EMA/CHMP/424195/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0071

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	04 Mar 2019	04 Mar 2018	☐
☐	CHMP Rapporteur Assessment Report	08 Apr 2019	8 Apr 2019	☐
☐	CHMP members comments	23 Apr 2019	23 Apr 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	25 Apr 2019	26 Apr 2019	☐
☐	Start of written procedure	30 Apr 2019	30 Apr 2019	☐
☐	Request for supplementary information	02 May 2019	02 May 2019	☐
	Submission of MAH's responses	28 May 2019	28 May 2019	
☐	Re-start of procedure:	29 May 2019	29 May 2019	☐
☐	CHMP Rapporteur Assessment Report	12 Jun 2019	12 Jun 2019	☐
☐	CHMP members comments	17 Jun 2019	17 Jun 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Jun 2019	n/a	☐
☐	Start of written procedure	25 Jun 2019	n/a	☐
☐	Opinion	27 Jun 2019	27 Jun 2019	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 8 February 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

To update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study KEYNOTE-051; this is an ongoing Phase I/II, single-arm study to evaluate the PK, pharmacodynamics, toxicity, safety, and anti-tumour activity of pembrolizumab in paediatric participants (Measure 2 of PIP01). Additionally, the results of study Study PD018 / PA-0064; evaluation of expression of PD-1, PD-L1, and PD-L2 in archival paediatric tumour tissues, were submitted (Measure 1 of PIP01).

The requested variation proposed amendments to the Summary of Product Characteristics.

2. Overall conclusion and impact on the benefit/risk balance

The purpose of this submission is to fulfil the regulatory requirement to submit the results of all studies performed in compliance with the agreed Paediatric Investigation Plan for pembrolizumab.

The MAH presented the results (cut-off date 03-Sep-2018) of the ongoing phase 1/2 study KEYNOTE-051 of pembrolizumab in paediatric patients aged 6 months-18 years with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma. Overall, 154 paediatric patients were treated with pembrolizumab 2 mg Q3W, which has been established as the recommended paediatric dosage. Observed PK concentrations in paediatric patients administered with 2 mg/kg Q3W were within the range of predicted concentration for adults administered with the same dose with 2 mg/kg Q3W.

Based on KEYNOTE-051 results, antitumor activity was minimal in patients with PD-L1 positive paediatric solid tumours and other lymphomas. ORR in the 136 patients with solid tumour and other lymphoma was only 5.9%, and enrolment was stopped for most solid tumours. Moreover, no PD-L1 negative cohorts were enrolled as per futility rules; therefore, analysis of association of PD-L1 status with response was not warranted.

A 50% ORR was on the contrary observed among patients with Hodgkin's lymphoma, for which the MAH is planning a future extension of indication. The cohort of HL is still open. Moreover, the MAH informed that data on MSI-h population will be reported separately.

No new safety signals emerged. Based on comparative safety tables of paediatric (KN-051) vs adult patients (RSD), the safety of paediatric patients appeared generally similar to that seen in adults according to available data. SmPC has been re-worded by the MAH accordingly. No paediatric therapeutic indication is proposed at this stage, but only SmPC has been updated to reflect the results of study KEYNOTE-051.

The changes to the SmPC are acceptable.

The benefit-risk balance of Keytruda remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

To update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study KEYNOTE-051; this is an ongoing Phase I/II, single-arm study to evaluate the PK, pharmacodynamics, toxicity, safety, and anti-tumour activity of pembrolizumab in paediatric participants (Measure 2 of PIP01). Additionally, the results of study Study PD018 / PA-0064; evaluation of expression of PD-1, PD-L1, and PD-L2 in archival paediatric tumour tissues, were submitted (Measure 1 of PIP01).

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

In KEYNOTE-051, 154 paediatric patients were administered pembrolizumab 2 mg/kg every 3 weeks. Pembrolizumab concentrations in these patients were comparable to those of adults at the same dose. Participants were enrolled across 28 tumour types by primary diagnosis. The most common tumour types by histology were Hodgkin lymphoma (11.7%), glioblastoma multiforme (9.1%), neuroblastoma (6.5%), osteosarcoma (6.5%) and melanoma (5.2%). In patients with solid tumours and other lymphomas, the ORR was 5.9%, no patient had a complete response and 8 patients (5.9%) had a partial response. In the Hodgkin lymphoma population, the ORR was 50.0%, 2 patients (11.1%) had a complete response and 7 patients (38.9%) had a partial response. The safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia (31%), vomiting (26%), headache (22%), abdominal pain (21%), anaemia (21%) and constipation (20%).

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The purpose of this submission is to fulfil the regulatory requirement to submit the results of all studies performed in compliance with the agreed Paediatric Investigation Plan for pembrolizumab (EMEA-001474-PIP01-13-M01 for treatment of all conditions included in the category of malignant neoplasms [except nervous system, haematopoietic and lymphoid tissue]) by the time of the submission of the next indication for KEYTRUDA following the PIP completion due date (31 January 2019), as per Article 8 of the Paediatric Regulation (EC) No 1901/2006.

This submission is not intended to fulfill Article 46 requirement since KN-051 is not fully completed (some cohorts including the HL cohort still open).

The results of the following studies have been provided:

- **Study PD018 / PA-0064** - Evaluation of expression of PD-1, PD-L1, and PD-L2 in archival paediatric tumor tissues (Measure 1 of PIP01)

- **KEYNOTE-051** - ongoing, two-part Phase I/II, nonrandomized, open-label, single-arm, study to evaluate the PK, pharmacodynamics, toxicity, safety, and anti-tumour activity of pembrolizumab in paediatric participants aged 6 months to <18 years of age with advanced melanoma; advanced, relapsed or refractory PD-L1 positive malignant solid tumours or other lymphoma; Hodgkin Lymphoma (3 to <18 years of age); or advanced, relapsed or refractory MSI-H solid tumours (Measure 2 of PIP01).

The MAH is requesting to update the PI (sections 4.2, 4.8, 5.1 and 5.2) of Keytruda with paediatric data from the study KEYNOTE-051. No pediatric therapeutic indication is proposed at this stage.

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

Pharmacokinetic Analysis

The Objective of PK report 052DCX was to evaluate serum concentrations of pembrolizumab in pediatric patients with an advanced solid tumor or lymphoma following administration of multiple I.V. doses of 2 mg/kg Q3W in KN051 (KEYNOTE-051). KEYNOTE-051 is an ongoing, 2-part Phase 1/2, nonrandomized, open-label, single-arm, study to evaluate the PK, pharmacodynamics, toxicity, safety, and antitumor activity of pembrolizumab in pediatric participants aged 6 months to <18 years of age with advanced melanoma; advanced, relapsed or refractory PD-L1 positive malignant solid tumors or other lymphoma; HL (3 to <18 years of age); or advanced, relapsed or refractory MSI-H solid tumors. The starting pembrolizumab dose and frequency was 2 mg/kg Q3W.

Overview of Pembrolizumab Cancer types Included in KN051 PK Analysis

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

[a] Number of unique subject numbers in dataset

Nos: Not otherwise specified
Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

In total, there were 151 participants with evaluable PK samples.

PK samples in KN051 were scheduled as follow: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 8 and every 4 cycles (12 weeks) thereafter. Postdose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1 and Cycle 8. Additional PK samples were drawn in Cycle 1 between 72 to 168 hours (4-8 days) postdose and at 264 to 408 hours (12-18 days) postdose.

Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.

Immunogenicity Analysis

An immunogenicity evaluation has been performed using data from study KN051. The objective of the immunogenicity report 052J8M was: 1) to evaluate the immunogenicity incidence in children treated with 2 mg/kg Q3W pembrolizumab (MK-3475) in study KN051, which is a Phase I/II clinical trial of pembrolizumab in children and 2) to compare the immunogenicity incidence after pembrolizumab therapy in children with the immunogenicity incidence after pembrolizumab therapy in adults.

6.1. Results

Pharmacokinetics

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations i pediatric subjects from KN051 are presented in the table below:

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

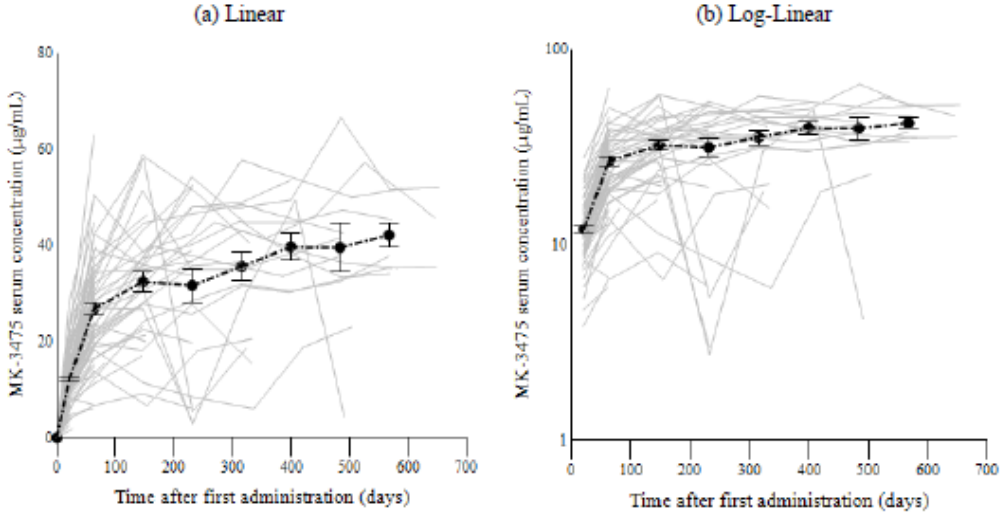
Cycle	NOMTAFD day	N	GM (%CV)	GM (SD)	AM (SD) (µg/mL)	Min	Median	Max
Predose (C_{trough})								
Cycle 2 (Week 3)	21	123	11.1 (47)	11.1 (5)	12.1 (5)	1.84	11.6	28.1
Cycle 4 (Week 9)	63	64	24.5 (48)	24.5 (11)	26.8 (11)	6.05	26.5	63.0
Cycle 8 (Week 21)	147	36	29.5 (52)	29.5 (13)	32.4 (13)	6.62	32.9	58.7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

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

Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

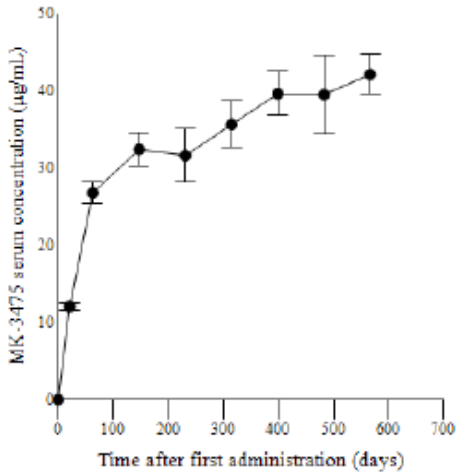
The following figures show the individual and mean predose concentration-time profiles:

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



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

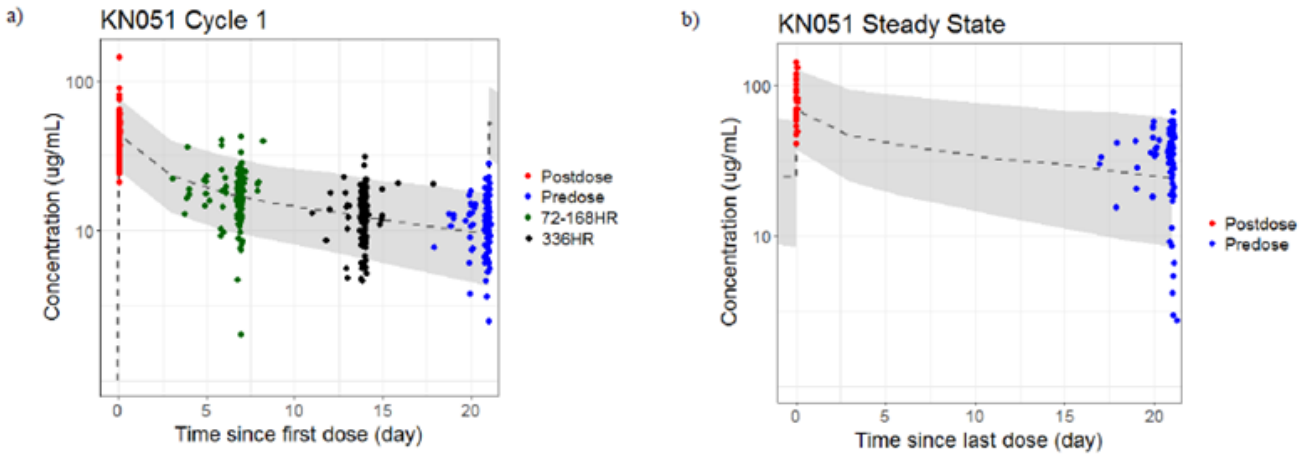
Arithmetic Mean (SE) Pembrolizumab Predose Concentration -Time Profiles Following Multiple I.V. Doses of 2 mg/kg Q3W to Subjects in Study KN051 (Linear scale)



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

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

Observed Concentration Data in KN051 Subjects Receiving 2 mg/kg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 2 mg/kg Q3W Dose Regimen



a) After 1st dose on log scale; b) At and after cycle 8 (21 weeks) on log scale. Symbols are individual observed data (actual time) from subjects in KN051; black dashed line is median predicted concentrations from the model for a regimen of 2 mg/kg Q3W and the grey shaded area represents the 90% prediction interval.
Data Source: [052DCX: analysis-p051pkdm0pip2018v3]

Immunogenicity

The table below presents an overview of the immunogenicity status of all assessable subjects.

To evaluate immunogenicity, the overall immunogenicity was defined as the proportion of emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

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

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

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

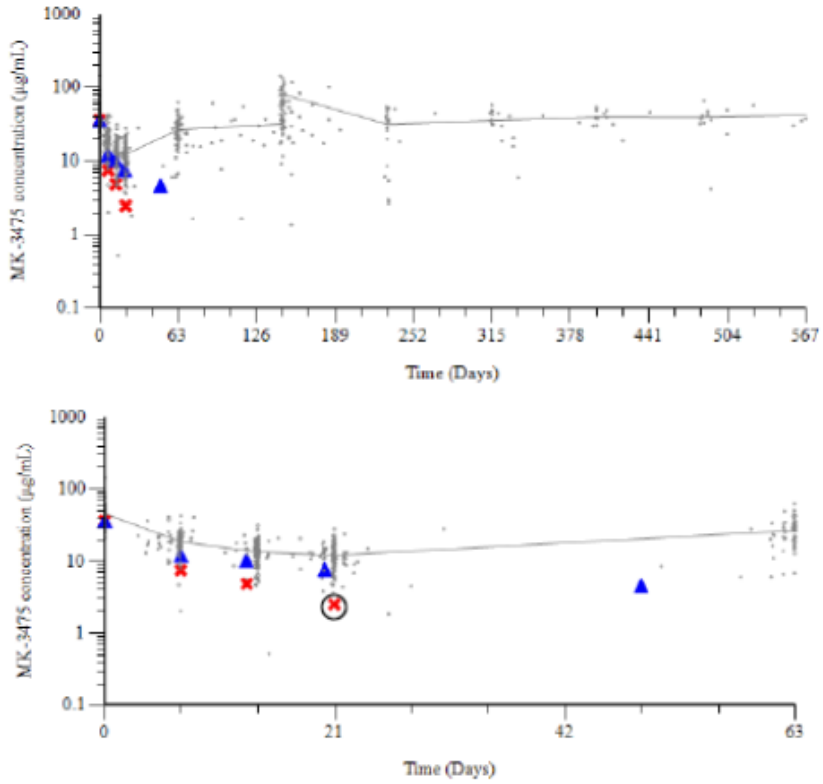
Data source [052J8M: analysis-p051pkada0pip2018v4]

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

Impact of ADA on Pembrolizumab Exposure

The effect of ADA on pembrolizumab levels, for the subjects with ADA positive samples, is compared with the subjects treated with the same regimen that only have ADA negative samples.

Effect of ADA on Pembrolizumab Exposure, for the non-Treatment Emergent Positive Subjects treated with 2 mg/kg Q3W (KN051)



Footnote: Individual pembrolizumab for the non-treatment emergent positive subjects [redacted] (red cross), [redacted] (blue triangle), other subjects (grey symbol o) and mean value (grey line -). Both positive subjects have a predose sample that is ADA positive. [redacted] also has an ADA positive post-treatment sample (day 21), this is indicated by a black circle around the PK sample. Figure includes pre- and post-treatment samples. Last ADA sample for [redacted] is taken 21 days after the first treatment. The last ADA sample for AN [redacted] is taken 49 days after the first treatment (is 29 days after the last treatment).
Data source [p051pkada0pip2018v4] and [p051pkdm0pip2018v3]

For all of the ADA positive subjects, the pembrolizumab exposure was similar to that for other subjects treated with the same regimen.

6.1. Discussion

The purpose of this submission is to fulfil the regulatory requirement to submit the results of all studies performed in compliance with the agreed Paediatric Investigation Plan for pembrolizumab and no pediatric therapeutic indication is proposed at this stage while SmPC section 4.8, 5.1 and 5.2 have been updated to reflect the results of study KEYNOTE-051.

A substantial characterization of the key clinical pharmacology and immunogenicity findings of pembrolizumab as monotherapy in adults has been provided in previous submissions.

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

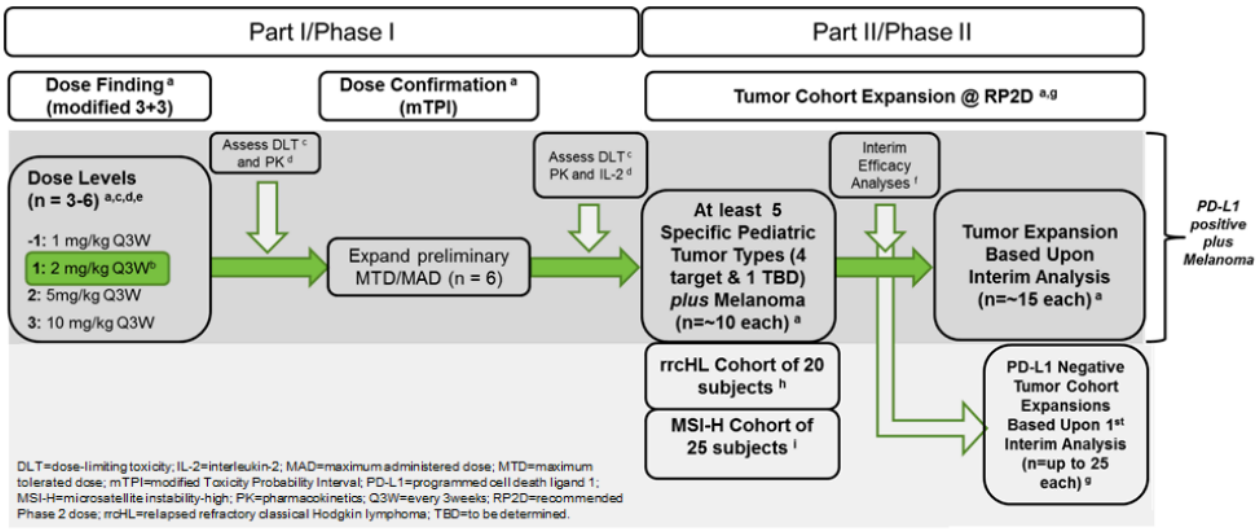
Observed PK concentrations in pediatric patients administered with 2 mg/kg Q3W were within the range of predicted concentration for adults administered with the same dose with 2 mg/kg Q3W.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

KEYNOTE-051 is a 2-part Phase 1/2, nonrandomized, open-label, single-arm, study to evaluate the PK, pharmacodynamics, toxicity, safety, and antitumor activity of pembrolizumab in pediatric participants aged 6 months to <18 years of age with advanced melanoma; advanced, relapsed or refractory PD-L1 positive malignant solid tumors or other lymphoma; HL (3 to <18 years of age); or advanced, relapsed or refractory MSI-H solid tumors. The starting pembrolizumab dose and frequency was 2 mg/kg Q3W.

Figure: trial diagram



a. Pediatric participants with melanoma or PD-L1 positive advanced relapsed or refractory solid tumor or lymphoma aged between 6 months and less than 18 years. Ten participants were to be enrolled into 4 target tumor cohorts (neuroblastoma, osteosarcoma, Ewing sarcoma/peripheral primitive neuroectodermal tumor (PNET), and glioblastoma). One additional tumor cohort from among any of the other solid tumor indications was to enroll at least 5 participants.
b. The starting dose level was 2 mg/kg Q3W (Dose Level 1).
c. **De-escalation** decisions were informed by DLT according to modified 3 +3 and mTPI approaches (ie, dose-limiting toxicities resulted in de-escalation of the dose according to a 3 + 3/mTPI design); if the starting dose was found to be generally safe and well-tolerated, dose escalation would only occur based on PK and/or pharmacodynamic results.
d. **Escalation** decisions were informed by assessment of PK and/or pharmacodynamics (ie, dose escalation to a maximum of 10 mg/kg every 2 weeks [Q2W] would occur if PK at the starting dose was <50% of adult value, and/or pharmacodynamics [IL-2 stimulation] was unsatisfactory).
e. Escalation to additional dose levels (eg, Q2W dosing frequency up to 10 mg/kg Q2W) may have occurred based upon PK/pharmacodynamic modeling.
f. Interim analysis as described in Section 8.1.3 of the study protocol.
g. PD-L1 negative participants to be enrolled following the first interim analysis. Enrollment was only to remain open for the PD-L1 negative cohort while enrollment to the PD-L1 positive cohort was open; futility rules might be applied as described in Section 8.1.2.3 of the study protocol.
h. All rrcHL participants who met the rrHL Cohort inclusion criteria.
i. At least 6 participants were to have central nervous system (CNS) tumors (other than brain stem).

Source: Study protocol.

The study was conducted at 51 centers in 12 countries. First patient was enrolled on 23 March 2015. The study is ongoing; the submitted data are based on an interim analysis with data cut-off date of 03-SEP-2018.

Study participants: Male and female participants between 6 months and less than 18 years of age; histologically or cytologically documented, locally advanced, or metastatic solid malignancy that was incurable and for which participants failed prior standard therapy/ no standard therapy/standard therapy was not considered appropriate; disease allowed were advanced melanoma, rrcHL, a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma; or an advanced, relapsed or refractory MSI-H solid tumor.

Table: Summary of Planned Cohorts

Cohort Name	Indication	Age	PD-L1 Status	Efficacy Criteria
Melanoma[a]	Melanoma	6 months to <18 years	Pos or Neg	RECIST 1.1
PD-L1 positive solid tumors and other lymphomas[b]	Any pediatric solid tumor (except brain stem tumors) and lymphoma	6 months to <18 years	Pos only	RECIST 1.1
PD-L1 negative[c] solid tumors and other lymphomas[b]	Any pediatric solid tumor (except brain stem tumors) and lymphoma	6 months to <18 years	Neg only	RECIST 1.1
rrcHL	Hodgkin lymphoma	3 years to <18 years	Pos or Neg	IWG[e]
MSI-H[d]	Any pediatric solid tumor (except brain stem tumors)	6 months to <18 years	Pos or Neg	RECIST 1.1

IWG=International Working Group; MSI-H=microsatellite instability-high; Neg=negative; PD-L1=programmed cell death ligand 1; Pos=positive; RECIST=Response Evaluation Criteria in Solid Tumors; rrcHL=relapsed or refractory classical Hodgkin lymphoma.

[a] Melanoma cohorts from 6 months to <12 years were closed starting with Amendment 8 of the study protocol [16.1.1].

[b] Participants with Hodgkin lymphoma (HL) were initially enrolled into the "other lymphoma" cohort. Beginning with Amendment 7, participants with HL were enrolled in the dedicated rrcHL Cohort.

[c] For solid tumors or other lymphoma, enrollment of participants with PD-L1 negative tumors may have been initiated only if participants with PD-L1 positive tumors demonstrated efficacy (see Section 8.1.2.2.2 and Table 14 of the study protocol [16.1.1]).

[d] Included documented biallelic mismatch repair (MMR) deficiency (constitutional mismatch repair deficiency [CMMRD] or biallelic mismatch repair deficiency [BMMRD]) regardless of MSI-H testing.

[e] [16.1.12.1].

Source: Study protocol [16.1.1].

Although this study's primary efficacy goals were to evaluate antitumor activity in PD-L1 positive tumors, preliminary exploration of antitumor activity was also to be conducted in a subset of PD-L1 negative solid tumors and other lymphomas based upon response observed in PD-L1 positive tumors in this study. Melanoma, MSI-H solid tumor, and rrcHL Cohort participants were evaluated regardless of PD-L1 status. As of Amendment 08, per futility rules, signals of efficacy were not met in solid tumor target cohorts, hence enrollment was stopped for most solid tumors. The melanoma, rrcHL, and MSI-H tumor cohorts continue to enroll participants regardless of PD-L1 status. Enrollment to the melanoma cohort will be limited to adolescent participants (≥12 and ≤18 years old).

Methodology:

Part I: Phase 1 safety, PK, pharmacodynamic, and dose-finding and confirmation evaluation in pediatric participants. Part I utilized a modified 3+3 design (dose-finding) and dose confirmation design according to a modified Toxicity Probability Interval approach.

Part II (ongoing): Phase 2 safety and efficacy evaluation in pediatric participants with advanced melanoma; PD-L1 positive advanced relapsed or refractory solid tumors or other lymphoma; rrcHL, or advanced, relapsed or refractory microsatellite instability-high (MSI-H) solid tumors.

The primary efficacy and safety population was the All Subjects as Treated (ASaT) population, which includes all participants who received at least 1 dose of pembrolizumab.

Endpoints:

Primary endpoints- Part I: rate of DLTs

Primary endpoints - Part I and part II: safety and tolerability, ORR

Secondary endpoints - Part I: PK parameters, outcome of the IL-2 assay.

Secondary endpoints - Part I and part II: DOR, DCR and PFS by RECIST 1.1, OS, ORR in PD-L1 positive vs negative tumor; genetic mutations detected with a custom Next Generation Sequencing assay in 8 genes: BRAF, KIT, MAP2K1 (MEK1), NRAS, RB1, TP53, PDGFA, and PDGFB; vaccinated antibody titers and B- and T-cell profiling.

7.2. Results

Patient disposition: A total of up to 310 participants was planned to be enrolled. As of the data cutoff date for this report, 155 participants were enrolled and **154** received at least 1 dose of pembrolizumab. Two participants completed maximum treatment duration (35 cycles, approximately 2 years), while 22 (14.3%) were still continuing on study treatment. Of the 132 (85.7%) participants who discontinued study treatment, the majority discontinued due to progressive disease (93) or clinical progression (19).

Baseline characteristics: Median age was 13 years (range 1 to 17 years). The majority were white, non-Hispanic (79.9%), and had Stage IV cancer (about 60%), and received prior treatment (89%).

Participants were enrolled across 28 tumor types by primary diagnosis. The most common tumor types by histology were HL (11.7%), glioblastoma multiforme (9.1%), neuroblastoma (6.5%), and melanoma (5.2%). A total of 29 patients (18.8%) have solid tumor nos, and 12 (7.8%) soft tissue neoplasm nos.

Table: Subject Characteristics (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
Gender		
Male	80	(51.9)
Female	74	(48.1)
Age (Years)		
6 months - <2 years	3	(1.9)
2 - 5 years	22	(14.3)
6 - 9 years	25	(16.2)
10 - 13 years	34	(22.1)
14 - 17 years	70	(45.5)
Mean	11.5	
SD	4.8	
Median	13.0	
Range	1 to 17	
Race		
American Indian Or Alaska Native	1	(0.6)
Asian	21	(13.6)
Black Or African American	14	(9.1)
Multi-Racial	12	(7.8)
Asian, White	1	(0.6)
Black, White	10	(6.5)
Native American, White	1	(0.6)
White	106	(68.8)
Ethnicity		

Hispanic Or Latino	17	(11.0)
Not Hispanic Or Latino	123	(79.9)
Not Reported	12	(7.8)
Unknown	2	(1.3)
Primary Diagnosis		
Adrenocortical Carcinoma	4	(2.6)
Alveolar Rhabdomyosarcoma	2	(1.3)
Alveolar Soft Part Sarcoma	1	(0.6)
Anaplastic Astrocytoma	2	(1.3)
Atypical Teratoid Rhabdoid Tumor	4	(2.6)
CNS Primary Tumor Nos	7	(4.5)
Diffuse Large B Cell Lymphoma	1	(0.6)
Embryonal Rhabdomyosarcoma	4	(2.6)
Ependymoma Nos	4	(2.6)
Glioblastoma Multiforme	14	(9.1)
Hepatoblastoma	5	(3.2)
Hepatocellular Carcinoma	3	(1.9)
High Grade Astrocytoma Nos	2	(1.3)
Hodgkin Lymphoma Nos	18	(11.7)
Low Grade Astrocytoma Nos	1	(0.6)
Medulloblastoma	2	(1.3)
Melanoma	8	(5.2)
Neuroblastoma	10	(6.5)
Non Rhabdomyosarcoma Soft Tissue Sarcoma Nos	1	(0.6)
Osteosarcoma	10	(6.5)
Pilocytic Astrocytoma	2	(1.3)
Precursor T Lymphoblastic Lymphoma	1	(0.6)
Renal Cell Carcinoma Nos	2	(1.3)
Rhabdoid Tumor Of The Kidney	1	(0.6)
Rhabdomyosarcoma Nos	1	(0.6)
Soft Tissue Neoplasm Nos	12	(7.8)
Solid Tumor Nos	29	(18.8)
Wilms Tumor Nephroblastoma	3	(1.9)
Lansky / Karnofsky Play Score		
100	61	(39.6)
90	38	(24.7)
80	24	(15.6)
70	16	(10.4)
60	7	(4.5)
50	6	(3.9)
Missing	2	(1.3)
Overall Staging#		
I	2	(1.3)
IA	2	(1.3)
IB	1	(0.6)
II	5	(3.2)
IIA	4	(2.6)
IIB	2	(1.3)
IIE	1	(0.6)
III	16	(10.4)
IIIA	3	(1.9)
IIIB	3	(1.9)
IV	87	(56.5)
IVA	1	(0.6)
IVB	5	(3.2)
Missing	22	(14.3)
Brain Metastases Present		
Yes	15	(9.7)

No	138	(89.6)
Missing	1	(0.6)
Prior Adjuvant/Neoadjuvant therapy		
Yes	11	(7.1)
No	143	(92.9)
Treatment Naive		
Yes	17	(11.0)
No	137	(89.0)
Number of Prior Therapies for recurrent/Metastatic Disease*		
0	22	(14.3)
1	46	(29.9)
2	41	(26.6)
3	23	(14.9)
4	9	(5.8)
5 or more	13	(8.4)

Overall Staging not required for diagnoses lacking standard staging systems.
* Those subjects who are naïve, or who received only adjuvant or neoadjuvant prior therapies are categorized as 0. (Data Cutoff Date: 03SEP2018).

Dose Limiting Toxicities (part 1): the starting pembrolizumab dose and frequency of 2 mg/kg Q3W was maintained throughout the trial. There were **no DLTs observed in the 12 participants** in Part I of the study. Thus the **pembrolizumab 2 mg/kg Q3W** dosing regimen was not changed and has been established as the **recommended pediatric dosage**.

Efficacy results: Efficacy analyses were based on the ASaT population. Of the 154 participants in the ASaT population, 134 were enrolled with solid tumors, 18 with HL, and 2 with other lymphomas.

- **Solid Tumors and Other Lymphomas (n=134+2)**

The **ORR per RECIST 1.1 by investigator assessment** in the solid tumor and other lymphoma population was **5.9%**. The 8 confirmed responders (all PR) had the following tumor types (by histology): adenocarcinoma and mesothelioma (2 participants each), and malignant ganglioglioma, epithelioid sarcoma, lymphoepithelial carcinoma, and malignant rhabdoid tumor (1 participant each).

Table: Summary of Best Overall Response Based on RECIST 1.1/MIBG per Investigator Assessment (All Relapsed/Refractory Tumors Except Hodgkin Lymphoma) (All Subjects as Treated Population - Parts I and II)

Response Evaluation	All Subjects as Treated (N=136)		
	n	%	95% CI[†]
Complete Response (CR)	0	0.0	(0.0, 2.7)
Partial Response (PR)	8	5.9	(2.6, 11.3)
Best Overall Response (CR+PR)	**8**	**5.9**	**(2.6, 11.3)**
Stable Disease (SD)	28	20.6	(14.1, 28.4)
Disease Control Rate (SD+CR+PR)	**36**	**26.5**	**(19.3, 34.7)**
Progressive Disease (PD)	74	54.4	(45.7, 63.0)
Non-evaluable (NE)	2	1.5	(0.2, 5.2)
No Assessment	24	17.6	(11.6, 25.1)

Confirmed responses by RECIST 1.1/ MIBG are included.
[†] Based on binomial exact confidence interval method.
No Assessment - subjects who discontinued prior to their first imaging.
NE per RECIST for two subjects, reported SD less than 42 days from first dose.

(Data Cutoff Date: 03SEP2018).

Response Evaluation	All Subjects as Treated (N=136)		
	n	%	95% CI*
Complete Response (CR)	0	0.0	(0.0, 2.7)
Partial Response (PR)	8	5.9	(2.6, 11.3)
Best Overall Response (CR+PR)	**8**	**5.9**	**(2.6, 11.3)**
Stable Disease (SD)	28	20.6	(14.1, 28.4)
Disease Control Rate (SD+CR+PR)	**36**	**26.5**	**(19.3, 34.7)**
Progressive Disease (PD)	74	54.4	(45.7, 63.0)
Non-evaluable (NE)	2	1.5	(0.2, 5.2)
No Assessment	24	17.6	(11.6, 25.1)

Confirmed responses by RECIST 1.1/ MIBG are included.
*Based on binomial exact confidence interval method.
No Assessment - subjects who discontinued prior to their first imaging.
NE per RECIST for subjects, [redacted], reported SD less than 42 days from first dose.
(Data Cutoff Date: 03SEP2018).

For the 8 responders in the solid tumor and other lymphoma population, the median **time to response** was **1.9 months**. Median **DOR** had **not been reached** at the time of data cutoff; responses ranged from 2.8+ to 23.2+ months. Per the KM estimate, 100% of responders had a response duration of at least 6 months and 83.3% had a response durations of at least 9 months.

Table: Summary of Time to Response and Duration of Response Based on Investigator Assessment in Subjects With Confirmed Response All Relapsed/Refractory Tumors Except Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=136)
Number of subjects with response†	8
Time to Response (months)	
Mean (SD)	4.2 (5.1)
Median (Range)	1.9 (1.9-16.6)
Response Duration‡ (months)	
Median (Range)	NR (2.8+ - 23.2+)
Number (%‡) of Subjects with Extended Response Duration:	
≥3 months	7 (100.0)
≥6 months	6 (100.0)
≥9 months	5 (83.3)

† Includes subjects with confirmed response.
‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached. (Data Cutoff Date: 03SEP2018).

The median **PFS** of the solid tumor and other lymphoma population was **1.9 months** (95% CI: 1.8, 1.9). PFS rates at 6 and 12 months were 18.7% and 12.9%, respectively, by KM estimation.

The median **OS** of the solid tumor and other lymphoma population was **9.0 months** (95% CI: 6.2, 14.5). OS rates at 6 and 12 months were 59.1% and 45.8%, respectively, by KM estimation.

- **Hodgkin Lymphoma (n=18)**

The **ORR per RECIST 1.1 by investigator assessment** in the HL population was **50.0%**. Of 9 confirmed responders, 2 had CR and 7 had PR. One additional participant had an unconfirmed PR.

Response Evaluation	All Subjects as Treated (N=18)		
	n	%	95% CI[†]
Complete Response (CR)	2	11.1	(1.4, 34.7)
Partial Response (PR)	7	38.9	(17.3, 64.3)
Best Overall Response (CR+PR)	**9**	**50.0**	**(26.0, 74.0)**
Stable Disease (SD)	3	16.7	(3.6, 41.4)
Disease Control Rate (SD+CR+PR)	**12**	**66.7**	**(41.0, 86.7)**
Progressive Disease (PD)	3	16.7	(3.6, 41.4)
No Assessment	3	16.7	(3.6, 41.4)
Confirmed responses by RECIST 1.1/ MIBG are included. [†] Based on binomial exact confidence interval method. No Assessment - subjects who were enrolled under Amendment 7. (Data Cutoff Date: 03SEP2018).			

For the 9 responders in the HL population, the median **time to response** was **1.9 months**. Median **DOR** was **17.3 months** (although the median could vary due to the small number of responders around that time, and the single event at the end of the curve); responses ranged from 3.9+ to 17.5 months. Per the KM estimate, all responders had a response duration of at least 6 months and 83.3% had a response durations of at least 9 months.

Table: Summary of Time to Response and Duration of Response Based on Investigator Assessment in Subjects With Confirmed Response Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=18)
Number of subjects with response[†]	9
Time to Response (months)	
Mean (SD)	1.9 (0.2)
Median (Range)	1.9 (1.6-2.1)
Response Duration[‡] (months)	
Median (Range)	17.3 (3.9+ - 17.5)
Number (%[‡]) of Subjects with Extended Response Duration:	
≥3 months	9 (100.0)
≥6 months	6 (100.0)
≥9 months	5 (83.3)
[†] Includes subjects with confirmed response. [‡] From product-limit (Kaplan-Meier) method for censored data. "+" indicates there is no progressive disease by the time of last disease assessment. (Data Cutoff Date: 03SEP2018).	

The median **PFS** of the HL population was **12.2 months** (95% CI: 2.1, 19.4). PFS rates at 6 and 12 months were 72.7% and 51.9%, respectively, by KM estimation.

Table: Summary of Progression-Free Survival (PFS) per Investigator Assessment Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=18)

Number (%) of PFS Events	9 (50.0)
Person-Months	136
Event Rate/100 Person-Months (%)	6.6
Median PFS (Months)[§]	12.2
95% CI for Median PFS[§] PFS	(2.1,19.4)
rate at 6 Months in % [§] PFS	72.7
rate at 12 Months in % [§]	51.9
Progression-free survival is defined as time from first dose to disease progression, death or start of new anti-cancer therapy, whichever occurs first. [§] From product-limit (Kaplan-Meier) method for censored data. (Data Cutoff Date: 03SEP2018).	

No death events occurred in the Relapsed/Refractory Hodgkin Lymphoma group. Therefore, the median **OS** of the HL population had **not been reached**. OS rates at 6 and 12 months were both 100.0% by KM estimation.

Biomarker Evaluations: Few hotspot mutations were observed in solid tumor samples from participants in this study, therefore no correlative testing was performed.

PD-L1 Expression Level and Clinical Response: Initially, only participants with PD-L1 positive tumors could be enrolled in this study, with the exception of the melanoma cohort. Because no tumor cohort met the tumor response threshold defined by the futility rules in the study protocol, no PD-L1 negative cohorts were allowed to be enrolled. However, 5 of the 8 participants with melanoma who enrolled had PD-L1 negative tumors. Given that no responses were observed in the entire melanoma cohort, analysis of association of PD-L1 status with response was not warranted.

7.3. Discussion-efficacy

Within this variation, the MAH presented the results (cutoff date 03-Sep-2018) of the ongoing phase 1/2 study KEYNOTE-051 of pembrolizumab in paediatric patients aged 6 months-18 years with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma. The number of study participants as per PIP01 was met, and all binding elements followed, the PIP was considered fulfilled (PIP compliance check EMEA-C-001474-PIP01-13- M01 started on 3 January 2019) (no new documents regarding PIP have been included in the submission). A separate specific HL cohort has not yet completed the accrual and will be presented separately. Additionally, it is reported that the participants in the MSI-H Cohort will also be analyzed in a separate report.

Overall, 154 paediatric patients were treated in KEYNOTE-051 study. Median age was 13 years (3 patients were 6 months-2 years aged). The most common tumor types by histology were Hodgkin lymphoma (11.7%), glioblastoma multiforme (9.1%), soft tissue neoplasm NOS (7.8%), neuroblastoma (6.5%), osteosarcoma (6.5%) and melanoma (5.2%), although it is noted high frequency of not otherwise specified solid tumor (18.8%). Most tumors were stage III and IV.

Part I of this study had rate of DLTs as primary endpoint. The starting dose was pembrolizumab 2 mg/kg Q3W. As no DLTs were observed in the 12 participants of part I, pembrolizumab 2 mg/kg Q3W dosing regimen was not changed and has been established as the recommended pediatric dosage.

Of the 154 participants, 134 were enrolled with solid tumours, 18 with Hodgkin lymphoma, and 2 with other lymphomas.

The ORR in participants with solid tumors and other lymphomas was 5.9% (95%CI 2.6, 11.3), with the responders split across multiple tumor histologies. Median time to response was 1.9 months, median DOR was not reached, median PFS was 1.9 months and median OS 9 months.

Per futility rules, signals of efficacy were not met in solid tumor target cohorts, hence enrollment was stopped for most solid tumors. The melanoma, rrcHL, and MSI-H tumor cohorts continue to enroll participants regardless of PD-L1 status. Enrollment to the melanoma cohort was limited to adolescent participants (≥12 and ≤18 years old). Based on KEYNOTE-051 results, antitumor activity was minimal in patients with PD-L1 positive pediatric solid tumors and other lymphomas.

In contrast, the ORR in the Relapsed/Refractory Hodgkin lymphoma population (n=18) was 50% (95%CI 26.0, 74.0). Median time to response was 1.9 months, median DOR was 17.3 months and median PFS 12.2 months. No deaths event occurred. The Applicant is considering submitting an indication for paediatric patients with Hodgkin lymphoma as part of a future adult filing.

No paediatric therapeutic indication is proposed with this variation, but only an update of the SmPC to reflect the results of KEYNOTE-051 to date is requested. This is accepted.

Analysis on PD-L1 status was not performed. Indeed, initially, only participants with PD-L1 positive tumors could be enrolled in this study, with the exception of the melanoma cohort. Because no tumor cohort met the tumor response threshold defined by the futility rules in the study protocol, no PD-L1 negative cohorts were allowed to be enrolled. However, 5 of the 8 participants with melanoma who enrolled had PD-L1 negative tumors. Given that no responses were observed in the entire melanoma cohort, analysis of association of PD-L1 status with response was not warranted. This is acknowledged.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

KEYNOTE-051 comprised 154 pediatric participants (aged 6 months-17 years) who received at least 1 dose of study intervention (ASaT population) as of the data cutoff of 03-SEP-2018, constituting the primary safety analysis population.

8.2. Results

Exposure: The mean number of pembrolizumab administrations in the solid tumor and other lymphoma population was 6.1, with a median duration of exposure of 43 days (range: 1 to 720 days).

Participants with HL experienced a higher response rate, and therefore received more study treatment, than other patients. In the HL population, the mean number of administrations was 14.4, with a median duration of exposure of 212 days (range: 1 to 712 days). At the data cut-off date, 10 out of 18 subjects with HL were still on treatment.

Exposure by duration is presented below:

Table: Exposure by Duration All Relapsed/Refractory Tumors Except Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=136)	
	n	(%)
Duration of Exposure		

> 0 m	136	(100.0)
>= 1 m	89	(65.4)
>= 3 m	44	(32.4)
>= 6 m	25	(18.4)
>= 12 m	13	(9.6)
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. (Data Cutoff Date: 03SEP2018).		

Table: Exposure by Duration Relapsed/Refractory Hodgkin Lymphoma (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated (N=18)	
	n	(%)
Duration of Exposure		
> 0 m	18	(100.0)
>= 1 m	17	(94.4)
>= 3 m	13	(72.2)
>= 6 m	11	(61.1)
>= 12 m	5	(27.8)
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. (Data Cutoff Date: 03SEP2018).		

Adverse events:

Table: Adverse Event Summary (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more adverse events	149	(96.8)
with no adverse event	5	(3.2)
with drug-related[†] adverse events	87	(56.5)
with toxicity grade 3-5 adverse events	69	(44.8)
with toxicity grade 3-5 drug-related adverse events	13	(8.4)
with serious adverse events	56	(36.4)
with serious drug-related adverse events	14	(9.1)
with dose modification[‡] due to an adverse event	23	(14.9)
who died	6	(3.9)
who died due to a drug-related adverse event	2	(1.3)
discontinued drug due to an adverse event	7	(4.5)
discontinued drug due to a drug-related adverse event	4	(2.6)
discontinued drug due to a serious adverse event	6	(3.9)
discontinued drug due to a serious drug-related adverse event	3	(1.9)

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

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE version 4.03.

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

Reporting for serious adverse events and serious drug-related adverse events goes through 90 days. (Database Cutoff Date: 03SEP2018).

Table: Subjects With Adverse Events by Decreasing Incidence (Incidence ≥5%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more adverse events	149	(96.8)
with no adverse events	5	(3.2)
Pyrexia	47	(30.5)
Vomiting	40	(26.0)
Headache	34	(22.1)
Abdominal pain	32	(20.8)
Anaemia	32	(20.8)
Constipation	31	(20.1)
Nausea	28	(18.2)
Cough	27	(17.5)
Fatigue	27	(17.5)
Diarrhoea	25	(16.2)
Lymphocyte count decreased	20	(13.0)
Asthenia	19	(12.3)
Decreased appetite	19	(12.3)
Aspartate aminotransferase increased	18	(11.7)
Back pain	18	(11.7)
Alanine aminotransferase increased	17	(11.0)
Arthralgia	16	(10.4)
Pruritus	16	(10.4)
Dyspnoea	15	(9.7)
Pain in extremity	15	(9.7)
Rhinitis	15	(9.7)
White blood cell count decreased	15	(9.7)
Hyponatraemia	13	(8.4)
Hypothyroidism	13	(8.4)
Platelet count decreased	13	(8.4)
Upper respiratory tract infection	13	(8.4)
Blood creatinine increased	12	(7.8)
Hypertension	12	(7.8)
Nasopharyngitis	12	(7.8)
Chest pain	11	(7.1)
Hypoalbuminaemia	11	(7.1)
Rash	11	(7.1)
Sinus tachycardia	11	(7.1)
Weight decreased	11	(7.1)
Dizziness	10	(6.5)
Hypophosphataemia	10	(6.5)
Pleural effusion	10	(6.5)
Rash maculo-papular	10	(6.5)
Rhinorrhoea	10	(6.5)
Neutrophil count decreased	9	(5.8)
Oropharyngeal pain	9	(5.8)
Device related infection	8	(5.2)
Dry skin	8	(5.2)
Hypokalaemia	8	(5.2)
Nasal congestion	8	(5.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Table: Subjects With Drug-related Adverse Events by Decreasing Incidence (Incidence ≥ 5%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more Adverse Events	87	(56.5)
with no Adverse Events	67	(43.5)
Anaemia	12	(7.8)
Fatigue	12	(7.8)
Lymphocyte count decreased	11	(7.1)
Pyrexia	11	(7.1)
Aspartate aminotransferase increased	9	(5.8)
Diarrhoea	8	(5.2)
Hypothyroidism	8	(5.2)
Nausea	8	(5.2)
Rash maculo-papular	8	(5.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Table: Subjects With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 5%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more Adverse Events	69	(44.8)
with no Adverse Events	85	(55.2)
Anaemia	14	(9.1)
Lymphocyte count decreased	9	(5.8)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Table: Subjects With Drug-related Grade 3-5 Adverse Events by Decreasing Incidence (Incidence > 0%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more Grade 3-5 Drug-related Adverse Events	13	(8.4)
with no Grade 3-5 Drug-related Adverse Events	141	(91.6)
Lymphocyte count decreased	3	(1.9)
Anaemia	2	(1.3)
Aspartate aminotransferase increased	1	(0.6)
Colitis	1	(0.6)
Dyspnoea	1	(0.6)
Gastric ulcer	1	(0.6)
Hypertension	1	(0.6)
Neutrophil count decreased	1	(0.6)
Photosensitivity reaction	1	(0.6)
Pleural effusion	1	(0.6)
Pneumonitis	1	(0.6)
Pruritus	1	(0.6)
Pulmonary oedema	1	(0.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Two participants experienced 3 drug-related Grade 5 AEs: 1 participant had Grade 5 pulmonary edema, and 1 participant had Grade 5 pleural effusion and Grade 5 pneumonitis.

Deaths:

Six participants had 1 or more AEs that resulted in death. Two of these deaths were reported by the investigator to be related to study drug: 1 participant had pulmonary edema and another experienced pneumonitis and pleural effusion. According to the MAH, for the participant experiencing the fatal event of pulmonary edema, the event was confounded by concomitant sepsis, and for the participant experiencing the fatal events of pneumonitis/pleural effusion, the outcome of these events was confounded by the extensive right chest involvement of the underlying epithelioid sarcoma.

Table: Subjects With Adverse Events Resulting in Death by Decreasing Incidence up to 90 Days From Last Dose (Incidence > 0%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more adverse events	6	(3.9)
with no adverse events	148	(96.1)
Adenocarcinoma gastric	1	(0.6)
Blood creatinine increased	1	(0.6)
Ependymoma malignant	1	(0.6)
Pleural effusion	1	(0.6)
Pneumonitis	1	(0.6)
Pulmonary oedema	1	(0.6)
Sepsis	1	(0.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Assessor's comment

Based on the narrative provided, one subject with solid tumor NOS (colloid carcinoma), received a total of 18 doses, however pembrolizumab was interrupted in response to worsening of anemia (Grade 3) and gastric ulcer (Grade 3), with approximately 6 weeks between Cycles 14 and 15; then discontinued in response to gastric adenocarcinoma (Grade 5). The investigator considered gastric ulcer related to study treatment (drug-related SAE), and it is reported that a biopsy on day 299 indicated a chronic gastritis with inflammatory infiltration with lymphoplasmacytoid cells. No corticosteroids were administered.

One subject with renal medullary carcinoma, who received one dose of pembrolizumab, died for a grade 5 pulmonary edema, considered by investigator related to study medication and immune related. The evaluation of the MAH that the event was confounded by sepsis is acknowledged, nevertheless a relation of the AE with study drug cannot be excluded.

One subject with sarcoma developed pneumonitis after one cycle of pembrolizumab, which was considered immune-related by investigator and classified as AEOSI by the MAH. Pneumonitis, including fatal events, is a known ADR of pembrolizumab.

Serious Adverse Events (SAE):

Table: Subjects With Serious Adverse Events by Decreasing Incidence up to 90 Days From Last Dose (Incidence ≥ 1%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more adverse events	56	(36.4)
with no adverse events	98	(63.6)
Pyrexia	11	(7.1)
Pleural effusion	5	(3.2)
Device related infection	4	(2.6)
Dyspnoea	2	(1.3)
Headache	2	(1.3)
Hypertension	2	(1.3)
Lung infection	2	(1.3)
Nausea	2	(1.3)
Pneumonitis	2	(1.3)
Seizure	2	(1.3)
Sepsis	2	(1.3)
Vomiting	2	(1.3)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Table: Subjects With Drug-related Serious Adverse Events by Decreasing Incidence up to 90 Days From Last Dose (Incidence > 0%) (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more adverse events	14	(9.1)
with no adverse events	140	(90.9)
Pyrexia	4	(2.6)
Hypertension	2	(1.3)
Pleural effusion	2	(1.3)
Adrenal insufficiency	1	(0.6)
Dyspnoea	1	(0.6)
Enterocolitis infectious	1	(0.6)
Gastric ulcer	1	(0.6)
Gastrooesophageal reflux disease	1	(0.6)
Oedema peripheral	1	(0.6)
Photosensitivity reaction	1	(0.6)
Pneumonitis	1	(0.6)
Pruritus	1	(0.6)
Pulmonary oedema	1	(0.6)
Tumour flare	1	(0.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Adverse Events Leading to Treatment Discontinuation and Treatment Interruption

As of the data cutoff date, a total of 7 participants (4.5%) had an AE that resulted in treatment discontinuation. AEs leading to treatment discontinuation were adenocarcinoma gastric, aspartate aminotransferase increased, blood creatinine increased, hypertension, pneumonitis, pulmonary edema, and sepsis in 1 participant each (0.6%). Of the 7 participants who discontinued study treatment due to an AE, 4 participants had AEs reported as drug related by the investigator (aspartate aminotransferase increased, hypertension, pneumonitis, pulmonary edema).

As of the data cutoff date, a total of 18 participants (11.7%) experienced at least 1 AE leading to interruption of study drug. The most frequently reported AE that led to interruption of study drug was alanine aminotransferase increased, experienced by 3 participants (1.9%). Of the 18 participants with treatment interruptions due to an AE, 8 participants (5.2%) had AEs considered to be drug-related per investigator assessment.

Adverse Events of Special Interest (AEOSI)

Twenty-eight participants (18.2%) experienced at least 1 AEOSI, most commonly involving the thyroid: hypothyroidism (8.4%), hyperthyroidism (3.9%), and thyroiditis (1.3%). Of 28 participants with AEOSI, 19 had AEOSI reported as drug related by the investigator and 3 had AEOSI reported as Grade 3, 4, or 5 (1 each of Grade 3 pruritus, Grade 3 colitis, and Grade 5 pneumonitis), all of which were reported as drug related. For 2 participants AEOSI (pneumonitis and pruritus) were reported by the investigator as serious and drug related. For the case of pneumonitis, it also lead to discontinuation, and ultimately was fatal.

As of the data cutoff date, AEOSI resolved for 12 of 28 participants (42.9%), were resolving for 3 (10.7%) participants, and resolved with sequelae in 1 participant (3.6%). AEOSI had not resolved for 10 participants (35.7%). All events that had not resolved as of the data cutoff date were endocrinopathies that require long-term hormone replacement therapy (7 events of hypothyroidism, 2 events of hyperthyroidism, and 1 event each of thyroiditis and adrenal insufficiency). The AEOSI outcome status was unknown in 1 participant (3.6%, hypothyroidism).

The most common AEOSI reported during pembrolizumab treatment was hypothyroidism, which occurred in 13 of 154 (8.4%) participants in the ASaT population. The median time to onset was 48.0 days. All events were Grade 1 or 2, and no participant received corticosteroid treatment. Hypothyroidism resolved for 2 participants. As of the data cutoff date, hypothyroidism had not resolved for 7 participants, was resolving in 3 participants, and the status of 1 was unknown. In the 13 participants with a reported AE of hypothyroidism during treatment, a total of 4 (30.8%) had a prior history of radiation therapy to the head, craniospinal, or lung, which may have contributed to the risk of hypothyroidism.

Table: Adverse Event Summary AEOSI - version 14.0 (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more adverse events	28	(18.2)
with no adverse event	126	(81.8)
with drug-related[†] adverse events	19	(12.3)
with toxicity grade 3-5 adverse events	3	(1.9)
with toxicity grade 3-5 drug-related adverse events	3	(1.9)
with serious adverse events	3	(1.9)
with serious drug-related adverse events	2	(1.3)
with dose modification[‡] due to an adverse event	4	(2.6)
who died	1	(0.6)
who died due to a drug-related adverse event	1	(0.6)
discontinued drug due to an adverse event	1	(0.6)
discontinued drug due to a drug-related adverse event	1	(0.6)
discontinued drug due to a serious adverse event	1	(0.6)
discontinued drug due to a serious drug-related adverse event	1	(0.6)

[†] Determined by the investigator to be related to the drug.
[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
Reporting for serious adverse events and serious drug-related adverse events goes through 90 days.
(Database Cutoff Date: 03SEP2018).

Table: Subjects With Adverse Events (Incidence > 0%) AEOSI (All Subjects as Treated Population - Parts I and II)

	All Subjects as Treated	
	n	(%)
Subjects in population	154	
with one or more AEOSI adverse events	28	(18.2)
with no AEOSI adverse events	126	(81.8)
Endocrine disorders	**21**	**(13.6)**
Adrenal insufficiency	1	(0.6)
Hyperthyroidism	6	(3.9)
Hypothyroidism	13	(8.4)
Thyroiditis	2	(1.3)
Gastrointestinal disorders	**2**	**(1.3)**
Colitis	2	(1.3)
Immune system disorders	**4**	**(2.6)**
Drug hypersensitivity	1	(0.6)
Hypersensitivity	3	(1.9)
Injury, poisoning and procedural complications	**1**	**(0.6)**
Infusion related reaction	1	(0.6)
Respiratory, thoracic and mediastinal disorders	**3**	**(1.9)**
Pneumonitis	3	(1.9)
Skin and subcutaneous tissue disorders	**1**	**(0.6)**
Pruritus	1	(0.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.
(Database Cutoff Date: 03SEP2018).

Other Events of Special Interest

Complications Post-allogeneic Stem Cell Transplantation in Participants Previously Treated With Pembrolizumab

As of the data cutoff date, there was 1 participant with HL who received an allogeneic SCT after treatment with pembrolizumab. The participant was treated with pembrolizumab for approximately 12 weeks, then discontinued the study. The participant continued to receive "immune checkpoint blockade" (name and duration unknown). Approximately 11 months after stopping pembrolizumab, the participant received an allogeneic SCT. Approximately 4 months after the allogeneic SCT, the participant was diagnosed with Grade 2 chronic GvHD. As of the data cutoff date, the participant was alive, approximately 10 months after the allogeneic SCT.

Immune System Function Analysis

Measurements of immune system function revealed the following:

- Minimal changes were observed in the concentration of vaccinated antibodies at posttreatment Cycle 4 compared to pretreatment.

- The total memory B- and T-cell counts showed an upward trend from pretreatment to posttreatment Cycle 4.

Taken together, according to the MAH these data indicate that treatment with pembrolizumab in pediatric patients does not seem to affect immunological competence in this patient population.

Clinical laboratory evaluations

The most frequently reported liver laboratory abnormalities in the ASaT population were: elevated alkaline phosphatase ≥1.5 × ULN (15.0%) and elevated ALT ≥3 × ULN (12.4%). No liver function abnormalities were consistent with potential drug-induced liver injury criteria (Hy's Law).

Comparison between pembrolizumab safety in adult and paediatric patients

Upon CHMP request, the MAH provided the paediatric data for adverse events compared with the pembrolizumab EU reference safety dataset (RSD), which is an internally validated dataset that includes adverse event data for the adult studies KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase), KEYNOTE-006, KEYNOTE-010, KEYNOTE- 012, KEYNOTE-013 Cohort 3, KEYNOTE-024, KEYNOTE-040, KEYNOTE-045, KEYNOTE-052, KEYNOTE-054, KEYNOTE-055, and KEYNOTE-087.

Table: Adverse Event Summary (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	149	(96.8)	4,788	(96.8)
with no adverse event	5	(3.2)	160	(3.2)
with drug-related[†] adverse events	87	(56.5)	3,536	(71.5)
with toxicity grade 3-5 adverse events	69	(44.8)	2,311	(46.7)
with toxicity grade 3-5 drug-related adverse events	13	(8.4)	734	(14.8)
with serious adverse events	56	(36.4)	1,857	(37.5)
with serious drug-related adverse events	14	(9.1)	530	(10.7)
with dose modification[‡] due to an adverse event	23	(14.9)	1,607	(32.5)
who died	6	(3.9)	212	(4.3)
who died due to a drug-related adverse event	2	(1.3)	23	(0.5)
discontinued drug due to an adverse event	7	(4.5)	608	(12.3)
discontinued drug due to a drug-related adverse event	4	(2.6)	321	(6.5)
discontinued drug due to a serious adverse event	6	(3.9)	436	(8.8)
discontinued drug due to a serious drug-related adverse event	3	(1.9)	194	(3.9)

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

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	149	(96.8)	4,788	(96.8)
with no adverse events	5	(3.2)	160	(3.2)
Pyrexia	47	(30.5)	627	(12.7)
Vomiting	40	(26.0)	637	(12.9)
Headache	34	(22.1)	622	(12.6)
Abdominal pain	32	(20.8)	448	(9.1)
Anaemia	32	(20.8)	656	(13.3)
Constipation	31	(20.1)	848	(17.1)
Nausea	28	(18.2)	1,075	(21.7)
Cough	27	(17.5)	978	(19.8)
Fatigue	27	(17.5)	1,686	(34.1)
Diarrhoea	25	(16.2)	1,066	(21.5)
Lymphocyte count decreased	20	(13.0)	90	(1.8)
Asthenia	19	(12.3)	574	(11.6)
Decreased appetite	19	(12.3)	963	(19.5)
Aspartate aminotransferase increased	18	(11.7)	300	(6.1)
Back pain	18	(11.7)	564	(11.4)
Alanine aminotransferase increased	17	(11.0)	305	(6.2)
Arthralgia	16	(10.4)	771	(15.6)
Pruritus	16	(10.4)	918	(18.6)
Dyspnoea	15	(9.7)	831	(16.8)
Pain in extremity	15	(9.7)	345	(7.0)
Rhinitis	15	(9.7)	96	(1.9)
White blood cell count decreased	15	(9.7)	46	(0.9)
Hyponatraemia	13	(8.4)	291	(5.9)
Hypothyroidism	13	(8.4)	514	(10.4)
Platelet count decreased	13	(8.4)	63	(1.3)
Upper respiratory tract infection	13	(8.4)	310	(6.3)
Blood creatinine increased	12	(7.8)	222	(4.5)
Hypertension	12	(7.8)	239	(4.8)
Nasopharyngitis	12	(7.8)	304	(6.1)
Chest pain	11	(7.1)	238	(4.8)
Hypoalbuminaemia	11	(7.1)	155	(3.1)
Rash	11	(7.1)	778	(15.7)
Sinus tachycardia	11	(7.1)	38	(0.8)
Weight decreased	11	(7.1)	447	(9.0)
Dizziness	10	(6.5)	389	(7.9)
Hypophosphataemia	10	(6.5)	114	(2.3)
Pleural effusion	10	(6.5)	150	(3.0)
Rash maculo-papular	10	(6.5)	175	(3.5)
Rhinorrhoea	10	(6.5)	97	(2.0)
Neutrophil count decreased	9	(5.8)	31	(0.6)
Oropharyngeal pain	9	(5.8)	169	(3.4)
Device related infection	8	(5.2)	15	(0.3)
Dry skin	8	(5.2)	271	(5.5)
Hypokalaemia	8	(5.2)	226	(4.6)
Nasal congestion	8	(5.2)	130	(2.6)
Insomnia	7	(4.5)	365	(7.4)
Musculoskeletal pain	7	(4.5)	342	(6.9)
Myalgia	6	(3.9)	386	(7.8)
Oedema peripheral	4	(2.6)	458	(9.3)
Urinary tract infection	2	(1.3)	336	(6.8)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	87	(56.5)	3,536	(71.5)
with no adverse events	67	(43.5)	1,412	(28.5)
Anaemia	12	(7.8)	153	(3.1)
Fatigue	12	(7.8)	1,072	(21.7)
Lymphocyte count decreased	11	(7.1)	42	(0.8)
Pyrexia	11	(7.1)	222	(4.5)
Aspartate aminotransferase increased	9	(5.8)	166	(3.4)
Diarrhoea	8	(5.2)	574	(11.6)
Hypothyroidism	8	(5.2)	451	(9.1)
Nausea	8	(5.2)	488	(9.9)
Rash maculo-papular	8	(5.2)	137	(2.8)
Asthenia	7	(4.5)	327	(6.6)
Arthralgia	4	(2.6)	400	(8.1)
Decreased appetite	4	(2.6)	402	(8.1)
Pruritus	4	(2.6)	729	(14.7)
Rash	4	(2.6)	580	(11.7)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Grade 3-5 Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	69	(44.8)	2,311	(46.7)
with no adverse events	85	(55.2)	2,637	(53.3)
Anaemia	14	(9.1)	202	(4.1)
Lymphocyte count decreased	9	(5.8)	27	(0.5)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Drug-Related Grade 3-5 Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	13	(8.4)	734	(14.8)
with no adverse events	141	(91.6)	4,214	(85.2)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	56	(36.4)	1,857	(37.5)
with no adverse events	98	(63.6)	3,091	(62.5)
Pyrexia	11	(7.1)	60	(1.2)
Pleural effusion	5	(3.2)	67	(1.4)
Device related infection	4	(2.6)	5	(0.1)
Dyspnoea	2	(1.3)	69	(1.4)
Headache	2	(1.3)	6	(0.1)
Hypertension	2	(1.3)	1	(0.0)
Lung infection	2	(1.3)	18	(0.4)
Nausea	2	(1.3)	25	(0.5)
Pneumonitis	2	(1.3)	87	(1.8)
Seizure	2	(1.3)	13	(0.3)
Sepsis	2	(1.3)	29	(0.6)
Vomiting	2	(1.3)	26	(0.5)
Anaemia	1	(0.6)	55	(1.1)
Pneumonia	1	(0.6)	154	(3.1)
Colitis	0	(0.0)	54	(1.1)
Diarrhoea	0	(0.0)	51	(1.0)
Pulmonary embolism	0	(0.0)	56	(1.1)
Urinary tract infection	0	(0.0)	57	(1.2)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Drug-Related Serious Adverse Events Up to 90 Days of Last Dose (Incidence > 0% in KN051 Treatment Group) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	14	(9.1)	530	(10.7)
with no adverse events	140	(90.9)	4,418	(89.3)
Pyrexia	4	(2.6)	15	(0.3)
Hypertension	2	(1.3)	0	(0.0)
Pleural effusion	2	(1.3)	4	(0.1)
Adrenal insufficiency	1	(0.6)	11	(0.2)
Dyspnoea	1	(0.6)	9	(0.2)
Enterocolitis infectious	1	(0.6)	0	(0.0)
Gastric ulcer	1	(0.6)	1	(0.0)
Gastrooesophageal reflux disease	1	(0.6)	1	(0.0)
Oedema peripheral	1	(0.6)	1	(0.0)
Photosensitivity reaction	1	(0.6)	0	(0.0)
Pneumonitis	1	(0.6)	81	(1.6)
Pruritus	1	(0.6)	0	(0.0)
Pulmonary oedema	1	(0.6)	0	(0.0)
Tumour flare	1	(0.6)	0	(0.0)

Table: Subjects with Adverse Events Resulting in Death Up to 90 Days of Last Dose (Incidence > 0% in KN051 Treatment Group) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	6	(3.9)	212	(4.3)
with no adverse events	148	(96.1)	4,736	(95.7)
Adenocarcinoma gastric	1	(0.6)	1	(0.0)
Blood creatinine increased	1	(0.6)	0	(0.0)
Ependymoma malignant	1	(0.6)	0	(0.0)
Pleural effusion	1	(0.6)	0	(0.0)
Pneumonitis	1	(0.6)	6	(0.1)
Pulmonary oedema	1	(0.6)	1	(0.0)
Sepsis	1	(0.6)	3	(0.1)

Table: Adverse Event Summary AEOSI – version14.0 (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	28	(18.2)	1,180	(23.8)
with no adverse event	126	(81.8)	3,768	(76.2)
with drug-related[†] adverse events	19	(12.3)	1,022	(20.7)
with toxicity grade 3-5 adverse events	3	(1.9)	291	(5.9)
with toxicity grade 3-5 drug-related adverse events	3	(1.9)	249	(5.0)
with serious adverse events	3	(1.9)	298	(6.0)
with serious drug-related adverse events	2	(1.3)	261	(5.3)
with dose modification[‡] due to an adverse event	4	(2.6)	399	(8.1)
who died	1	(0.6)	9	(0.2)
who died due to a drug-related adverse event	1	(0.6)	9	(0.2)
discontinued drug due to an adverse event	1	(0.6)	175	(3.5)
discontinued drug due to a drug-related adverse event	1	(0.6)	173	(3.5)
discontinued drug due to a serious adverse event	1	(0.6)	121	(2.4)
discontinued drug due to a serious drug-related adverse event	1	(0.6)	119	(2.4)

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

‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

§ Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table: Subjects with Adverse Events of Special Interest (Incidence > 0% in One or More Treatment Groups) By AEOSI Category and Preferred Term (Subjects in ASaT Population Treated with Pembrolizumab)

	KN032, KN042 and KN151 for MK-3475‡		Current EU SmPC Reference Safety Dataset for MK-3475††	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	28	(18.2)	1,180	(23.8)
with no adverse events	126	(81.8)	3,768	(76.2)
Adrenal Insufficiency	**1**	**(0.6)**	**39**	**(0.8)**
Adrenal insufficiency Adrenocortical	1	(0.6)	36	(0.7)
insufficiency acute Secondary	0	(0.0)	2	(0.0)
adrenocortical insufficiency	0	(0.0)	1	(0.0)
Colitis	**2**	**(1.3)**	**98**	**(2.0)**
Autoimmune colitis	0	(0.0)	6	(0.1)
Colitis	2	(1.3)	86	(1.7)
Colitis microscopic	0	(0.0)	4	(0.1)
Enterocolitis	0	(0.0)	5	(0.1)
Encephalitis	**0**	**(0.0)**	**1**	**(0.0)**
Encephalitis	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**4**	**(0.1)**
Axonal neuropathy	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	2	(0.0)
Hepatitis	**0**	**(0.0)**	**39**	**(0.8)**
Autoimmune hepatitis	0	(0.0)	17	(0.3)
Drug-induced liver injury	0	(0.0)	4	(0.1)
Hepatitis	0	(0.0)	19	(0.4)
Hyperthyroidism	**6**	**(3.9)**	**198**	**(4.0)**
Hyperthyroidism	6	(3.9)	198	(4.0)
Hypophysitis	**0**	**(0.0)**	**32**	**(0.6)**
Hypophysitis	0	(0.0)	20	(0.4)
Hypopituitarism	0	(0.0)	12	(0.2)
Hypothyroidism	**13**	**(8.4)**	**515**	**(10.4)**
Hypothyroidism	13	(8.4)	514	(10.4)
Myxoedema	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	1	(0.0)
Infusion Reactions	**5**	**(3.2)**	**121**	**(2.4)**

Infusion Reactions	**5**	**(3.2)**	**121**	**(2.4)**
Anaphylactic reaction	0	(0.0)	7	(0.1)
Anaphylactoid reaction	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	8	(0.2)
Drug hypersensitivity	1	(0.6)	18	(0.4)
Hypersensitivity	3	(1.9)	39	(0.8)
Infusion related reaction	1	(0.6)	50	(1.0)
Myasthenic Syndrome	**0**	**(0.0)**	**3**	**(0.1)**
Myasthenia gravis	0	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	2	(0.0)
Myocarditis	**0**	**(0.0)**	**4**	**(0.1)**
Myocarditis	0	(0.0)	4	(0.1)
Myositis	**0**	**(0.0)**	**19**	**(0.4)**
Myopathy	0	(0.0)	4	(0.1)
Myositis	0	(0.0)	14	(0.3)
Rhabdomyolysis	0	(0.0)	1	(0.0)
Nephritis	**0**	**(0.0)**	**17**	**(0.3)**
Acute kidney injury	0	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	3	(0.1)
Nephritis	0	(0.0)	1	(0.0)
Nephrotic syndrome Renal	0	(0.0)	1	(0.0)
failure Tubulointerstitial	0	(0.0)	2	(0.0)
nephritis	0	(0.0)	8	(0.2)
Pancreatitis	**0**	**(0.0)**	**13**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	11	(0.2)
Pancreatitis acute	0	(0.0)	2	(0.0)
Pneumonitis	**3**	**(1.9)**	**183**	**(3.7)**
Interstitial lung disease	0	(0.0)	14	(0.3)
Pneumonitis	3	(1.9)	170	(3.4)
Sarcoidosis	**0**	**(0.0)**	**10**	**(0.2)**
Sarcoidosis	0	(0.0)	10	(0.2)
Severe Skin Reactions	**1**	**(0.6)**	**66**	**(1.3)**

Severe Skin Reactions	**1**	**(0.6)**	**66**	**(1.3)**
Dermatitis bullous	0	(0.0)	5	(0.1)
Dermatitis exfoliative	0	(0.0)	3	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	2	(0.0)
Erythema multiforme	0	(0.0)	3	(0.1)
Exfoliative rash	0	(0.0)	2	(0.0)
Pemphigoid	0	(0.0)	3	(0.1)
Pemphigus	0	(0.0)	1	(0.0)
Pruritus	1	(0.6)	6	(0.1)
Pruritus generalised	0	(0.0)	1	(0.0)
Pruritus genital	0	(0.0)	1	(0.0)
Rash	0	(0.0)	19	(0.4)
Rash erythematous	0	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	4	(0.1)
Rash maculo-papular	0	(0.0)	11	(0.2)
Rash pruritic	0	(0.0)	1	(0.0)
Rash pustular	0	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	3	(0.1)
Toxic skin eruption	0	(0.0)	2	(0.0)
Thyroiditis	**2**	**(1.3)**	**46**	**(0.9)**
Autoimmune thyroiditis	0	(0.0)	9	(0.2)
Thyroid disorder	0	(0.0)	3	(0.1)
Thyroiditis	2	(1.3)	34	(0.7)
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**20**	**(0.4)**
Diabetic ketoacidosis	0	(0.0)	9	(0.2)
Type 1 diabetes mellitus	0	(0.0)	16	(0.3)
Uveitis	**0**	**(0.0)**	**19**	**(0.4)**
Iridocyclitis	0	(0.0)	4	(0.1)
Iritis	0	(0.0)	3	(0.1)
Uveitis	**0**	**(0.0)**	**19**	**(0.4)**
Uveitis	0	(0.0)	12	(0.2)

Every subject is counted a single time for each applicable row and column.

A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

§ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN045, KN052, KN054, KN055 and KN087.

8.3. Discussion - safety

The safety database presented included 154 participants of KEYNOTE-051 who received at least one dose of pembrolizumab at 2 mg/kg Q3W. Data cut off for the analysis is 03-SEP-2018.

Median number of pembrolizumab administration was 3 for the 136 patients with solid tumor and other lymphoma, while higher exposure was observed in the 18 subjects with HL, experiencing higher response rate (median number of administration was 11, range 1-35). Overall, 18 patients were exposed to pembrolizumab for ⩾12 months.

Overall, 96.8% of patients experienced one or more adverse events, most common (reported in at least 20% of paediatric patients) being pyrexia (31%), vomiting (26%), headache (22%), abdominal pain (21%), anaemia (21%) and constipation (20%). AEs considered as drug-related by investigator occurred in 56.5% of subjects, most common being anemia and fatigue (7.8% each), lymphocyte count decreased and pyrexia (7.1% each), AST increased (5.8%). Grade 3-5 AEs were 44.8% (anemia 9.1% and lymphocyte count decrease 5.8% the most common), drug-related Grade 3-5 8.4% (lymphocyte count decrease 1.9% and anemia 1.3% the most common). AEs lead to treatment discontinuation in 4.5% of

the patient. The most frequent laboratory abnormalities pertain to transaminases, however the MAH stated that no liver function abnormalities were consistent with potential drug-induced liver injury criteria (Hy's Law).

SAE occurred in 36.4% of subjects, (drug-related SAE 9.1%), most common being pyrexia. A drug related SAE of gastric ulcer grade 3 was reported, and a biopsy revealed "a chronic gastritis with inflammatory infiltration with lymphoplasmacytoid cells." Inflammation of the upper gastrointestinal tract, with gastric ulcers and inflammatory infiltrate on gastric biopsy, have been described in literature in patients receiving immune checkpoint inhibitors (see for example "Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. M Collins et al Annals of Oncology, Volume 28, Issue 11, November 2017, Pages 2860–2865"). While colitis, including rare cases of small intestinal perforation, is reported in the SmPC of Keytruda, gastritis and gastric ulcers are not included. The MAH has been requested to perform a revision of the cases of gastric ulcer across the whole (adult) safety database (including evaluation of biopsy report when available), and to evaluate whether appropriate wording should be included in the SmPC. The MAH provided the requested data and did not consider a change of the SmPC warranted. Based on the data provided, it is agreed that several cases with biopsy available lack of sufficient information or present confounding factors, although a relation with pembrolizumab cannot be totally excluded in most of them. In particular, one spontaneous report described a case in which a gastric biopsy after one month of pembrolizumab showed lymphocytic gastritis, which was not evident from a biopsy taken before starting pembrolizumab. The issue is not further pursued in the context of this procedure. Indeed, the signal of gastrointestinal ulcer is under investigation by the PRAC, therefore a more updated and extensive evaluation of this safety issue will be however performed.

Six participants had 1 or more AEs resulting in death. Investigator considered a pulmonary edema and pneumonitis/pleural effusion as treatment-related. For the grade 5 pulmonary edema, the evaluation of the MAH that the event was confounded by sepsis is acknowledged, however a relation of the AE with study drug cannot be excluded. The event of pneumonitis was considered immune-related by investigator and classified as AEOSI by the MAH. Pneumonitis, including fatal events, is a known ADR of pembrolizumab. It has been requested to mention in the SmPC that fatal events occurred in the paediatric population of KEYNOTE-051.

Twenty-eight participants (18.2%) experienced at least 1 AEOSI, most commonly involving the thyroid (hypothyroidism 8.4%, hyperthyroidism 3.9%, and thyroiditis 1.3%). AEOSI were grade $\geqslant$3 in 3 patients (1 each of Grade 3 pruritus, Grade 3 colitis, and Grade 5 pneumonitis).

Overall, no new safety signals have been reported in KEYNOTE-051 study.

The MAH concluded in the SmPC section 4.8 that "the safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab". Upon CHMP request, the MAH has provided supporting data comparing the safety of paediatric patients in KEYNOTE-051 with safety of adult from the Reference Safety Dataset. Based on the available data, taking into account the limited number of paediatric subjects (154 paediatrics vs 4,948 adults), the above statement is agreed.

9. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8, 5.1, 5.2 of the SmPC are being updated to include data from KEYNOTE-051.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

1. A drug related SAE of gastric ulcer grade 3 was reported, and a biopsy revealed "a chronic gastritis with inflammatory infiltration with lymphoplasmacytoid cells". Inflammation of the upper gastrointestinal tract, with gastric ulcers and inflammatory infiltrate on gastric biopsy, have been described in literature in patients receiving immune checkpoint inhibitors (see for example "Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. M Collins et al Annals of Oncology, Volume 28, Issue 11, November 2017, Pages 2860– 2865"). While colitis, including rare cases of small intestinal perforation, is reported in the SmPC of Keytruda, gastritis/gastric ulcers are not included. The MAH has been requested to perform a revision of the cases of gastric ulcer across the whole (adult) safety database (including evaluation of biopsy report when available), and to evaluate whether appropriate wording should be included in the SmPC.
2. The MAH concluded in the SmPC that "the safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab", however no supporting data to appropriately compare the safety of paediatric to adult patients have been found. The MAH is requested to provide the paediatric safety in KEYNOTE-051 with (please use the safety tables reported in the AR and report side by side the frequencies included in the most recent RSD of pembrolizumab monotherapy in adult patients). If relevant higher frequencies in single items are found in the paediatric compared to adult population, those should be discussed and, if appropriate, reflected in the SmPC.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1

A drug related SAE of gastric ulcer grade 3 was reported, and a biopsy revealed "a chronic gastritis with inflammatory infiltration with lymphoplasmacytoid cells". Inflammation of the upper gastrointestinal tract, with gastric ulcers and inflammatory infiltrate on gastric biopsy, have been described in literature in patients receiving immune checkpoint inhibitors (see for example "Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. M Collins et al Annals of Oncology, Volume 28, Issue 11, November 2017, Pages 2860– 2865"). While colitis, including rare cases of small intestinal perforation, is reported in the SmPC of Keytruda, gastritis/gastric ulcers are not included. The MAH has been requested to perform a revision of the cases of gastric ulcer across the whole (adult) safety database (including evaluation of biopsy report when available), and to evaluate whether appropriate wording should be included in the SmPC. (OC)

Summary of the MAH's response

Background

Immune-mediated adverse events associated with immune checkpoint inhibitors (ICI) including

pembrolizumab, a PD-1 inhibitor, have been well-described in the literature and are thought to be generally caused by non-specific activation of the immune system.

Pembrolizumab has been associated with immune-mediated colitis as well as other immunemediated organ disorders; the putative mechanism for gastritis or gastric ulcer associated with pembrolizumab would be immune-mediated as well. It is important to understand the differential diagnosis of gastritis and gastric ulcer and consider alternative explanations for an immune-mediated event. A cumulative review of case reports of gastritis and/or gastric ulcer is provided below.

Gastritis can be defined as an acute or chronic inflammation of the stomach resulting in epithelial damage of the mucosal lining. This term should be distinguished from "gastropathy," which refers to mucosal damage without inflammation resulting from epithelial cell chemical injury (such as with NSAIDs, alcohol bile reflux), vascular gastropathy primarily due to portal hypertension, or ischaemic injury, such as is seen with burn injuries, sepsis, hypovolemia, trauma or cocaine, or auto-immune, as is seen with celiac disease. Adverse event reports received by the MAH that described clinical disease consistent with gastropathy rather than gastritis would not be considered immune-mediated, and unlikely attributable to pembrolizumab.

The etiologies of inflammatory gastritis/gastric ulcer are primarily infectious or autoimmune. Helicobacter pylori (H.pylori) bacteria are the most common infectious agents and are clearly associated with peptic ulcer disease, both duodenal and gastric ulcer disease. It is estimated that 50 to 75% of the world adult population is infected with H. pylori.

Mucosal injury is induced by cytotoxic enzymes secreted by the organisms, which also produce number of antigenic substances, including heat shock protein, urease, and lipopolysaccharide, all of which can be taken up and processed by lamina propria macrophages and activated T-cells. H.pylori can be detected by non-invasive serologic or stool antigen testing, however, biopsy is necessary, especially for confirmation for patients on proton pump inhibitors (PPIs) due to antimicrobial properties of PPIs [Ref. 5.4: 057M8J].

Gastritis cannot be confirmed by macroscopic observation alone: mucosal erythema seen on endoscopy is not proof of an inflammatory process. Histologically confirmed inflammation of the gastric mucosa is necessary for confirmation of an inflammatory pathology [Ref. 5.4: 057MZ6]. Therefore, the MAH considers case reports with description of tissue biopsy as the most relevant for review.

Review of Case Reports

The MAH's review includes the clinical trial database, which included non-serious and serious events, and the safety database, which includes serious adverse events and nonserious adverse events of interest from clinical trial as well as non-interventional and spontaneous reporting sources. The evaluation of the clinical database was performed using the pembrolizumab ongoing aggregate safety evaluation (OASE). OASE is the MAH's largest source of unblinded aggregate monotherapy clinical trial safety data. The most recent dataset contains all safety data for subjects who received pembrolizumab monotherapy in an open-label or unmasked, completed randomized trial for which there has been a database lock on or before 31-Mar-2018 (n=9118). Comparator safety data from these trials is also included in the OASE. At present, comparators include ipilimumab, cetuximab and chemotherapy (all cytotoxic treatments combined).

The reporting rates for gastritis in subjects who received pembrolizumab monotherapy was similar to patients who received chemotherapy or ipilimumab. There were 54 reports of gastritis in pembrolizumab, which represents 0.6% of all AEs reported for pembrolizumab monotherapy. The reporting rates gastritis in 1,324 patients exposed to chemotherapy was 0.4% (n=5), and 0.4% for 256 patients exposed to ipilimumab (n=1), with no events reported in the placebo (n=502) or cetuximab (n=71) arms. Similarly, the reporting rate of gastric ulcer for pembro monotherapy was 0.1% (n=13) compared with 0.1% in the

chemo group (n=1). No events of gastric ulcer were reported in the placebo, ipilimumab or cetuximab groups.

The MAH's adverse event reporting and review database included cumulative reports received by the MAH up to a data lock point (DLP) of 9 April 2019. Using MedDRA High Level Term (HLT) categories for "Gastric ulcers and perforations" and "gastritis", 143 cases were evaluated including the following reported Preferred Terms (PTs): chronic gastritis, gastric perforation, gastric ulcer, gastric ulcer haemorrhage, gastric ulcer perforation, gastritis, gastritis erosive, gastritis haemorrhagic, haemorrhagic erosive gastritis, necrotizing gastritis, reflux gastritis and ulcerative gastritis These reports described patients who had received at least one dose of pembrolizumab in a clinical trial, or as a marketed drug. Overall, most reports were from clinical trials (75 serious, 1 non-serious), 21 reports were from non-interventional studies (17 serious and 4 non-serious) and 46 reports were spontaneous (42 serious and 4 non-serious) cases. The median age was 65.3 years, and most (83) reports were from male subjects. The median time to onset of the event was 129 days, with a range from 3 days to 1111 days.

Melanoma was the most common indication reported with 39 reports, followed by NSCLC (36), gastric and head and neck cancers (9 each). This distribution roughly reflects the composition of the clinical development population studied, and currently labelled indications for Keytruda. Review of the 128 reports without biopsy did not suggest features concerning for an association with pembrolizumab. Most reports did include endoscopic descriptions of erythema, but this is a non-specific finding and cannot be interpreted as evidence of an immune-mediated process. As noted above, histopathology is critical for confirming an inflammatory process; therefore, only reports that contained biopsy results were considered evaluable for a possible immune-mediated etiology. Of the 15 reports that included a description of histopathology of the stomach, 7 reports contained insufficient information to reasonably conclude a causal association with pembrolizumab. Three reports attributed the gastric event with other medical conditions: 2 reports described progression of metastatic disease and one report described a severe H. pylori infection. Two reports were confounded by concomitant use of NSAIDs or cytotoxic chemotherapy medications. Two reports were confounded by critical illness, and one report described a patient who recovered without corticosteroid treatment, suggesting a non-immune process. Reports with biopsy results are summarized below in Table 1. Of 11 reports which described outcomes, all subjects recovered or were recovering at the time of the report. Four subjects continued pembrolizumab treatment without interruption; three of these reports included outcome, which was recovered or recovering at the time of the report.

Table 1 Case Reports with Biopsies in Pembrolizumab Recipients

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
Attributed to metastases									
PPD investigational	PPD	Malignant Melanoma	3d	Gastritis	3	Dose Interrupted	Recovered/ Resolved	Gastric biopsy: "stomach metastases"	Attributed to disease progression
PPD investigational	PPD	Malignant Melanoma	149d	Gastritis	3	Dose Not Changed	Recovered/ Resolved	Biopsy of fundic tumor lesion showed erosive duodenitis and a gastric biopsy showed melanoma	Attributed to disease progression, NSAID use.
Attributed to H. pylori									
PPD investigational	PPD	Neoplasm Malignant/ nasopharyngeal carcinoma	124d	Gastritis	3	N/A	Recovered/ Resolved	Biopsy: severe gastritis with organisms consistent with H-pylori	Concurrent radiation enteritis; Helicobacter pylori infection: treated with PPI and antibiotics with outcome recovered.
Confounded by concomitant medications, including NSAIDs or chemotherapy									
PPD investigational	PPD	Malignant Melanoma	139d/225d	Gastritis	NR	Dose Not Changed	Recovered/ Resolved	Stomach biopsy: inflammation and not cancer cells	Concurrent condition of gastritis; negative alcohol and smoking.

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
									concomitant use of salicylic acid. Treated with sucralfate and PPI. Investigator considered event NR to pembrolizumab.
PPD spontaneous	PPD	Metastatic Malignant Melanoma	NR	Chronic gastritis	NR	Unknown	Not Recovered/ Not Resolved	Stomach biopsy: "marked active chronic gastritis with prominent intraepithelial lymphocytosis, ulcerated, favor drug reaction"	Concomitant NSAID use of indomethacin (for arthritis grade 4).
Confounded by critical illness or other medical condition									
PPD investigational	PPD	NSCLC	268 d	Gastric ulcer	3	Dose Interrupted	Recovered/ Resolved	Gastric mucosa with severe acute and chronic inflammation, abundant granulation tissue and fibrinoleukocyte material. No malignancy. No H.pylori.	Gastric ulcer occurred shortly after grade 4 middle cerebral artery infarction and hospitalization. Questionable use of NSAID. Stress ulcer due to underlying stroke is possible.
PPD	PPD	Squamous	70d	Gastritis	3	Withdrawn	Recovering	Biopsy: showed	Distant history of

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
spontaneous	PPD	Cell Carcinoma of lung	NR	Chronic gastritis	NR	Dose Not Changed	/Resolving Unknown	predominance of gastric cancer proto-cells as well as lymphocyte and severe inflammatory cell infiltration including neutrophils. Intrinsic factor antibody was positive and anti-parietal cell antibody was negative; H.pylori positive. Atrophic gastritis. Repeat biopsy 2 months later: protocancer cells, lymphocyte and neutrophil infiltration	tobacco (10/day x PPD Treated with steroid taper 2 months prior to onset of symptoms for interstitial lung disease. Also developed bacterial pneumonia at time of gastritis. Limited details about treatment of H.pylori. Second biopsy could be attributed to H.pylori infection.
Limited or incomplete information for causal assessment									
PPD spontaneous	PPD	Renal Cell Carcinoma	213d	Gastritis	NR	Withdrawn	Recovered/ Resolved with Sequelae	Biopsy: gastritis	Past medical history, concurrent conditions, and concomitant medications were not provided. Treated with PPI only outcome

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
									recovered with sequelae.
PPD Spontaneous	PPD	MSI-H Endometrial Carcinoma	216d	Gastritis	NR	Dose Interrupted	Recovering /Resolving	Duodenum biopsy: Duodenal mucosa with increase in marked increase in lamina propria and intraepithelial eosinophils, mildly prominent crypt apoptosis. Stomach biopsy: oxyntic mucosa with prominent pit apoptosis, loss of oxyntic glands, and prominent lamina propria and intraepithelial eosinophils, no helicobacter pylori organisms were identified	Treated with palliative stereotactic radiation to pelvis x 6 up to 2 weeks prior to onset of gastritis. Also, with diarrhea; limited details regarding infectious work-up. H.pylori negative by H&E.
PPD spontaneous	Unk/ Unk	Urothelial cell cancer	Unk	Gastric ulcer	NR	Dose Interrupted	Recovered/ Resolved	Stomach biopsy: no evidence of infection	Limited details, no medical history, concomitant meds or details regarding dates of treatment.
PPD	PPD	Non-small	591d	Gastritis	3	N/A	Recovered/	Biopsy: helicobacter	Previous history

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
investigational	PPD	Cell Lung Cancer Metastatic		Erosive			Resolved	type flora was not detected (normal). No histopathology reported.	of gastric ulcer. PPD . No histopathology.
PPD spontaneous	PPD	Metastatic melanoma	249d	Ulcerative gastritis Necrotiz-ing gastritis	NR NR	Withdrawn Withdrawn	Recovering /Resolving Recovering /Resolving	Ulceration with "necrosis flesh bud" in stomach and duodenum; moderate intraepithelial lymphocytes with light villous atrophy	Distant history of tobacco use until PPD No other details regarding PMH, prior medications.
PPD spontaneous	PPD	NSCLC	264d	Gastric ulcer	NR	Withdrawn	Recovering /Resolving	Specimen 1, necrotic tissue accompanied by "conglobata" infiltration of neutrophil was noted. Crypt epithelium was coated by irregular regenerated epithelium in the gastric mucosa of specimen 2, and lamina propria mucosae was accompanied by infiltration of mild chronic	History of GERD; H. pylori testing not reported.

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
								inflammatory cell and mild neutrophil. The surface was accompanied by necrotic tissue. Open ulcer was suggested. No malignant findings were noted in specimen 1 or 2.	
PPD spontaneous	PPD	Metastatic malignant melanoma	32d	Gastritis	NR	Unknown	Unknown	Esophagogastroduo denoscopy, performed in PPD PPD Pre-PPD EGD showed a 2cm hiatus hernia. Biopsies from the gastric antrum demonstrated mild chronic, minimally active antral gastritis, notably without increased intraepithelial lymphocytes. Immunohistochemis try (IHC) for Helicobacter organisms was negative.	Patient with symptoms of gastroesophageal reflux prior to pembrolizumab, had EGD and biopsy prior to pembrolizumab. Repeated EGD and biopsy after pembrolizumab. Started pembrolizumab in PPD GERD symptoms did not improve with PPI and repeat EGD and biopsy in PPD Though acute onset of

Case Number/ Report type	Age/ Sex	Indication	Time to Onset from the Earliest Therapy Start date (days)	MedDRA Preferred Terms	Max CTCAE grade	Action Taken	Event Outcome	Diagnostic Results	Comments
								PPD biopsies of the gastric antrum now revealed lymphocytic gastritis with increased intraepithelial lymphocytes, supported by IHC for CD3 and CD8. IHC for Helicobacter organisms was again negative	lymphocytic infiltration of stomach was noted after exposure to pembrolizumab, significant information was not provided including: non-invasive H.pylori testing results if any, patient's prior GI or autoimmune history, further infectious or autoimmune diagnostic work-up.
Other									
PPD spontaneous	PPD	Metastatic malignant melanoma	NR	Chronic gastritis	NR	Dose Interrupted	Recovering /Resolving	Moderate chronic erosive antral and corporal gastritis with intraepithelial lymphocytosis and the absence of Helicobacter pylori	Patient recovered with PPI only; no steroid or other immunosuppressive treatment given.

Summary

In the MAH's cumulative review of adverse events of PTs reported under the MedDRA HLTs of gastritis and gastric and duodenal ulcer, the clear majority of 143 reports described gastritis or gastric ulcer based on endoscopy alone, without tissue biopsy. It is not possible to ascribe an immune-mediated etiology to these events. Of the 15 reports which included biopsy results, confounding factors, reasonable alternative explanations (such as other medications, H.pylori infection, metastatic disease or critical illness), or limited information to rule out common explanations, including H.pylori and celiac disease precluded drawing a conclusion that pembrolizumab was primarily or causally associated with the clinical events reported.

The referenced article (Collins et al., 2017) is also difficult to interpret, and does not provide satisfactory information to implicate pembrolizumab in events of immune-mediated gastritis. The paper describes upper GI tract inflammation in 4 patients exposed to PD-1 inhibitor therapy, either pembrolizumab or nivolumab, but does not specify which treatment the 2 patients with gastric biopsy results received. None of the 4 cases described information regarding prior history of GI disease, or description of testing/results for H.pylori or celiac disease. Though NSAID use was denied in all 4 patients, other concomitant medication exposure (including chemotherapy and/or radiation therapy) was not described except to note that ipilimumab was not concurrently given. The report lacked convincing evidence that other pathologic processes were excluded before concluding that the disease process with lymphocytic infiltration of the stomach was due to pembrolizumab and could not be attributed to other causes.

Therefore, upon review of the totality of currently available information the MAH asserts that there is insufficient evidence to reasonably conclude that pembrolizumab is causally associated with events of inflammatory gastritis or gastric ulcer. Therefore, no changes to the Company Core Data Sheet, or the SmPC are warranted at this time. The MAH continues to closely monitor all serious adverse event reports, especially reports of potentially immunemediated events using a vigorous pharmacovigilance system that

includes both individual case report review, literature review and quarterly aggregate analyses of data, and will report any confirmed safety signals to regulatory authorities as required.

Assessment of the MAH's response

As requested, the MAH performed a revision of the cases of gastric ulcer across the whole (adult) safety database from all sources, following the observation during the assessment of this procedure of a SAE of gastric ulcer grade 3 with stomach biopsy revealing inflammatory infiltration. The MAH did not further discuss this case, which was however considered drug-related by investigator.

According to this review, made using MedDRA High Level Term (HLT) categories for "Gastric ulcers and perforations" and "gastritis", the reporting rate for gastritis was 0.6% (n=54) and of gastric ulcer 0.1% (n=13) for pembrolizumab monotherapy. A total of 143 cases were evaluated. Of those, 76 were from clinical trials (75 serious and 1 non-serious), 21 from non-interventional studies (17 serious and 4 non-serious) and 46 from spontaneous report (42 serious and 4 non-serious). The MAH considered as evaluable for a possible immune related aetiology only 15 cases which had biopsy report available. According to the MAH's assessment, 7 cases lack sufficient information to conclude on a causal relationship with pembrolizumab, 2 cases described progressive disease, 2 were confounded by concomitant NSAID/cytotoxic chemotherapy and 2 confounded by critical illness, 1 was associated with H.Pylori infection and 1 case recovered without corticosteroids. The MAH concluded that there is insufficient evidence to reasonably conclude that pembrolizumab is causally associated with events of inflammatory gastritis or gastric ulcer, and does not consider changes of the SmPC warranted.

It is agreed that several cases lack of sufficient information or present confounding factors, although a relation with pembrolizumab cannot be excluded for most of them. The spontaneous report [case number redacted] describes a case of gastritis in a subject with metastatic melanoma, who performed a gastric biopsy after one month of pembrolizumab showing lymphocytic gastritis, which was not evident from a biopsy taken two months before starting pembrolizumab. IHC for H.Pylori was negative in both biopsies. The outcome of this event is "unknown". The MAH stated that information on prior GI or autoimmune history was not provided, as well as further infectious or autoimmune diagnostic work-up. Based on the available data, this case is highly suggestive of a possible causal relationship of pembrolizumab with gastritis, acknowledging the lack of some information on possible concomitant alternative explanations.

Given the mechanism of action of pembrolizumab, it is considered also that there is biological plausibility in the possible induction of inflammatory gastritis/gastric ulcer. Further, gastritis and duodenal ulcers are reported as ADRs for nivolumab.

It is noted that the signal of gastrointestinal ulcer is included in the PRAC agenda of June 2019 published on EMA website (https://www.ema.europa.eu/en/documents/agenda/agenda-prac-draft-agenda-meeting-11-14-june-2019_en.pdf)

Conclusion: issue not further pursued within this procedure.

Signal of gastrointestinal ulcer is currently under discussion by the PRAC.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 2

The MAH concluded in the SmPC that "the safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab", however no supporting data to appropriately compare the safety of paediatric to adult patients have been found. The MAH is requested to provide the paediatric safety in KEYNOTE-051 with (please use the safety tables reported in the AR and report side by side the frequencies included in the most recent RSD of pembrolizumab monotherapy in adult patients). If relevant higher frequencies in single items are found in the paediatric compared to adult population, those should be discussed and, if appropriate, reflected in the SmPC. (OC)

Summary of the MAH's response

The MAH provided the requested paediatric data for adverse events compared with the pembrolizumab EU reference safety dataset (RSD), which is an internally validated dataset that includes adverse event data for the adult studies KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase), KEYNOTE-006, KEYNOTE-010, KEYNOTE- 012, KEYNOTE-013 Cohort 3, KEYNOTE-024, KEYNOTE-040, KEYNOTE-045, KEYNOTE-052, KEYNOTE-054, KEYNOTE-055, and KEYNOTE-087.

The overall incidence of adverse events and serious adverse events, including drug-related adverse events, in the KEYNOTE-051 population was similar compared with the RSD. The most frequent drug-related adverse events in KEYNOTE-051 were anemia, fatigue, lymphocyte count decreased and pyrexia, consistent with what might be anticipated in a paediatric population or with the underlying disease conditions (See Tables 4,5 and 8). Overall, the rates of AEs and adverse events of special interest (AEOSI) in tables 10 and 11 reported in KEYNOTE-051 were comparable to those observed in the adult population treated with pembrolizumab monotherapy represented by the RSD. No new immunemediated events were identified in the paediatric population.

The Applicant is of the opinion that these data support the proposed statement in section 4.8 that 'the safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab'.

Table 2
Adverse Event Summary
(Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	149	(96.8)	4,788	(96.8)
with no adverse event	5	(3.2)	160	(3.2)
with drug-related[†] adverse events	87	(56.5)	3,536	(71.5)
with toxicity grade 3-5 adverse events	69	(44.8)	2,311	(46.7)
with toxicity grade 3-5 drug-related adverse events	13	(8.4)	734	(14.8)
with serious adverse events	56	(36.4)	1,857	(37.5)
with serious drug-related adverse events	14	(9.1)	530	(10.7)
with dose modification[‡] due to an adverse event	23	(14.9)	1,607	(32.5)
who died	6	(3.9)	212	(4.3)
who died due to a drug-related adverse event	2	(1.3)	23	(0.5)
discontinued drug due to an adverse event	7	(4.5)	608	(12.3)
discontinued drug due to a drug-related adverse event	4	(2.6)	321	(6.5)
discontinued drug due to a serious adverse event	6	(3.9)	436	(8.8)
discontinued drug due to a serious drug-related adverse event	3	(1.9)	194	(3.9)

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

‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

§ Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 3
Subjects with Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab§		Reference Safety Dataset for Pembrolizumab††	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	149	(96.8)	4,788	(96.8)
with no adverse events	5	(3.2)	160	(3.2)
Pyrexia	47	(30.5)	627	(12.7)
Vomiting	40	(26.0)	637	(12.9)
Headache	34	(22.1)	622	(12.6)
Abdominal pain	32	(20.8)	448	(9.1)
Anaemia	32	(20.8)	656	(13.3)
Constipation	31	(20.1)	848	(17.1)
Nausea	28	(18.2)	1,075	(21.7)
Cough	27	(17.5)	978	(19.8)
Fatigue	27	(17.5)	1,686	(34.1)
Diarrhoea	25	(16.2)	1,066	(21.5)
Lymphocyte count decreased	20	(13.0)	90	(1.8)
Asthenia	19	(12.3)	574	(11.6)
Decreased appetite	19	(12.3)	963	(19.5)
Aspartate aminotransferase increased	18	(11.7)	300	(6.1)
Back pain	18	(11.7)	564	(11.4)
Alanine aminotransferase increased	17	(11.0)	305	(6.2)
Arthralgia	16	(10.4)	771	(15.6)
Pruritus	16	(10.4)	918	(18.6)
Dyspnoea	15	(9.7)	831	(16.8)
Pain in extremity	15	(9.7)	345	(7.0)
Rhinitis	15	(9.7)	96	(1.9)
White blood cell count decreased	15	(9.7)	46	(0.9)
Hyponatraemia	13	(8.4)	291	(5.9)
Hypothyroidism	13	(8.4)	514	(10.4)
Platelet count decreased	13	(8.4)	63	(1.3)
Upper respiratory tract infection	13	(8.4)	310	(6.3)
Blood creatinine increased	12	(7.8)	222	(4.5)
Hypertension	12	(7.8)	239	(4.8)
Nasopharyngitis	12	(7.8)	304	(6.1)
Chest pain	11	(7.1)	238	(4.8)
Hypoalbuminaemia	11	(7.1)	155	(3.1)
Rash	11	(7.1)	778	(15.7)
Sinus tachycardia	11	(7.1)	38	(0.8)
Weight decreased	11	(7.1)	447	(9.0)
Dizziness	10	(6.5)	389	(7.9)
Hypophosphataemia	10	(6.5)	114	(2.3)
Pleural effusion	10	(6.5)	150	(3.0)
Rash maculo-papular	10	(6.5)	175	(3.5)

Rhinorrhoea	10	(6.5)	97	(2.0)
Neutrophil count decreased	9	(5.8)	31	(0.6)
Oropharyngeal pain	9	(5.8)	169	(3.4)
Device related infection	8	(5.2)	15	(0.3)
Dry skin	8	(5.2)	271	(5.5)
Hypokalaemia	8	(5.2)	226	(4.6)
Nasal congestion	8	(5.2)	130	(2.6)
Insomnia	7	(4.5)	365	(7.4)
Musculoskeletal pain	7	(4.5)	342	(6.9)
Myalgia	6	(3.9)	386	(7.8)
Oedema peripheral	4	(2.6)	458	(9.3)
Urinary tract infection	2	(1.3)	336	(6.8)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 4
Subjects with Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	87	(56.5)	3,536	(71.5)
with no adverse events	67	(43.5)	1,412	(28.5)
Anaemia	12	(7.8)	153	(3.1)
Fatigue	12	(7.8)	1,072	(21.7)
Lymphocyte count decreased	11	(7.1)	42	(0.8)
Pyrexia	11	(7.1)	222	(4.5)
Aspartate aminotransferase increased	9	(5.8)	166	(3.4)
Diarrhoea	8	(5.2)	574	(11.6)
Hypothyroidism	8	(5.2)	451	(9.1)
Nausea	8	(5.2)	488	(9.9)
Rash maculo-papular	8	(5.2)	137	(2.8)
Asthenia	7	(4.5)	327	(6.6)
Arthralgia	4	(2.6)	400	(8.1)
Decreased appetite	4	(2.6)	402	(8.1)
Pruritus	4	(2.6)	729	(14.7)
Rash	4	(2.6)	580	(11.7)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 5
Subjects with Grade 3-5 Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	69	(44.8)	2,311	(46.7)
with no adverse events	85	(55.2)	2,637	(53.3)
Anaemia	14	(9.1)	202	(4.1)
Lymphocyte count decreased	9	(5.8)	27	(0.5)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 6
Subjects with Drug-Related Grade 3-5 Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	13	(8.4)	734	(14.8)
with no adverse events	141	(91.6)	4,214	(85.2)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 7
Subjects with Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	56	(36.4)	1,857	(37.5)
with no adverse events	98	(63.6)	3,091	(62.5)
Pyrexia	11	(7.1)	60	(1.2)
Pleural effusion	5	(3.2)	67	(1.4)
Device related infection	4	(2.6)	5	(0.1)
Dyspnoea	2	(1.3)	69	(1.4)
Headache	2	(1.3)	6	(0.1)
Hypertension	2	(1.3)	1	(0.0)
Lung infection	2	(1.3)	18	(0.4)
Nausea	2	(1.3)	25	(0.5)
Pneumonitis	2	(1.3)	87	(1.8)
Seizure	2	(1.3)	13	(0.3)
Sepsis	2	(1.3)	29	(0.6)
Vomiting	2	(1.3)	26	(0.5)
Anaemia	1	(0.6)	55	(1.1)
Pneumonia	1	(0.6)	154	(3.1)
Colitis	0	(0.0)	54	(1.1)
Diarrhoea	0	(0.0)	51	(1.0)
Pulmonary embolism	0	(0.0)	56	(1.1)
Urinary tract infection	0	(0.0)	57	(1.2)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 8
Subjects with Drug-Related Serious Adverse Events Up to 90 Days of Last Dose (Incidence > 0% in KN051 Treatment Group) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	14	(9.1)	530	(10.7)
with no adverse events	140	(90.9)	4,418	(89.3)
Pyrexia	4	(2.6)	15	(0.3)
Hypertension	2	(1.3)	0	(0.0)
Pleural effusion	2	(1.3)	4	(0.1)
Adrenal insufficiency	1	(0.6)	11	(0.2)
Dyspnoea	1	(0.6)	9	(0.2)
Enterocolitis infectious	1	(0.6)	0	(0.0)
Gastric ulcer	1	(0.6)	1	(0.0)
Gastrooesophageal reflux disease	1	(0.6)	1	(0.0)
Oedema peripheral	1	(0.6)	1	(0.0)
Photosensitivity reaction	1	(0.6)	0	(0.0)
Pneumonitis	1	(0.6)	81	(1.6)
Pruritus	1	(0.6)	0	(0.0)
Pulmonary oedema	1	(0.6)	0	(0.0)
Tumour flare	1	(0.6)	0	(0.0)

Table 9
Subjects with Adverse Events Resulting in Death Up to 90 Days of Last Dose (Incidence > 0% in KN051 Treatment Group) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	6	(3.9)	212	(4.3)
with no adverse events	148	(96.1)	4,736	(95.7)
Adenocarcinoma gastric	1	(0.6)	1	(0.0)
Blood creatinine increased	1	(0.6)	0	(0.0)
Ependymoma malignant	1	(0.6)	0	(0.0)
Pleural effusion	1	(0.6)	0	(0.0)
Pneumonitis	1	(0.6)	6	(0.1)
Pulmonary oedema	1	(0.6)	1	(0.0)
Sepsis	1	(0.6)	3	(0.1)

Table 10
Adverse Event Summary
AEOSI – version14.0 (Subjects in ASaT Population)

	KN051 Data for Pembrolizumab[§]		Reference Safety Dataset for Pembrolizumab[††]	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	28	(18.2)	1,180	(23.8)
with no adverse event	126	(81.8)	3,768	(76.2)
with drug-related[†] adverse events	19	(12.3)	1,022	(20.7)
with toxicity grade 3-5 adverse events	3	(1.9)	291	(5.9)
with toxicity grade 3-5 drug-related adverse events	3	(1.9)	249	(5.0)
with serious adverse events	3	(1.9)	298	(6.0)
with serious drug-related adverse events	2	(1.3)	261	(5.3)
with dose modification[‡] due to an adverse event	4	(2.6)	399	(8.1)
who died	1	(0.6)	9	(0.2)
who died due to a drug-related adverse event	1	(0.6)	9	(0.2)
discontinued drug due to an adverse event	1	(0.6)	175	(3.5)
discontinued drug due to a drug-related adverse event	1	(0.6)	173	(3.5)
discontinued drug due to a serious adverse event	1	(0.6)	121	(2.4)
discontinued drug due to a serious drug-related adverse event	1	(0.6)	119	(2.4)

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

[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[§] Includes all subjects who received at least one dose of Pembrolizumab in KN051.

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

Table 11
Subjects with Adverse Events of Special Interest
(Incidence > 0% in One or More Treatment Groups) By
AEOSI Category and Preferred Term
(Subjects in ASaT Population Treated with Pembrolizumab ‡‡)

	KN032, KN042 and KN151 for MK-3475‡		Current EU SmPC Reference Safety Dataset for MK-3475††	
	n	(%)	n	(%)
Subjects in population	154		4,948	
with one or more adverse events	28	(18.2)	1,180	(23.8)
with no adverse events	126	(81.8)	3,768	(76.2)
Adrenal Insufficiency	**1**	**(0.6)**	**39**	**(0.8)**
Adrenal insufficiency Adrenocortical	1	(0.6)	36	(0.7)
insufficiency acute Secondary	0	(0.0)	2	(0.0)
adrenocortical insufficiency	0	(0.0)	1	(0.0)
Colitis	**2**	**(1.3)**	**98**	**(2.0)**
Autoimmune colitis	0	(0.0)	6	(0.1)
Colitis	2	(1.3)	86	(1.7)
Colitis microscopic	0	(0.0)	4	(0.1)
Enterocolitis	0	(0.0)	5	(0.1)
Encephalitis	**0**	**(0.0)**	**1**	**(0.0)**
Encephalitis	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**4**	**(0.1)**
Axonal neuropathy	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	2	(0.0)
Hepatitis	**0**	**(0.0)**	**39**	**(0.8)**
Autoimmune hepatitis	0	(0.0)	17	(0.3)
Drug-induced liver injury	0	(0.0)	4	(0.1)
Hepatitis	0	(0.0)	19	(0.4)
Hyperthyroidism	**6**	**(3.9)**	**198**	**(4.0)**
Hyperthyroidism	6	(3.9)	198	(4.0)
Hypophysitis	**0**	**(0.0)**	**32**	**(0.6)**
Hypophysitis	0	(0.0)	20	(0.4)
Hypopituitarism	0	(0.0)	12	(0.2)
Hypothyroidism	**13**	**(8.4)**	**515**	**(10.4)**
Hypothyroidism	13	(8.4)	514	(10.4)
Myxoedema	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	1	(0.0)
Infusion Reactions	**5**	**(3.2)**	**121**	**(2.4)**

Infusion Reactions	**5**	**(3.2)**	**121**	**(2.4)**
Anaphylactic reaction	0	(0.0)	7	(0.1)
Anaphylactoid reaction	0	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	8	(0.2)
Drug hypersensitivity	1	(0.6)	18	(0.4)
Hypersensitivity	3	(1.9)	39	(0.8)
Infusion related reaction	1	(0.6)	50	(1.0)
Myasthenic Syndrome	**0**	**(0.0)**	**3**	**(0.1)**
Myasthenia gravis	0	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	2	(0.0)
Myocarditis	**0**	**(0.0)**	**4**	**(0.1)**
Myocarditis	0	(0.0)	4	(0.1)
Myositis	**0**	**(0.0)**	**19**	**(0.4)**
Myopathy	0	(0.0)	4	(0.1)
Myositis	0	(0.0)	14	(0.3)
Rhabdomyolysis	0	(0.0)	1	(0.0)
Nephritis	**0**	**(0.0)**	**17**	**(0.3)**
Acute kidney injury	0	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	3	(0.1)
Nephritis	0	(0.0)	1	(0.0)
Nephrotic syndrome Renal	0	(0.0)	1	(0.0)
failure Tubulointerstitial	0	(0.0)	2	(0.0)
nephritis	0	(0.0)	8	(0.2)
Pancreatitis	**0**	**(0.0)**	**13**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	1	(0.0)
Pancreatitis	0	(0.0)	11	(0.2)
Pancreatitis acute	0	(0.0)	2	(0.0)
Pneumonitis	**3**	**(1.9)**	**183**	**(3.7)**
Interstitial lung disease	0	(0.0)	14	(0.3)
Pneumonitis	3	(1.9)	170	(3.4)
Sarcoidosis	**0**	**(0.0)**	**10**	**(0.2)**
Sarcoidosis	0	(0.0)	10	(0.2)
Severe Skin Reactions	**1**	**(0.6)**	**66**	**(1.3)**

Severe Skin Reactions	**1**	**(0.6)**	**66**	**(1.3)**
Dermatitis bullous	0	(0.0)	5	(0.1)
Dermatitis exfoliative	0	(0.0)	3	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	2	(0.0)
Erythema multiforme	0	(0.0)	3	(0.1)
Exfoliative rash	0	(0.0)	2	(0.0)
Pemphigoid	0	(0.0)	3	(0.1)
Pemphigus	0	(0.0)	1	(0.0)
Pruritus	1	(0.6)	6	(0.1)
Pruritus generalised	0	(0.0)	1	(0.0)
Pruritus genital	0	(0.0)	1	(0.0)
Rash	0	(0.0)	19	(0.4)
Rash erythematous	0	(0.0)	1	(0.0)
Rash generalised	0	(0.0)	4	(0.1)
Rash maculo-papular	0	(0.0)	11	(0.2)
Rash pruritic	0	(0.0)	1	(0.0)
Rash pustular	0	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	3	(0.1)
Toxic skin eruption	0	(0.0)	2	(0.0)
Thyroiditis	**2**	**(1.3)**	**46**	**(0.9)**
Autoimmune thyroiditis	0	(0.0)	9	(0.2)
Thyroid disorder	0	(0.0)	3	(0.1)
Thyroiditis	2	(1.3)	34	(0.7)
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**20**	**(0.4)**
Diabetic ketoacidosis	0	(0.0)	9	(0.2)
Type 1 diabetes mellitus	0	(0.0)	16	(0.3)
Uveitis	**0**	**(0.0)**	**19**	**(0.4)**
Iridocyclitis	0	(0.0)	4	(0.1)
Iritis	0	(0.0)	3	(0.1)
Uveitis	**0**	**(0.0)**	**19**	**(0.4)**
Uveitis	0	(0.0)	12	(0.2)

Every subject is counted a single time for each applicable row and column.

A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

§ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 HNSCC, KN013 Cohort 3, KN024, KN040, KN045, KN052, KN054, KN055 and KN087.

Assessment of the MAH's response

The MAH has provided the requested comparative tables (KN-051 in paediatrics vs RSD in adults). The overall incidence of (all causality and drug related) AEs, G3-5 AEs, SAE and AEOSI was similar in KN-051 compared to RSD. No new immune-mediated events have been reported in the paediatric population. Based on the available data, and taking into account the limited number of paediatric subjects (154 paediatrics vs 4,948 adults), the statement "the safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab" proposed by the MAH for inclusion in section 4.8 of the SmPC is agreed.

Conclusion: issue solved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance