	1	(0.0)
Autoimmune disorder	0	(0.0)	1	(0.0)	1	(0.0)
Autoimmune haemolytic anaemia	0	(0.0)	1	(0.0)	1	(0.0)
Autoimmune hepatitis	0	(0.0)	4	(0.1)	4	(0.1)
Autoimmune pancreatitis	0	(0.0)	1	(0.0)	1	(0.0)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	1	(0.0)
Blood bilirubin increased	0	(0.0)	1	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	1	(0.0)	1	(0.0)
Cerebrovascular accident	0	(0.0)	1	(0.0)	1	(0.0)
Cognitive disorder	0	(0.0)	1	(0.0)	1	(0.0)
Colitis	0	(0.0)	14	(0.5)	15	(0.4)

Immunogenicity

According to the study protocol anti-pembrolizumab antibody (ADA) samples in study KN087 were collected at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug and 3 months after

discontinuation of study drug (or until the subject starts new anti-cancer therapy). In study KN013, ADA samples were drawn at pre-dose trough and post-dose peak at Cycles 1 and 2. Pre-dose samples only were collected at Cycle 4, Cycle 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug.

An integrated immunogenicity evaluation has been performed across data from studies KN001, KN002, KN006, KN010, KN012, KN013, KN024, KN052, KN055, KN087 and KN164. A total of 3268 subjects were assessed in this evaluation: 1535 melanoma subjects, 1237 NSCLC subjects, 101 HNSCC, 121 UC, 54 MSI-H and 220 HL subjects, and the immunogenicity status is presented in Table 5.

The overall immunogenicity incidence was defined as the proportion of treatment emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status). Out of 3268 subjects included in the immunogenicity assessment, 1619 subjects were evaluable. The observed incidence of treatment emergent ADA in evaluable subjects based on a pooled analysis of Melanoma, NSCLC, HNSCC, UC, MSI-H and HL subjects is 1.8% (29 out of 1619), based on 29 subjects with confirmed treatment emergent positive status, relative to all evaluable subjects including 29 with treatment emergent positive, 16 with non-treatment emergent positive and 1574 with negative immunogenicity status.

The subjects (N=29) with a treatment emergent immunogenicity response were evaluated for potential impact on exposure, safety and efficacy. Pembrolizumab exposure for these treatment emergent subjects were in the range of exposures observed for other subjects who were treated with pembrolizumab in the same regimen that only have ADA negative or ADA inconclusive samples. Therefore, exposure to pembrolizumab was not compromised by the observed immune response. The treatment emergent positive subjects did not have any adverse events associated with neutralizing antibodies, such as hypersensitivity events (e.g. anaphylaxis, urticaria, angioedema) or injection site reactions. No clinically significant impact on efficacy (i.e. tumour size change) was found.

Furthermore, the immunogenicity evaluation was stratified by treatments (2 mg/kg Q3W, 10 mg/kg Q3W, 10 mg/kg Q2W, or 200 mg) or indications (Melanoma, NSCLC, HNSCC, UC, MSI-H and HL subjects). The incidence of treatment emergent ADA was low (less than 2.8%) for all different stratifications used (dose levels or indication). In the subgroup of HL subjects, 1 out of 182 evaluable subjects (179 negative, 2 non-treatment emergent positive and 1 treatment emergent positive) had treatment emergent ADA yielding an incidence rate for treatment emergent antibodies of 0.5%.

The percentage of subjects with the final sample below the drug tolerance level of the ADA screening assay was determined (Table 5). At the dosing regimen of 2 mg/kg, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level for 80.6% of the subjects. At the dosing regimen of 200 mg fixed dose, 95.0% of the subjects had a pembrolizumab concentration in the last post-dose sample below the drug tolerance level. Among HL patients only, 38 out of 220 (17 %) subjects were inconclusive.

Post marketing experience

See PSUR.

2.5.1. Discussion on clinical safety

Results from the overall 241 patients treated in study KEYNOTE-013 (31 patients) and 210 patients KEYNOTE-087 have been presented to support the clinical safety of pembrolizumab in classical Hodgkin Lymphoma population. In parallel, safety data in the Reference Population (overall 2799 NSCLC and melanoma patients from studies KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), are discussed in order to allow a comparison with the already established pembrolizumab safety profile reported in the melanoma and NSCLC patients. Furthermore, safety data have been provided by comparison from the Cumulative Running Population in a total of 3475 patients, including, besides HL and Reference Populations, additional patients with different cancer types treated with pembrolizumab across the ongoing studies KEYNOTE-012 Cohort B and B2 (head and neck cancer), KEYNOTE-016 Cohort A (colorectal cancer), KEYNOTE-024 (NSCLC), and KEYNOTE-164 (colorectal carcinoma).

In line with the Hodgkin Lymphoma characteristic epidemiology, the population is overall younger compared to Reference and Current Cumulative Datasets, with a median age of 35 years vs 62 and 61, respectively.

An updated safety analysis with approximately 3 months of additional follow-up for KEYNOTE-087 (cutoff date 25 Sep 2016) and 3.8 months for KEYNOTE-013 (cutoff date 27 Sep 2016) has been provided. No major changes to the pembrolizumab safety profile in cHL population were reported.In terms of exposure to pembrolizumab, a longer median time on therapy was reported for HL patients compared to Reference Population and Cumulative Running Population (8.28 months vs 4.17 and 4.83 months), with a higher number of dose administered (13 vs 7 and 8). Overall, 70% of HL population (128 patients) were exposed to pembrolizumab for at least 6 months. However, long-term (≥12 months) safety profile is still based on limited data (26 patients in total).

Overall, no major differences are reported compared to the larger safety datasets, with even a lower frequency in HL patients for some AE categories, such as drug-related AEs, Grade ≥3 AEs, SAEs and discontinuation due to AEs. In general, the pembrolizumab safety profile was consistent with what previously reported and to that current cumulative. Indeed, with the exception of pyrexia, that is twice as frequent in HL population compared to reference safety dataset (24.1% vs 12.8%), the incidence of characteristic AEs is similar or even lower in HL population. In particular, *Diarrhea* (19.9%), *Fatigue* (19.9%), *Nausea* (14.9%), *Pruritus* (12.9 %), *Rash* (12 %) and *Arthralgia* (10.8%) were reported.

In terms of drug-related AEs, a higher rate was reported in HL patients for hypothyroidism (12.4% vs 7.6% and 7.9%, in the Reference and Cumulative Datasets respectively) and pyrexia (9.1% vs 4.5% and 5.2%, in the Reference and Cumulative Datasets respectively). However, the higher frequency of hypothyroidism could be justified by prior RT to the neck and/or mediastinum (in 36.9% of HL patients), while for pyrexia it should be taken into consideration that fever is part of the know B symptoms of Hodgkin Lymphoma.

The rate of SAEs was lower in HL patients compared to larger safety database (18.7% vs 37.2% in Reference dataset and 36.5% in Cumulative Running Dataset). SAEs by PT were consistent across population, with *Pneumonia*, *Pneumonitis* and *Pyrexia* most frequently reported (incidence ≥1%).

The incidence of AEOSI in the HL population has been reported as comparable to that in the Reference population and in the Cumulative dataset. *Hypothyroidism* was the most frequently observed AEOSI across populations. The higher rate of events in HL patients, as well as the shorter time to onset of first Hypothyroidism event, can be justified by the prior exposure to radiation therapy. A higher rate of *Infusion related reactions* was observed in HL population (8.3%) than in Reference Safety Dataset (2.5%) and Cumulative Running Safety Dataset (2.7%), though the majority of events did not require corticosteroid treatment.

Overall, 4 fatal cases occurred in HL patients, all in study KN087, two were related to AEs (1 Graft-versus-host

disease (GVHD) and 1 septic shock), and the remaining 2 patients died due to disease progression.

Hepatic veno-occlusive disease (VOD) and severe GVHD as complication of allogenic SCT, including fatal reports, were reported in patients previously treated with anti PD-1 agents.

Overall, 23 patients treated with pembrolizumab (10 in KN087 and 13 in KN013) received thereafter an allogenic SCT. In total, complications were experienced by 7 patients with 2 drug-related SAE of veno-occlusive disease, including 1 fatal case, and 6 reports of GvHD, including 1 fatal case.

Even though data on the feasibility of allogenic SCT after pembrolizumab are still limited, considering the immunomodulatory mechanism and the prolonged clinical activity possibly enhancing the allogeneic T-cell responses, it is agreed with the MAH that the increased risk of severe complications of allogeneic SCT is a new safety concern to be considered as an Important Potential Risk of pembrolizumab. A warning on the potential risk of severe complications from allogenic SCT in patients previously treated with pembrolizumab should be added in Section 4.4 and reported events should be listed in Section 4.8. The pembrolizumab contribution to the frequency and the nature of these events will be clarified by information on complications from allogenic SCT performed within 2 years of pembrolizumab last dose collected in the ongoing study KN-204, directly comparing pembrolizumab and brentuximab in rr-HL.

Changes in laboratory findings in HL population were in line with those reported in the larger dataset.

No major and unexpected differences in the tolerability of pembrolizumab treatment were observed across the different class of age, ECOG PS categories, and gender.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of pembrolizumab in HL population is in line with that reported in melanoma and NSCLC patients. The increased risk of severe complications of allogeneic SCT in previously treated pembrolizumab patients was a newly identified safety concern.

In order to further investigate the long-term safety in this population, in particular considering the recognized risk of exacerbating GVHD related to checkpoint inhibition, updated safety data will be provided.

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

- The final CSR of studies KN-087 and KN-013, also including long-term safety data should be provided post-approval.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 5.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

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

The CHMP endorsed the Risk Management Plan version 5.3 with the following content:

Safety concerns (updates marked in red italic)

Summary of safety concerns	
Important identified risks	- Immune-Related Adverse Reactions • Immune-related pneumonitis • Immune-related colitis • Immune-related hepatitis • Immune-related nephritis • Immune-related endocrinopathies o Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) o Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) o Type 1 diabetes mellitus • Other immune-related adverse reactions o Uveitis o Myositis o Pancreatitis o Severe Skin Reactions o Guillain-Barre Syndrome - Infusion-Related Reactions
Important potential risks	- Immune-Related Adverse Events • Gastrointestinal perforation secondary to colitis • *For haematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab* - Immunogenicity
Missing information	- Safety in patients with moderate or severe hepatic impairment - Safety in patients with severe renal impairment - Safety in patients with active systemic autoimmune disease - Safety in patients with HIV or Hepatitis B or Hepatitis C - Safety in pediatric patients - Reproductive and lactation data - Long term safety - Safety in various ethnic groups - Potential pharmacodynamic interaction with systemic immunosuppressants - Safety in patients with previous hypersensitivity to another monoclonal antibody - Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs

With the proposed extension of indication to cHL, one newly identified important potential risk has been added to the RMP concerning an increased risk of severe complications of allogenic stem cell transplantation (SCT) in patients who have previously received pembrolizumab.

Having considered the updated data in the safety specification, the safety concerns listed in the RMP by the MAH is considered appropriate.

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan (updates marked in red italic)

Activity / Study title (type of activity, study title, category)	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports**
Validation report for anti-MK-3475 neutralizing antibody assay (Category 3)	To validate the assay for the determination of neutralizing capacity of anti-MK-3475 antibodies and to report the results in an assay validation report.	-Important potential risk (Immunogenicity)	started	Final assay validation report September 2016
Clinical trial Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma (P001) (Category 3)	To evaluate and characterize the tolerability and safety profile of single agent MK 3475 in adult patients with unresectable advanced carcinoma (including NSCLC or MEL)	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*, Immunogenicity) -Long term safety	started	Final Study Report Dec 2016
Clinical trial Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma (P002) (Category 3)	To evaluate the progression-free-survival (PFS) in patients with ipilimumab refractory advanced MEL receiving either MK-3475 or chemotherapy	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*, Immunogenicity)	started	Final Study Report Jan 2017

Activity / Study title (type of activity, study title, category)	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
		-Long term safety		
Clinical trial A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to IPI in Patients with Advanced Melanoma (P006) (Category 3)	To evaluate progression-free-survival (PFS) in patients with advanced MEL receiving either MK-3475 or IPI	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*, Immunogenicity) -Long term safety	started	Final Study Report Jan 2017
Clinical trial A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (P010) (Category 3)	To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*, Immunogenicity) -Long term safety	started	Final Study Report Aug 2019
Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (P024) (Category 3)	To compare the Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central radiologists' review in subjects with PDL1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*, Immunogenicity) -Long term safety	started	Final Study Report Sep 2018
Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival	To compare the overall survival (OS) in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab	-Important identified risks (Immune-related adverse reactions, Infusion-related	started	Final Study Repost Dec 2019

Activity / Study title (type of activity, study title, category)	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (P042) (Category 3)	compared to standard of care (SOC) chemotherapies	reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*, Immunogenicity) -Long term safety		
Clinical trial *A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Haematologic Malignancies (P013) (Category 3)*	*To determine the safety and tolerability of pembrolizumab in subjects with relapsed/refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma, relapsed/refractory mediastinal large B cell lymphoma (MLBCL), and relapsed/refractory non-Hodgkin lymphoma (NHL), that have failed, are ineligible for, or refused a stem cell transplant.*	*-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)* *-Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For haematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; Immunogenicity)*	*started*	*Final Study Report* *Mar 2019*
Clinical trial *A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (P087) (Category 3)*	*To determine the safety and tolerability of pembrolizumab.*	*-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)* *-Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For haematologic*	*started*	*Final Study Report* *Aug 2021*

Activity / Study title (type of activity, study title, category)	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports
		malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; Immunogenicity)		
Clinical trial *A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (P204) (Category 3)*	*To compare PFS as assessed by blinded independent central review according to the IWG response criteria between treatment arms.*	*-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)* *-Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For haematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; Immunogenicity)*	*started*	*Final Study Report* *Apr 2021*
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 (P051) (Category 3)	To define the rate of dose-limiting toxicities (DLTs) at the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab when administered as monotherapy to children from 6 months to < 18 years of age pooled across all indications including advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumour or lymphoma.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- *GI perforation secondary to colitis*) -Safety in pediatric patients	started	Final Study Report July 2019

For the newly included safety concern regarding severe complications following allogenic SCT in patients who previously received pembrolizumab, the MAH proposes to monitor the risk in the ongoing Hodgkin Lymphoma trials P013, P087 and P204, which is considered acceptable.

The proposed post-authorisation PhV plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Summary table of Risk Minimisation Measures, update marked in red italic

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Immune-related pneumonitis	SmPC section 4.2, 4.4, 4.8	Educational materials
Immune-related colitis	SmPC section 4.2, 4.4, 4.8	Educational materials
Immune-related hepatitis	SmPC section 4.2, 4.4, 4.8	Educational materials
Immune-related nephritis	SmPC section 4.2, 4.4, 4.8	Educational materials
Immune-related endocrinopathies -Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis) - Type 1 Diabetes Mellitus	SmPC section 4.2, 4.4, 4.8	Educational materials
Other immune-related adverse reactions: o Uveitis o Myositis o Pancreatitis o Severe Skin Reactions o Guillain-Barre Syndrome	SmPC section 4.4, 4.8	Educational materials
Infusion-related reactions	SmPC section 4.2, 4.4, 4.8	Educational materials
Important Potential Risks		
Immune-related adverse events: Gastrointestinal perforation secondary to colitis	SmPC section 4.4, 4.8	None
Immune-related adverse events: For Haematologic malignancies: increased risk of severe	*For Haematologic malignancies: the increased risk of severe complications of allogeneic SCT in*	*Educational materials*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
complications of allogenic SCT in patients who have previously received pembrolizumab	*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.*	
Immunogenicity	SmPC section 4.8	None
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	SmPC section 4.2, 4.4	None
Safety in patients with active systemic autoimmune disease	SmPC section 4.4, 5.1	None
Safety in patients with HIV or Hepatitis B or Hepatitis C	SmPC section 4.4, 5.1	None
Safety in Paediatric patients	SmPC section 4.2	None
Reproductive and lactation data	SmPC section 4.6, 5.3	None
Long term safety	None	None
Safety in various ethnic groups	None	None
Potential pharmacodynamic interaction with systemic immunosuppressants	SmPC section 4.4, 4.5	None
Safety in patients with previous hypersensitivity to another monoclonal antibody	SmPC section 4.4, 5.1	None
Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs	SmPC section 4.4, 5.1	None

For the newly included safety concern regarding severe complications following allogenic SCT in patients who previously received pembrolizumab, the MAH proposes to introduce educational material as additional risk minimisation measures- which is considered acceptable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to complications of allogeneic stem cell transplant in cHL has been added

to the product information section 4.4. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Classical Hodgkin lymphoma (cHL) is a B cell lymphoma with distinct clinic and biologic features; it accounts for approximately 10% of all lymphomas and 0.6% of all cancers. The incidence in Europe is approximately 2.4 cases per 100.000 persons, and presents a characteristic bimodal age distribution curve, with one peak in young adults (median age of onset 20 years) and one in older adults (median age of onset 65 years). Overall, the majority of patients are young adults, with a slightly higher prevalence in males. However, the actual incidence pattern is known to vary according to race and region.

From a histological point of view, cHL is characterised by the presence of the pathognomonic Reed-Sternberg (RS) cells in the context of a mixed inflammatory background. Programmed death 1 (PD-1) ligands, PD-L1 and PD-L2, frequently responsible of cancer cell evasion of immune surveillance, have been shown to be over-expressed by Reed-Sternberg cells.

cHL is usually characterized by a high sensitivity to chemotherapy and considered a highly curable lymphoproliferative disease. However and despite aggressive treatment plans, also including salvage and consolidation therapy, approximately 50% of the patients with relapsed/refractory disease will not achieve long-term disease control.

3.1.2. Available therapies and unmet medical need

Choice of treatment in cHL is based on disease stage and the presence/absence of known risk factors. Most patients are able to attain disease remission with upfront combination chemotherapy (e.g. ABVD, BEACOPP or STANFORD-V regimens) ± involved-field radiation therapy. However, 10 to 40% of patients will experience relapse or will be refractory to the initial therapy. Salvage therapy, currently based on non cross-resistant chemotherapy regimens (i.e. DHAP, IGeV, GemOX, ICE etc.), can obtain responses in approximately 50% of relapsed/refractory (r/r) patients. Unfortunately, at this stage, long-term disease control following conventional therapy alone is uncommon and further consolidation is needed. Fit patients are usually candidate to high dose chemotherapy followed by autologous haematopoietic cell transplantation (ASCT). The long-term prognosis of patients not eligible ASCT, or who have failed ASCT, is poor, with a three-year OS of approximately 30%. Brentuximab vedotin (BV), a CD30-directed antibody linked to an anti-tubulin agent (MMAE), is currently approved for the treatment of adult patients with r/r cHL following ASCT, or at least two prior therapies when ASCT is not a treatment option. Prognosis after failure of BV is poor. A selected subset of patients might be eligible to allogeneic haematopoietic stem cell transplant (allo-HSCT), which might still result in long-term remission. However, transplant-related mortality and toxicity is not negligible. Other treatment options (i.e.

lenalidomide, everolimus etc.) should still be considered experimental and do not appear to be associated with long-term clinical benefit.

A clear unmet medical need is therefore evident for relapsed or refractory cHL patients who have failed both ASCT and BV. Programmed death 1 (PD-1) ligands, have been shown to be over-expressed in cHL, making PD-1 an attractive target. In this regard, the CHMP has recently granted a positive opinion for nivolumab, an anti-PD-1 monoclonal antibody, for the treatment of adult patients with r/r cHL after ASCT and treatment with BV.

3.1.3. Main clinical studies

Pivotal trial KEYNOTE-087 is a multi-center, single-arm, multi-cohort, non-randomized Phase 2 trial investigating pembrolizumab (200mg Q3W) efficacy (primary endpoint ORR) and safety in 210 patients with r/r cHL who were: refractory to /relapsed after ASCT and BV received after transplantation (Cohort 1); refractory to salvage chemotherapy, ASCT naïve, refractory to /relapsed after BV (Cohort 2); refractory to/relapsed after ASCT, naïve to BV post-transplantation but who could have received BV as part of primary treatment, or salvage treatment (Cohort 3).

Supportive study KEYNOTE-013 is a multicenter, multi-cohort phase 1b trial to determine the safety and efficacy of pembrolizumab (10 mg/kg Q2W) in subjects with haematological malignancies. Efficacy (primary endpoint CRR) and safety data come from Cohort 3 (n=31) which included subjects with r/r nodular sclerosing or mixed cellularity cHL that had failed, were ineligible for, or refused ASCT and had relapsed after treatment with (or failed to respond to) BV.

3.2. Favourable effects

In pivotal study (KEYNOTE-087), the ORR per BICR in the ASaT population (primary endpoint) at the time of the latest data cut-off date was 69% (145/210; 95% CI: 62.3%, 75.2%), and CRR 22.4% (47/210, 95% CI 16.9%, 28.6%).

ORRs by central review were 73.9%, 64.2% and 70% and CRRs were 21.7%, 24.7% and 20% in Cohorts 1, 2 and 3 respectively.

An ORR ranging between 65% and 70% was observed in patients already exposed to BV with few or none recognized alternatives (i.e. patients in Cohorts 1 and 2). With a 10.1 months median follow-up median DOR and PFS in the ASaT population by BICR were 11.1 and 11.3 months, respectively). By Kaplan-Meier estimation, 6-month DOR and 6-month PFS rates were 75.6% and 72.4 %, respectively. PFS and DOR results across the 3 Cohorts were also consistent with those observed in the overall ASaT population.

In study KEYNOTE-013 ORR according to BICR was 58% (18/31). CRR by BICR (19.4%) was similar to that observed in the pivotal study. With a significantly longer follow-up of 28.7 months compared to the pivotal trial, median DOR was not reached (95% CI 3.7 months, NR), 7 patients out of 18 responders had a response duration of at least 12 months, median PFS per BICR was 11.4 months and the 12-month PFS rate was 48.2%.

3.3. Uncertainties and limitations about favourable effects

Pivotal study KEYNOTE-087 was a single-arm, uncontrolled study. While for Cohorts 1 and 2 the absence of an adequate comparator can be justified by the lack of standard alternatives for r/r cHL patients who have failed both ASCT and BV, this is not applicable to Cohort 3, in which 60% of patients were BV naïve. Therefore an

indication on BV naïve patients cannot be supported as the clinical relevance in this case is questionable; the proposed indication was revised not to include this patient population. A phase 3 study KEYNOTE-204 comparing pembrolizumab and BV in rr cHL patients is at present ongoing (see RMP).

The indication also includes patients ineligible to ASCT due reasons other than chemoresistance. Apart from chemoresistance, transplant ineligibility is usually determined by age and comorbidities. In this regard, only 18 patients were aged ≥ 65 years in pivotal study KN-087 and the activity of pembrolizumab in this subpopulation (ORR 50%) seems to be somehow reduced compared to younger subjects (ORR 71%). Similarly, with all the limits of looking at performance status as a surrogate measure of comorbidity, median DOR and PFS appear to be slightly reduced in patients with ECOG score ≥1 vs. ECOG score 0. However, although only 5 patients not eligible to ASCT due to reasons other than chemo-refractoriness to salvage therapy received pembrolizumab in pivotal study KN-087 (unplanned protocol deviations), the results observed in this small subset are nonetheless encouraging (2 CR, 1 PR). Further, the high unmet need and the absence of effective alternatives for patients with r/r cHL who have failed BV and are ineligible to ASCT due to reasons other than failure of salvage chemotherapy are acknowledged. Therefore, also in light of the overall favourable toxicity profile of pembrolizumab, the indication is considered appropriate.

The provided PFS analysis is largely immature, with 70 out of 210 patients having experienced an event . OS data from both studies KEYNOTE-087 and KEYNOTE-013 is also immature. At the time of the most recent data cut-off date, the median follow-up in study KEYNOTE-087 was 10.1 months. In order to fully capture long-term clinical benefit with pembrolizumab the MAH will submit the final CSRs from these studies (See Annex II and RMP).

Information on other planned secondary/exploratory endpoints and in particular, data regarding response rates by BICR using the 5-point scale according to the Lugano Classification and the analyses investigating the relationship between biomarkers and response to pembrolizumab will only be available in the final CSR for study KN-087 (See Annex II and RMP).

3.4. Unfavourable effects

Drug-related AEs were reported in 65.6% of HL patients across study KN087 and KN013, with drug-related Grade ≥3 AEs affecting 10% of them.

The most commonly observed drug-related AEs were *Hypothyroidism* (10.8%), *Pyrexia* (9.5%), *Diarrhea* (8.3%), *Fatigue* (7.1%) and *Nausea* (6.6%).

Grade ≥3 drug-related AEs were mainly observed in SOCs *Blood and lymphatic system disorders* (2.1%), *Musculoskeletal and connective tissue disorders* (2.1%), *Gastrointestinal disorders* (1.7%) and *Infections and infestations* (1.7%).

The incidence of serious drug-related AEs was 5.4%, with pneumonitis as the most frequently occurred (1.7%). Among AEOSI, *Hypothyroidism* was reported at the higher frequency, affecting 12.9% of patients, with the event considered not resolved in 5.8% of them.

Complications to allogenic HSCT (i.e, VOD and GVHD) were experienced in 3 of the 17 pembrolizumab treated patients who receive transplantation after progression, and a fatal outcome was reported in 2 of them. All Adverse drug reactions and revised frequencies of already reported ones are reflected in the SmPC section 4.8. A new warning was added under section 4.4 of the SmPC on complications of allogeneic haematopoietic stem cell transplantation (allo-HSCT) after pembrolizumab. Patients should be followed closely for early evidence of transplant-related complications, such as hyperacute graft-versus-host-disease (GVHD), severe (grade 3 to 4)

acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions (See SmPC and RMP).

3.5. Uncertainties and limitations about unfavourable effects

Overall, 70% of HL population (128 patients) were exposed to pembrolizumab for at least 6 months. However, long-term (≥12 months) safety profile is still based on limited data (26 patients in total). The final CSRs from studies 087 and 013 will provide additional data on long term safety (See Annex II and RMP).

Data on the feasibility of allogenic HSCT after pembrolizumab are still limited. The safety of allogeneic HSCT after pembrolizumab therapy will be further studied in KEYNOTE 204 (see RMP).

3.6. Effects Table

Table: Effects Table for Keytruda in the treatment of classical Hodgkin Lymphoma (cHL) in adults who have refractory disease, or who have relapsed after greater than or equal to 3 prior lines of therapy (KN087 data cut-off: 25 SEP2016; KN013 data cut-off: 27 SEP 2016)

Effect	Short Description	Unit	Pembrolizumab 200 mg Q3W	Uncertainties / Strength of evidence	References
Favourable Effects					
ORR	CR+PR rate by BICR (25/09/2016 data cut-off date)	% (95% CI)	69% (62.3, 75.2)	High consistency of results across subgroups and cohorts in the pivotal study. Clinically meaningful results in patients who have failed both ASCT and BV. Results overall consistent between the pivotal and the supportive study. Differences in patient population and small sample size hamper the generalizability of the results from KEYNOTE-013	(1)
			58.1% (39.1, 75.5)		(2)
CRR	CR rate by BICR	% (95% CI)	21.9% (16.5, 28.1)		(1)
			22.4% (16.9, 28.6)		(1)
			19.4% (7.5, 37.5)		(2)
DOR	Duration of CR/PR until documented PD	months (95% CI)	11.1 (8.7, 11.1)	Results are still immature.	(1)
			NR (3.7, NR)		(2)
PFS	duration of survival without progression from randomization to PD or death whichever	months (95% CI)	11.3 (10.8, NR)	PFS still immature (only 25 out of 210 subjects had an event at the time of data cutoff).	(1)

Effect	Short Description	Unit	Pembrolizumab 200 mg Q3W	Uncertainties / Strength of evidence	References
	occurred first		11.4 (4.9, 27.8)	PFS in the supportive study is mature (24.9 months). Sample size is limited (n=31).	(2)
OS	duration of survival from randomization to death regardless of cause	months (95% CI)	NR (NR, NR)	Results are still not mature in both studies	(1), (2)
Unfavourable Effects					
Tolerability	drug related AEs	%	68.5	Pembrolizumab safety profile is in line with that reported in the reference melanoma and NSCLC population.	(3)
	drug related Gr≥3 AE	%	12.0		
	drug related SAEs	%	6.2		
	death drug related	%	0.0		
	discontinuation drug related AEs	%	5.0		
	discontinuation drug related SAEs	%	2.5		
Drug-related AEs	Incidence of Hypothyroidism	%	12.4		
	Incidence of Pyrexia		9.1		
	Incidence of Fatigue	%	9.1		
	Incidence of Diarrhoea	%	8.7		
	Incidence of Rash	%	6.6		
	Incidence of Nausea	%	6.6		
	Incidence of Pneumonitis	%	4.1		
	Incidence of Arthralgia	%	4.6		
	Incidence of Pruritus	%	3.7		

(1) KEYNOTE-087 CSR; (2) KEYNOTE-013 CSR; (3) Pooled data from KN087 and KN013.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The overall ORR ranging between 64% and 73.9% observed across studies in heavily pretreated subjects is considered clinically meaningful. A high degree of inter internal consistency in response rates was observed across all cohorts and subgroups of study KEYNOTE-087 whereas the responses durable, even in this advanced setting of disease. In this regard, the 24.7% CRR observed in Cohort 2 (i.e. patients ineligible to ASCT) is considered of particular clinical relevance: since CR before transplant is known to affect both DFS and OS post ASCT (see e.g. Sureda A. et al., JCO 2001), transplant eligibility is dependent on the possibility to achieve pre-transplant remission. Achieving CR with pembrolizumab aims to restore transplant eligibility (with all the significant implications on long-term disease control) to those patients with persistent disease after failure of salvage therapy and BV. The efficacy of pembrolizumab is not influenced by disease status (relapsed, refractory or primary refractory), number of prior treatments or time since transplant failure. Of note, an analysis conducted in 36 primary refractory subjects (i.e. patients refractory to first line therapy who never achieved a response to subsequent therapies) showed an ORR based on IWG criteria by BICR of 80.6% (29/36; 95% CI:

64.0%, 91.8%), with a 25% CRR (9/36; 95% CI: 12.1%, 42.2%). Results from the supportive study KEYNOTE-013 were overall consistent with those observed in the pivotal study.

Time-to-event data from the supportive study (with a significantly longer follow-up of 28.7 months) confirm that responses with pembrolizumab are durable, and overall the results were consistent with DOR data and PFS data from the pivotal study. Although overall favourable, results in terms of time-to-event endpoints are difficult to put into context in the framework of an uncontrolled study with a limited median follow-up to fully capture long-term clinical benefit in terms of PFS and OS.

Overall, 70% of HL population (169 patients) were exposed to pembrolizumab for at least 6 months, while safety data with treatment exposure ≥12 months are only available for 26 patients. No major differences are reported compared to the larger safety datasets. The safety profile was consistent with what previously reported. Drug-related AEs were mainly Grade 1-2 in severity.

The higher rate of events in HL patients, as well as the shorter time to onset of first Hypothyroidism event, can be justified by the prior exposure to radiation therapy. A higher rate of Infusion related reactions was observed in HL population (8.3%) than in Reference Safety Dataset (2.5%) and Cumulative Running Safety Dataset (2.7%), though the majority of events did not require corticosteroid treatment.

Complication from allogenic HSCT (including fatal cases) in patients previously treated with pembrolizumab was reported as a newly identified safety concern to be considered as an Important Potential Risk of pembrolizumab. The contribution of pembrolizumab to the frequency and the nature of these events will be clarified by information on complications from allogenic SCT performed within 2 years of pembrolizumab last dose collected in the ongoing study KN-204, directly comparing pembrolizumab and brentuximab in rr-HL.

3.7.2. Balance of benefits and risks

The overall ORR observed across studies in heavily pretreated subjects is considered clinically meaningful. In particular, in patients already exposed to BV with few or none recognized alternatives (i.e. patients in Cohorts 1 and 2) the lack of a comparative arm is acceptable, the reported ORR, ROR and PFS are deemed meaningful. Further, since CR is a key factor for transplant eligibility, the observed CRR in cohort 2 is regarded as potential added value.

Overall, pembrolizumab safety profile was consistent with that previously reported in the larger safety datasets, with even a lower frequency in HL patients for some AE categories.

A warning in Section 4.4 has been added and information on potential complications of allogenic Haematopoietic Stem Cell Transplantation (HSCT) will be included in the Educational Material. The contribution of pembrolizumab to the frequency and the nature of these events will be clarified by information on complications from allogenic SCT performed within 2 years of pembrolizumab last dose collected in the ongoing study KN-204, directly comparing pembrolizumab and brentuximab in rr-HL.

The final CSR of PAES studies KN-087 and KN-013, and randomised PAES study KN-204 - also including long-term safety data will be provided post-approval.

3.7.3. Additional considerations on the benefit-risk balance

There is a need to investigate the long term efficacy of pembrolizumab discontinuation due to maintained CR and relevant strategies will be proposed by the MAH. Additional information about the long term efficacy of

pembrolizumab in CR subjects (including subjects who have discontinued pembrolizumab) will be included in the final CSRs for KEYNOTE-087 and KEYNOTE-204 -both PAES (as stated in the RMP and Annex II).

Efficacy in subjects who have transplantation following treatment with pembrolizumab will also be further investigated and additional data will be provided with the CSR for the PAES KEYNOTE-204 (see Annex II and RMP). Subjects in both treatments arms who achieve CR or PR and discontinue study treatment to receive SCT will continue to be followed in the trial. Disease assessments will be conducted every 12 week until disease progression.

3.8. Conclusions

The overall Benefit /Risk of Keytruda, as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV - is positive.

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

- Submission of the final CSR from the Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Haematologic Malignancies KEYNOTE – 013.
- Submission of the final CSR from the Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) KEYNOTE 087
- Submission of the results from a Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma KEYNOTE 204.

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 Indication to include monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV, based on the results from study KEYNOTE-087, an open-label Phase II trial of pembrolizumab in subjects with relapsed or refractory cHL and study KEYNOTE-013, a Phase Ib multi-cohort trial of pembrolizumab in subjects with haematologic malignancies. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. Annex II has been updated to include changes to the 'additional risk minimisation measures' and the 'obligation

to conduct post-authorisation measures'. An updated RMP version 5.3 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following new and/or amended conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Additional risk minimisation measures**

For the newly included safety concern regarding severe complications following allogenic SCT in patients who previously received pembrolizumab, the following additional risk minimisation measure has been introduced:

-The below key element has been added to the healthcare professional FAQ Brochure:
Potential risk of "Severe complications of allogeneic stem cell transplant in patients who have previously received pembrolizumab for haematologic malignancies"

-The below key element has been added to the patient information brochure and patient alert card:
Information that patients treated with pembrolizumab who then go on to stem cell transplant that uses donor cells (allogenic) can experience transplant complications, that can be severe and can lead to death, and that their doctor will monitor them for these complications. These patients should inform their transplant physicians that they have received pembrolizumab in the past.

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

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

Description	Due date
Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P087, A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) – Final Study Report	3Q 2021
Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P013, A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Haematologic Malignancies – Final Study Report	1Q 2019
Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P204: A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma – Final Study Report	2Q 2021

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. See appendix 1