26 July 2018
EMA/543713/2018/corr.
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0042

Note

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

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

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List of abbreviations

Abbreviation	Definition
1L	First-line therapy (subjects who have not received any prior therapy)
2L	Second-line therapy (subjects who have received 1 prior therapy)
2L+	Second-line or later therapy (subjects who have received 1 or more prior therapies)
5-FU	5-Fluorouracil
AE(s)	Adverse event(s)
AESOI	Adverse event of special interest
ASaT	All Subjects as Treated
CI	Confidence interval
CL	Low clearance
CPS	Combined positive score
DDI	Drug-drug interactions
DOR	Duration of response
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
ITT	Intention to treat
KN	Keynote
KM	Kaplan Meier
LS	Least square
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate

Abbreviation	Definition
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand
PD-L2	Programmed cell death 2 ligand
PFS	Progression-free survival
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PS	Performance Score
PTs	Preferred Terms
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
R/M	Recurrent/metastatic
SAEs	Serious adverse events
SD	Stable disease
SOCs	System Organ Classes
TPS	Tumor proportion score
ULN	Upper limit of normal
US	United States
Vc	Volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 20 December 2017 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) on or after platinum-containing chemotherapy based on the results from KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012/ KEYNOTE-055). KN040 is a randomized, multi-center, pivotal phase III study investigating KEYTRUDA as a monotherapy versus standard treatment (methotrexate, docetaxel or cetuximab) in 495 patients with recurrent or metastatic HNSCC who have previously progressed on prior platinum. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include in SmPC section 5.2 the description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure.

An updated RMP version 15.1 was provided as part of the application.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0059/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0059/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

Scientific Advice related to the design of the pivotal study (Protocol 040/PN040) was received from the CHMP (EMEA/H/SA/2437/3/2014/II - EMA/CHMP/SAWP/545618/2014).

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	20 December 2017
Start of procedure	27 January 2018
CHMP Co-Rapporteur Assessment Report	23 March 2018
CHMP Rapporteur Assessment Report	26 March 2018
PRAC Rapporteur Assessment Report	28 March 2018
PRAC Outcome	12 April 2018
CHMP members comments	18 April 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 April 2018
Request for supplementary information (RSI)	26 April 2018
CHMP Rapporteur Assessment Report	4 June 2018
CHMP members comments	18 June 2018
Updated CHMP Rapporteur Assessment Report	22 June 2018
Request for supplementary information (RSI)	28 June 2018
CHMP Rapporteur Assessment Report	11 July 2018
PRAC Rapporteur Assessment Report	11 July 2018
PRAC members comments	n/a
CHMP members comments	20 July 2018
Updated CHMP Rapporteur Assessment Report	20 July 2018
Updated PRAC Rapporteur Assessment Report	20 July 2018
Opinion	26 July 2018

2. Scientific discussion

2.1. Introduction

Keytruda (pembrolizumab) is a humanized monoclonal anti-PD-1 antibody that blocks the interaction between programmed cell death 1 (PD-1) receptor and its ligands, programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2). The PD-1 pathway, especially the PD-1 receptor-ligand interaction, represents a major immune-control switch that may be engaged by ligands expressed in the tumor microenvironment to overcome active antitumor-specific T cell immune surveillance.

Keytruda is currently approved in EU for metastatic melanoma, metastatic non-small cell lung carcinoma, refractory classical Hodgkin lymphoma and advanced/metastatic urothelial carcinoma.

Problem statement

Head and neck squamous cell carcinoma (HNSCC) describe an anatomically heterogeneous group of cancers encompassing a variety of tumours originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx or larynx, oral cavity and laryngeal cancers being the most common. It is the sixth most common malignancy worldwide, accounting for 6% of all cancer cases and responsible for an estimated 1–2% of all cancer deaths[1][2][3]. In Europe, approximately 140.000 new cases of HNSCC were diagnosed in 2014, corresponding to an annual incidence of 43/100.000. Median age of diagnosis is in the late 60s and 70s[4][5].

More than 90% of head and neck cancers are squamous cell carcinomas, originating from the epithelium of the mucosal lining of the upper aerodigestive tract. These neoplasms are aggressive in their biologic behaviour, resulting in significant destructive disease above the clavicle, with the development of local (cervical) lymph node metastases and distant metastases, even after effective local therapy. Significantly, 10 to 30% of patients with cancer of the lip or oral cavity subsequently develop second primary neoplasms of the upper aerodigestive tract.

Tobacco, alcohol, male gender and older age are risk factors for HNSCC, together with HPV infection for cancers located in the oropharynx. Tobacco-related HNSCC disease has declined, whereas HPV-positive disease has increased[6].

Survival in HNSCC is predicted primarily by stage, anatomical site and HPV status. HPV-related oropharyngeal cancers represent a distinct entity in terms of biology, where HPV-negative HNSCC disease is driven by stepwise accumulation of mutations whereas HPV-positive disease is driven by the integration of 2 viral oncogenes that target the P53 tumour suppressor gene. Therefore, tumours have different clinical behavior, with HPV-positive disease having better prognosis and better response to treatment compared to HPV-negative cancers.

Classical presentation of HNSCC includes pain, dysphagia, odynophagia, dysphonia, otalgia, hoarseness, and citrus intolerance. Human papillomavirus-positive oropharyngeal disease is characterized with early cervical lymph node metastases. Common sites of metastases include lymph nodes, bone, and lung.

The challenges of R/M HNSCC include pain, speech, swallowing, breathing, and social function.

Patients with recurrent or metastatic (R/M) HNSCC have a poor prognosis with median overall survival of under 1 year[7].

Current Therapies in Head and Neck Squamous Cell Carcinoma

Treatment options for patients with this disease vary according to the disease setting as well as other clinical characteristics. Patients with localized HNSCC (American Joint Committee on Cancer stages I-IVB) are treated with potentially curative therapy using ≥1 treatment modalities (surgery, radiation therapy, chemotherapy, and biologic therapy). However, many patients develop recurrent disease, with a recurrence rate in early-stage HNSCC of 10-20% and in locally advanced HNSCC of about 50%, with a predominance of locoregional failure. This population includes patients whose disease recurred locally or who developed distant metastasis after initial treatment for localized disease and the rare patients with distant metastasis at first presentation. Only a limited percentage of patients with localized recurrence

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics 2016. Cancer J Clin 2016; 7-30.
[2] Argiris A, Karamouzis MV, Raben D, et al. Head and neck cancer. Lancet 2008;371:1695-709.
[3] Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell
[4] Gatta G, Botta L, Sanchez MJ, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer. 2015;51:2130.
[5] Gregoire V, Lefebvre JL, Licitra L, et al. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2010; 21 (Suppl 5): v184-v186.
[6] Leemans CR, Braakhuis B, Brakenhoff R. Molecular biology of head and neck cancer. Nature Reviews Cancer Vol 11 Jan 2011
[7] NCCN guidelines version 2.2018 – Head and Neck Cancers

can be treated with curative intent, but the vast majority receives palliative treatment with systemic therapy. Treatment of patients with unresectable, persistent, recurrent or metastatic HNSCC is dictated in large part by the patient's performance status, which is one of the most important factors associated with clinical outcome. The main treatment objectives are to prolong survival and/or provide symptom palliation.

In the first-line treatment of R/M HNSCC, combination therapy with cetuximab plus cisplatin/carboplatin plus 5-fluorouracil followed by maintenance cetuximab (the "EXTREME" regimen) has shown the best results so far, with median survival of 10-14 months[8]. In clinical practice, other combinations, such as a taxane or cisplatin plus cetuximab, are also sometimes used as first-line treatment for R/M SCCHN when patients are not fit enough for the EXTREME regimen. After disease progression on or after 1L therapy in R/M HNSCC, the treatment options are participation in a clinical trial, systemic therapy or best supportive care. Systemic therapies may include cisplatin/carboplatin, 5-FU, cetuximab, docetaxel, paclitaxel, gemcitabine, vinorelbine, methotrexate, capecitabine and nivolumab. Overall, clinical trials showed a response rate up to 20%. Combination chemotherapy has not produced better survival outcomes compared to single-agent treatment.

In 2017, Nivolumab was authorized in EU for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy, based on the result of the phase 3, randomised, open-label study (CA209141- Checkmate 141), where 361 HNSCC patients who have experienced disease progression during or within 6 months of receiving platinum-based therapy regimen were randomised 2:1 to receive either nivolumab 3 mg/kg Q2W (n=240) or investigator's choice of either cetuximab (n=15), methotrexate (n = 52) or docetaxel (n=54). The primary efficacy outcome OS was in favour of nivolumab, showing HR of 0.71 (95% CI 0.55, 0.90) p-value 0.0048, median OS 7.72 (95%CI 5.68, 8.77) vs 5.06 (95%CI 4.04, 6.24) months in nivolumab vs standard treatment respectively. PFS HR was 0.87 (95% CI 0.69, 1.11) p-value 0.2597, for a median PFS of 2.04 (95%CI 1.91, 2.14) vs 2.33 (95%CI 1.97, 3.12). Confirmed ORR were 13.3% vs 5.8%, with a median duration of response of 9.7 (2.8-20.3+) vs 4.0 (1.5+-8.5+) months.

[8] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008; 359(11):1116–1127.

Table 1: Published Clinical Trial Outcomes for Refractory Subjects with R/M HNSCC

Author	Trial Design	Population	Treatment	ORR	DCR	Median DOR	Median PFS/TTP	Median OS
Vermorken 2007 [Ref. 5.4: 048BMC]	Phase 2, open-label, uncontrolled	103 subjects with disease progression following platinum-based therapy for R/M HNSCC	Cetuximab	13%	46%	126 days	TTP 70 days	178 days
			For subjects with disease progression following cetuximab treatment would be given salvage regimen of cetuximab + platinum-based therapy (53/103 [51%] subjects received this salvage therapy)	0%	26%	-	TTP 50 days	-
Baselga 2005 [Ref. 5.4: 0488YW]	Phase 2, open-label, uncontrolled	96 subjects with disease progression following platinum-based therapy for R/M HNSCC	Cetuximab + cisplatin or carboplatin	10%	53%	153.5 days	TTP 85 days	183 days
		64 subjects were confirmed independently to have progressive disease at trial enrolment		11%	52%	100 days	TTP 72 days	150 days
Herbst 2005 [Ref. 5.4: 0488Z3]	Phase 2, open-label, uncontrolled	131 subjects treated with cisplatin + paclitaxel or cisplatin + 5-FU for two 2 week cycles;	Cetuximab + cisplatin					
		Subjects with CR or PR were given no further treatment (N=30)	PD1 subjects (N=25)	20%	64%	4.2 months	PFS 3.0 months	6.1 months
		Subjects with SD or PD (PD1) were treated further (only PD data are included)	PD2 subjects (N= 54)	16%	52%	4.1 months	PFS 2.0 months	4.3 months
		Protocol amendment permitted subjects with disease progression within 90 days after platinum-based treatment to be enrolled (PD2)						
Hitt 2011 [Ref. 5.4: 04SPK2]	Phase 2, open-label, uncontrolled	46 platinum resistant subjects	Cetuximab + paclitaxel	54%	-	-	PFS 4.2 months	8.1 months
Ferris 2016 [Ref. 5.4: 04M4TZ]	Phase 3, RCT	361 subjects who progressed within 6 months after platinum-based. Subjects were randomized on 2:1 ration, 236 subjects to nivolumab and 111 subjects to chemotherapy	Nivolumab	13.3%	-	-	PFS 2.0 months	7.5 months
			Chemotherapy (either methotrexate [N=46], docetaxel [N=52], cetuximab [N=13])	5.8%	-	-	PFS 2.2 months	5.1 months (p=0.01)

Abbreviations: 5-FU=5-fluorouracil, CR=complete response, DCR=disease control rate, DOR=duration of response, HNSCC=Head and neck squamous cell carcinoma, N=number, ORR=objective response rate, OS=overall survival, PD=progressive disease, PD1=subjects with progressive disease following trial treatment, PD2=subjects who have progressive disease within 90 days after platinum-based treatment, PFS=progression-free survival, PR=partial response, R/M=recurrent/metastatic, SD=stable disease, TTP=time to progression.

Pembrolizumab in Head and Neck Squamous Cell Carcinoma

Pembrolizumab clinical development programme in R/M HNSCC included three clinical trials in 2L+ where pembrolizumab is used as monotherapy: the controlled study KN040 (presented as pivotal in this application) and the single arm trials KN012 and KN055 (supportive studies for the sought indication). In addition, the KN048 trial is ongoing in the 1L setting, exploring both the monotherapy and pembrolizumab in combination with chemotherapy. Estimated primary completion date of KN048 is December 2018 (from ClinicalTrials.gov, NCT02358031).

The MAH applied for the following indication:

"KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy".

Based on the CHMP request to restrict pembrolizumab indication in the treatment of recurrent-metastatic HNSCC to PD-L1 expressing tumor with a TPS score ≥50%, the MAH updated the wording of the indication as follows:

"KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy (see section 5.1)."

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from preparation of an Environmental Risk Assessment (ERA) as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on the non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), an ERA justifying the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

PIVOTAL STUDY

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-040	3	Worldwide: US, EU, Rest of World (ROW)	A Phase III Randomized Trial of MK-3475 (Pembrolizumab) Versus Standard Treatment in Subjects With Recurrent or Metastatic Head and Neck Cancer	Randomized, multicenter, active-controlled, open-label clinical trial	Pembrolizumab 200 mg IV, Q3W Methotrexate 40 mg/m^2 IV QW (maximum of 60 mg/m^2 QW in the absence of toxicity) Docetaxel 75 mg/m^2 IV Q3W Cetuximab 400 mg/m^2 IV loading dose followed by 250 mg/m^2 IV QW	Males/females subjects ≥18 years of age on the day of consent Subjects with recurrent or metastatic head and neck squamous cell carcinoma	Pembrolizumab: 246 subjects Standard Treatment: 234 subjects (methotrexate n=84, docetaxel n=99, cetuximab n=71)

SUPPORTIVE STUDIES

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-3475-055V02	II	Worldwide USA Denmark Norway	Title: A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab Objectives: determine the safety, tolerability, and antitumor activity of pembrolizumab in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) who progressed on platinum and cetuximab therapy	Multicenter, non-randomized, single cohort	MK-3475 (pembrolizumab) 200 mg IV every 3 weeks on Day 1 of each 3-week treatment cycle	Males/ females, Age ≥18	171 subjects
MK-3475-012V03	Ib	Worldwide USA Japan Israel Korea Belgium Taiwan	Title: A Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Tumors Objectives: determine the safety, tolerability, and antitumor activity of pembrolizumab in subjects with recurrent, metastatic, or persistent head and neck squamous cell carcinoma (HNSCC) (trial Cohorts B and B2)	Multicenter, non-randomized, multicohort	Cohort B: MK-3475 (pembrolizumab) 10 mg/kg IV every 2 weeks on Day 1 of each treatment cycle Cohort B2: pembrolizumab 200 mg IV every 3 weeks on Day 1 of each treatment cycle	Males/females, Age ≥18 Cohort B: HNSCC, tumors with positive PD-L1 status Cohort B2: HNSCC, tumors with positive or negative PD-L1 status	Cohort B: 60 subjects Cohort B2: 132 subjects

2.3.2. Pharmacokinetics

Clinical pharmacology results for pembrolizumab specific to support approval in the treatment of adult patients with recurrent or metastatic HNSCC on or after platinum containing chemotherapy are available from study KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012 Cohort B and KEYNOTE-055).

The updated clinical pharmacology results in this submission include:

• The available data supporting the appropriateness of the 200 mg Q3W dose of pembrolizumab for HNSCC.

• Pharmacokinetic (PK) data from KN040 at 200 mg every 3 weeks (Q3W), with support from KN012-B at 10 mg/kg Q2W and from KN055 at 200 Q3W.

• The description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure, included in SmPC section 5.2.

Overview of bioanalytical methods and assay validation

To support human PK assessment, an immunoassay method employing electrochemiluminescence (ECL) detection on the Meso Scale Discovery (MSD) assay platform was used for quantification of MK-3475 in serum samples collected during clinical studies.

Initial method validation was conducted by Merck Sharp & Dohme Research Laboratories (Oss, The Netherlands). Following method transfer of a refined version of the assay and subsequent validation at the contract research organization (CRO), Intertek (San Diego, CA), the method (2nd generation assay, Report 4020) was used to support bioanalysis of MK-3475 in serum samples from clinical study P001. An updated version of the method (3rd generation assay, Report 5018) was used to support bioanalysis of all samples from clinical studies subsequent to P001. The 3rd generation assay method was later transferred and cross-validated at a second CRO, PPD (Richmond, VA) to increase the level of automation, increase of sample throughput and reduce variability.

The method validation documents for the quantitative determination of pembrolizumab are listed and summarised in the following tables:

Report 100023	1st Generation Method at Merck Sharp & Dohme Oss Site
Report 4020	2nd Generation Method at Intertek: Transfer Validation
Report 5018	3rd Generation Method at Intertek: Re-Validation
Report RCVB2	3rd Generation Method at PPD: Transfer And Cross-Lab Validation

Table 2: List of MK-3475 PK assay validation reports

Report #	Title	Date issued	Testing Facility	Key Information
100023 {3T5WK}	Validation of the electrochemiluminiscence (ECL) assay for the determination of SCH 900475 in human serum	9/2/2010	MSD, Molenstraat 110, 5342 CC Oss, The Netherlands	First drug assay validation report at Merck Not used for clinical studies.
4020 {03T5YJ}	MK-3475: Transfer validation of a quantitative ECL immunoassay using Meso Scale Discovery's sector imager 2400 for the detection of MK-3475 concentration in human serum	8/23/2011	Intertek dba ALTA Analytical Laboratory, 3985 Sorrento Valley Blvd., Suite C, San Diego, CA 92121 USA	Assay transfer validation at Intertek
5018 {03T5X5}	Re-Validation of an electrochemiluminescence immunoassay methos to quantify MK-3475 in human serum using Meso Scale Discovery's sector imager 2400 with LowCross-Buffer®	5/14/2013	Intertek dba ALTA Analytical Laboratory, 3985 Sorrento Valley Blvd., Suite C, San Diego, CA 92121 USA	Assessed the selectivity at LLOQ in normal and various cancer patient serum samples as well as specificity with LowCross-Buffer
RCVB2 {0425H2}	Validation Report: Validation of an ECL Method for the Quantitation of MK-3475 in Human Serum	11/19/2014	PPD, 2244 Dabney Road, Richmond, Virginia 23230, USA	Cross-lab valdiation

During the continued use of the 3rd generation assay at PPD it was noticed that variability at the LLOQ level of 10 ng/mL prevented the appropriate assessment of the influence of new disease states on the assay. Therefore it was decided to raise the LLOQ of the assay and change the concentration of the QCs to appropriately span the new range of the assay.

Accuracy and precision of the new QCs were assessed and appeared to be within the already established accuracy and precision (Report 04GRV4). Moreover, due to the logistical difficulties in shipping clinical serum samples collected in China from China to PPD laboratories in USA, the 3rd generation assay at PPD was transferred and cross-validated at Wuxi AppTec laboratories in Shanghai, China (Report 04RYSL) and (Report 04P467).

The validated method at Wuxi is utilized to support Pembrolizumab drug concentration analysis for study protocols where Chinese subjects are enrolled through clinical sites in China. The performance of the Wuxi validated method is summarized in the following table:

Table 3: Performance of the Wuxi drug concentration assay (3rd generation assay) validation parameters

Validation Parameters	Assay Performance
Assay Range	25 - 800 ng/mL in Human Serum
Standard Curve Accuracy	% Bias between -5.7 to 14
Standard Curve Precision	CV ≤ 4.6%
QC Accuracy	Intra Assay % Bias: between -17.0% to 4.7%
	Inter Assay % Bias: between -10.7% to 1.3%
QC Precision	Intra Assay %CV ≤ 6.3%
	Inter Assay %CV ≤ 8.4%
Dilutional Linearity	Up to 1,000,000 ng/mL
Sensitivity (LLOQ)	25 ng/mL
Prozone/Hook Effect	No apparent "hook effect" was observed at concentrations up to 1,000,000 ng/mL
Freeze/Thaw Stability	Up to 8 freeze/thaw cycles
QC Sample Stability at Room Temperature	Up to 26 hours
QC Sample Stability at Refrigerated Condition (2-8 °C)	Up to 26 hours
QC Sample Stability at -20 °C	Up to 6 Months
QC Sample Stability at -70 °C	Up to 6 Months
Selectivity	Demonstrated unspiked and at LLOQ of 10 ng/mL for Healthy subjects, and Non-Small Cell Lung Cancer,Demonstrated unspiked and at LLOQ of 25 ng/mL for Melanoma and Gastric Cancer
	Demonstrated unspiked and at LLOQ of 10 ng/mL for Hemolysis and Lipemia
Specificity	100 ng/mL PD-L1 and PD-L2, and 500 µg/mL human IgG4 had no effect on ULOQ and LLOQ quantitation
Cross-Lab (PPD – Wuxi) Validation Test on Spiked QCs	Wuxi Demonstrated cross-lab reproducibility with a set of high, med and low spiked QC samples prepared by PPD (All QCs were within 20% from nominal concentration)
Cross-Lab (PPD – Wuxi) Validation Test on Pooled Study Samples	Demonstrated cross-lab reproducibility on the same set of 30 pooled study samples (29 out of 30, 97%% of tested samples were within 30% relative bias)

ng/mL = nanogram per milliliter; CV = coefficient of variation; QC = quality control; %CV = CV, expressed as a percent

Overview of pembrolizumab ADA Method Validation

The ADA assay was originally developed and validated at Merck Sharp & Dohme Research Laboratories (Oss, The Netherlands) in November 2010, with a full assay validation. The assay was transferred to Intertek (San Diego, CA) and underwent method transfer validation in September 2011.

The method was later transferred and re-validated at a second CRO, PPD (Richmond, VA) to perform ADA analysis at the same lab conducting quantitation of pembrolizumab in serum samples.

Due to the logistical difficulties in shipping clinical serum sample out of China for bioanalytical testing, ADA method was fully validated at Wuxi AppTec laboratory in Shanghai, China to perform ADA analysis of samples for studies in which Chinese subjects are enrolled through clinical sites in China. A summary of these assay parameter performances is reported in the following table:

Table 4: Performance of the Wuxi ADA assay validation parameters

Validation Parameter	Assay Performance		
Screening Signal to Noise Cut-Point (SNC) (*Plate Cutpoint = median NC * SNC)*	Normal: SNC= 1. 22[a]		
Confirmatory Cut Point *(% abrogation)*	25.7%[a]		
Titer Cut Point Factor (TCPF) Titer Cut Point (TCP)= median NC * TCPF	Normal: TCPF= 1.39		
Sensitivity	Screening Assay: Rabbit Polyclonal Anti-CDR-Enriched anti-MK-3475 Antibody: 0.81ng/mL		
	Confirmatory Assay: Rabbit Polyclonal Anti-CDR-Enriched anti-MK-3475 Antibody: 1.01 ng/mL		
Precision *Screening assay*	Intra-assay	4.5 ng/mL	≤14.5%
		500 ng/mL	≤19.1%
	Inter-assay	4.5ng/mL	16.4%
		500 ng/mL	15.4%
Precision *Confirmatory assay*	Intra-assay	4.5 ng/mL	≤5.7%
		500 ng/mL	≤0.1%
	Inter-assay	4.5 ng/mL	13.0%
		500 ng/mL	0.1%
Precision Titer Assay: Titer Value Range	Intra Assay Titer Value Range: 658-1907 Inter Assay Titer Value Range: 856		
Selectivity/Matrix Interference	Normal: 10/10 individuals spiked at 500 ng/mL and 4.5.00 ng/mL ADA tested above the assay cut point and 9/10 unspiked individuals tested below cut point		
	Melanoma: 10/10 individuals spiked at 500 ng/mL and 4.5 ng/mL ADA tested above the assay cut point and 10/10 unspiked individuals tested below cut point		
	NSCLC: 10/10 individuals spiked at 500 ng/mL and 4.5 ng/mL ADA tested above the assay cut point and 9/10 unspiked individuals tested below cut point.		
	Gastric Cancer: 10/10 individuals spiked at 7.00500 ng/mL and 4.5 ng/mL ADA tested above the assay cut point and 2010/120 unspiked individuals tested below cut point		
	No effect of Hemolysis or Lipemia was observed in the assay.		
Drug Tolerance	Samples containing 250 ng/mL of antibody remained positive in the presence of up to 98 µg/mL of pembrolizumab		
Hook Effect	No Hook Effect observed up to 100,000 ng/mL of anti-MK-3475 antibody		
Stability	Freeze Thaw: 5cycles		
	Room Temperature: 24 hours		
	Refrigerated (2-8°C): 24 hours		

a: The screening and confirmatory cut points were established using commercially purchased drug-naïve individual normal human serum lots. Study specific cut-points may have been used during sample analysis. Refer to bioanalytical study reports for details.

SNC = Signal to Noise Cut-Point; NC = negative control; CDR = complementarity determining region; ng/mL = nanogram per milliliter; ADA = anti-drug antibody; µg/mL = microgram per milliliter.
Data Source: [Ref. 5.3.1.4: 04RYS3]

With method developed at Intertek, the anti-CDR enriched ADA positive control at 250 ng/mL can tolerate up to 25 µg/mL of pembrolizumab. The method at PPD, which includes extended overnight incubation times and optimized acid neutralization timing for further drug tolerance enhancement, can tolerate up to 124 µg/mL drug in an ADA positive control spiked at 250 ng/mL of anti-CDR enriched ADA.

The method used at Wuxi achieved comparable drug tolerance to PPD; the method can tolerate up to 98 µg/mL drug in an ADA positive control spiked at 250 ng/mL of anti-CDR enriched ADA.

A statistical evaluation was conducted to compare the drug tolerance values obtained at Wuxi and PPD and it was concluded that PPD's drug tolerance of 124 µg/mL drug at 250 ng/mL of ADA, being statistically similar to Wuxi's drug tolerance, will be used for study data obtained from both of these laboratories to assess clinical relevance of immunogenicity.

Pharmacokinetic in target population

A focused PK analysis was conducted primarily to show the similarity of observed concentrations in subjects with HNSCC from study KN040 (with supportive data from study KN012 and KN055) with the predictions from the definitive population PK analysis. This analysis is presented in the PK report (Report 04R7X0).

The definitive population TDPK model seems adequate to describe the PK data in subjects with HNSCC (see below section on PK/PD Modelling for a description of the time-dependent pharmacokinetic (TDPK) model structure).

Pharmacokinetic data in HNSCC adult subjects

PK samples were collected and measured for 241 subjects in KN040 HNSCC (200 mg Q3W).

PK schedule in KN040: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4 and 8 and every 4 cycles (12 weeks) thereafter. Post-dose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1 and Cycle 8. One additional PK sample is drawn between 72 and 168 hours (3-7 days) after Cycle 1 dosing.

Table 5: Overview of pembrolizumab included in KN-040 PK analysis

Study	Cohort/Part	Treatment	Cancer Type	Number of subjects providing PK [a]	Data cutoff
KN040	HNSCC	200 mg Q3W	HNSCC	241	15-May-2017

[a] unique subjects providing PK samples, not all subjects have Cycle 1 day 1 samples.
HNSCC : head and neck squamous-cell carcinoma
Data Source: [04R7X0: analysis-p040pkdm08]

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in HNSCC subjects from KN040 are presented in the table below.

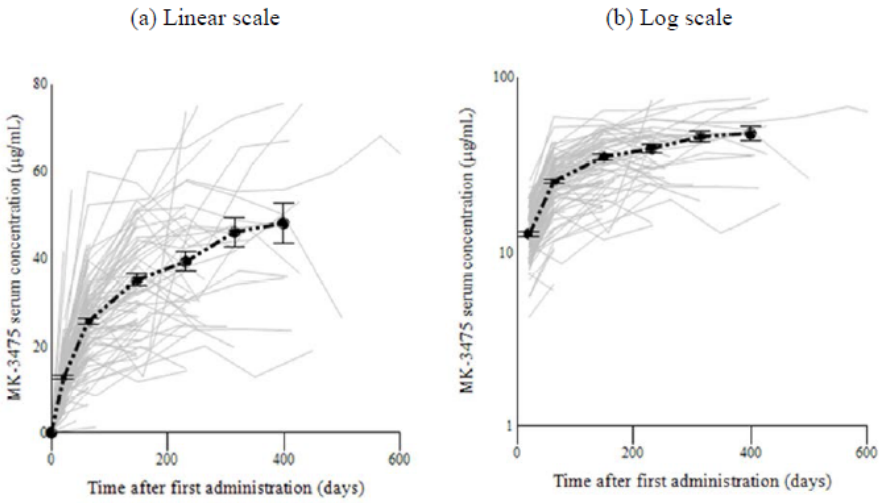
Table 6: Summary statistics of pembrolizumab predose (Ctrough), postdose (Cmax) and post Cycle 1 serum concentrationvalues following administration of multiple 200 mg IV doses with a 3 week dosing interval in KN040 HNSCC subjects

Cycle	NOM TAFD (Day)	N	GM (%CV)	GM (SD)	AM (SD)	Min	Median	Max
			(µg/mL)					
Predose (C_{trough})								
Cycle 2 (Week 3)	21	204	11.8 (44.5)	11.8 (5.6)	12.9 (5.6)	1.24	12.5	55.7
Cycle 4 (Week 9)	63	133	24.0 (38.2)	24.0 (8.5)	25.5 (8.5)	6.01	25.6	59.9
Cycle 8 (Week 21)	147	68	33.0 (38.7)	33.0 (11.9)	35.2 (11.9)	11.9	33.7	64.8
Cycle 12 (Week 33)	231	45	36.4 (41.3)	36.4 (14.9)	39.2 (14.9)	14.4	38.0	75.1
Cycle 16 (Week 45)	315	18	43.4 (40.7)	43.4 (14.0)	46.1 (14)	13.0	46.8	72.4
Cycle 20 (Week 57)	399	14	44.8 (42.0)	44.8 (17.2)	48.0 (17.2)	19.0	49.0	75.6
Postdose (C_{max}) (within 30 min post end of infusion)								
Cycle 1 (Week 0)	0	221	57.8 (22.8)	57.8 (12.9)	59.2 (12.9)	24.9	58.8	95.1
Cycle 8 (Week 21)	147	64	92.3 (26.2)	92.3 (23.8)	95.3 (23.8)	50.6	95.4	153
Post Cycle 1 (Day 3-7 post cycle 1)								
Cycle 1 (Week 0)	5	204	24.9 (32.6)	24.9 (7.3)	26.0 (7.3)	2.92	25.5	50.6

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

Data Source: [04R7X0: analysis-p040pkdm08]

The individual and arithmetic mean observed pembrolizumab trough concentrations from these same subjects are presented in the figure below.

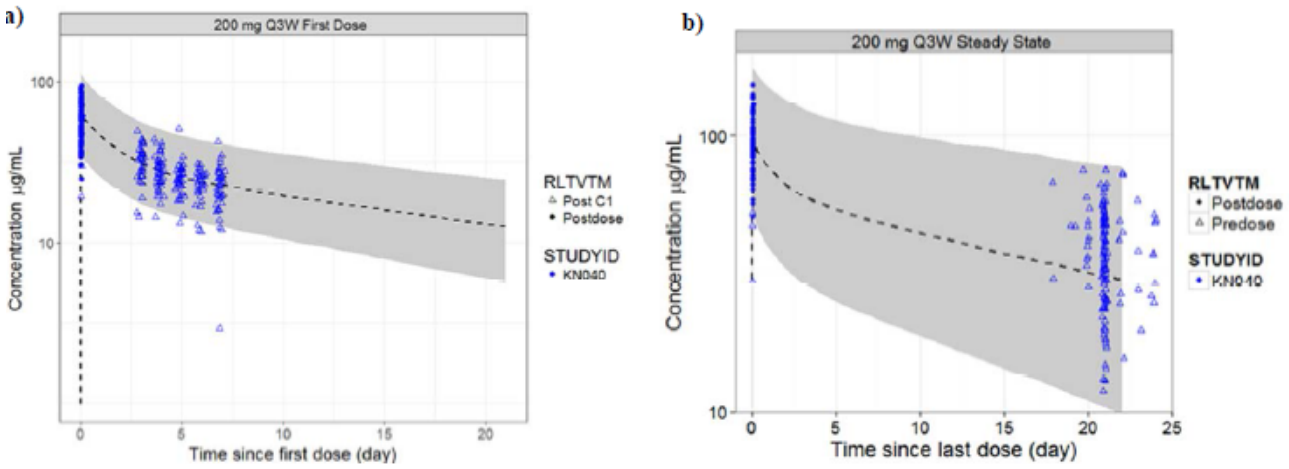


Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE. Actual times from CDR data were used for this analysis.

Data Source: [04R7X0: analysis-p040pkdm08]

Figure 1: Individual and arithmetic mean predose serum concentration of pembrolizumab following administration of multiple 200 mg IV doses with a 3 week dosing interval in KN040 HNSCC subjects (a) Linear scale, (b) Log scale

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration at cycle 1 (after first dose) and cycle 8 and beyond (at and after 21 weeks) are illustrated in the following figure.



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 with HNSCC in KN040; black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval.

Data Source: [04R7X0: analysis-p040pkdm08]

Figure 2: Observed concentration data in KN040 HNSCC subjects receiving 200 mg Q3W pembrolizumab with reference model-predicted pharmacokinetic profile for 200 mg Q3W dose regimen

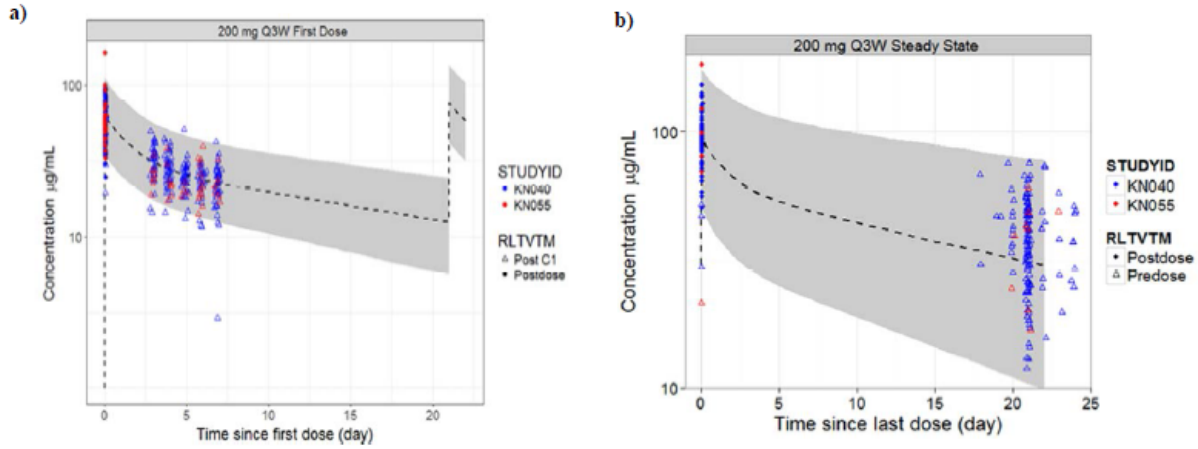
Comparison of PK data from HNSCC KN040, KN055 AND KN012-B HNSCC cohort

A comparison of the observed PK data from studies KN040, KN055 and KN012-B HNSCC subjects with predicted PK was made, by using the reference time-dependent population pharmacokinetic (TDPK) model.

Table 7: Overview of pembrolizumab studies included in PK comparison

Indication	Study/Cohort	Treatment	Number of Subjects providing PK[a]	Date cut off
HNSCC	KN040	200 mg Q3W	241	15-May-2017
HNSCC	KN055	200 mg Q3W	50	23 October 2015
HNSCC	KN012-B/HNSCC cohort	10 mg/kg Q2W	62	04 June 2015

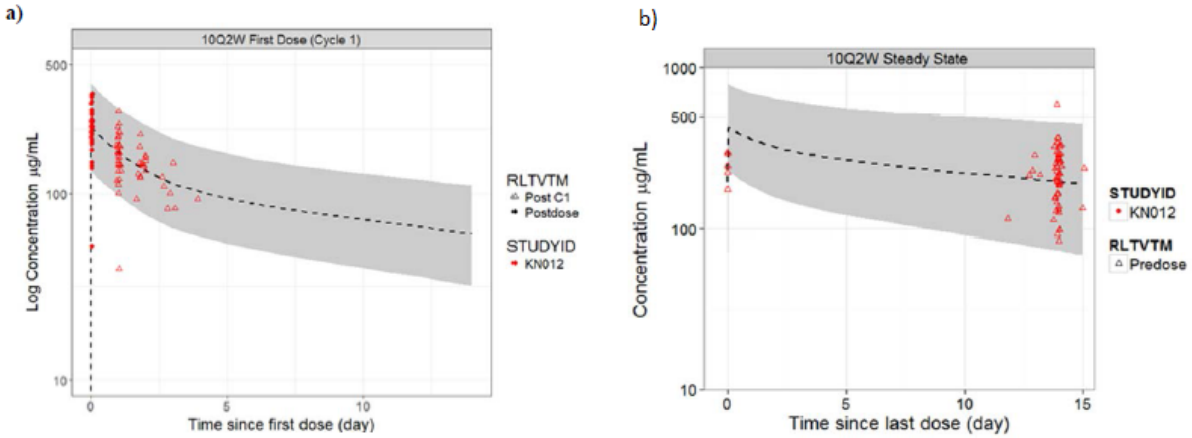
[a] number of unique subject numbers in dataset
HNSCC : head and neck squamous-cell carcinoma



a) After 1st dose on log scale; b) At and after cycle 8 (21 weeks) on log scale; Symbols are individual observed data from subjects with HNSCC in KN040 (blue triangle) and KN055 (red triangle); black dashed line (–) represents median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% PI.

Data Source: [04R7X0: analysis-p040pkdm08], [Ref. 5.3.5.3: 04D0HJ]

Figure 3: Observed concentration data in KN040 and KN055 HNSCC subjects receiving 200 mg Q3W pembrolizumab with reference model-predicted PK profile for 200 mg Q3W dose regimen



a) After 1st dose on log scale; b) At and after cycle 13 (24 weeks) on log scale, (5 samples are shown at Time Since Last Dose =0 because the dosing time and PK draw time are reported exactly the same). with a; Symbols are individual observed data from subjects with HNSCC in KN012-B (red triangle); black dashed line (–) represents median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% PI.

Data Source: [04R7X0: analysis-p040pkdm08], [Ref. 5.3.5.3: 04D0HJ]

Figure 4: Observed concentration data in KN012-B HNSCC subjects receiving 10 mg/kg Q2W pembrolizumab with reference model-predicted PK profile for 10 mg/kg Q2W dose regimen

2.3.3. Pharmacodynamics

Mechanism of action

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

Preclinical in vitro and in vivo experiments have shown that use of mAb to block PD-1 and/or PD-L1 enhances tumour-cell specific T-cell activation, cytokine production, anti-tumour effector mechanisms, and clearance of tumour cells by the immune system. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. Importantly, the antibody potentiates existing immune responses only in the presence of antigen and does not non-specifically activate T cells.

Primary and secondary pharmacology

Dose regimen

A dosing regimen of 200 mg Q3W is recommended for pembrolizumab in the treatment of adult subjects with HNSCC. The pembrolizumab dosing regimen selected for KN040 was based upon the collective clinical experience of pembrolizumab monotherapy across multiple tumor types.

Clinical response in patients from the HNSCC trials including treatment arms dosed at 200 mg Q3W (KN040, KN055 and KN012-B2) and 10 mg/kg Q2W (KN012-B) support the comparability of patient outcomes at the proposed dosing regimen of 200 mg Q3W versus 10 mg/kg Q2W. Efficacy results in

subjects with HNSCC show no clinically meaningful difference between 200 mg Q3W and 10 mg/kg Q2W dosing regimens.

In KN012-B, patients received a pembrolizumab regimen of 10 mg/kg Q2W. The objective response rate (ORR) was 16.7% (95% CI: 8.3, 28.5) with median time to response of 3.7 months (range, 1.7-16.7 months).

In KN012-B2, where pembrolizumab was administered 200 mg Q3W, ORR was 18.2% (95% CI: 12.0, 25.8) with median time to response of 2.1 months (range, 1.6-11.1 months).

In KN055, the ORR for all subjects administered with 200 mg Q3W pembrolizumab was 16.4% (95% CI: 11.2, 22.8) and the median time to response was 2.1 months (range, 1.6-11.6 months).

The lack of a meaningful difference in efficacy across a >5-fold dose range from 200 mg Q3W to 10 mg/kg Q2W in subjects with HNSCC is consistent with the previously established dose- and/or exposure-response relationships for approved indications.

Immunogenicity

No new data are available for this submission since no more data are collected with respect to previous immunogenicity dataset. The existing immunogenicity assessment for pembrolizumab is based on a sufficiently large dataset of patients.

In clinical studies in patients treated with pembrolizumab 2 mg/kg Q3W, 200 mg Q3W, or 10 mg/kg Q2W or Q3W, 36 of 2,034 (1.8%) evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralizing antibody development.

2.3.1. PK/PD modelling

Previously, a pooled population PK analysis using data from the KN001, KN002 and KN006 studies was performed to characterize serum pembrolizumab concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications (Report 04DDV3).

Subsequently, Pharmacokinetic data from KN010 and KN024 patients with NSCLC were added to the dataset, and the parameters from the existing model were re-estimated.

The dataset of 2188 subjects with advanced melanoma and Non-Small Cell Lung Cancer (NSCLC) used in the definitive population PK analysis was expanded to include data from 653 subjects from KEYNOTE-010 and 152 subjects from KEYNOTE-024 for a total N of 2993 subjects (16800 PK observations) included in the analysis.

The addition of concentration data from KEYNOTE-010 and 024 did not meaningfully alter the previously established population PK model for Pembrolizumab (Report 04DDV3). This confirms that the prior analysis can be considered definitive with respect to informing the PK characteristics. The most recent reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001 (KN001), KEYNOTE-002 (KN002), KEYNOTE-006 (KN006), KEYNOTE-010 (KN010), and KEYNOTE-024 (KN024), with an overall sample size of 2993.

Over the course of recent clinical development, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies. While earlier population PK analyses were conducted using a two-compartment PK structural model with static clearance (CL) (i.e. no time-dependent changes in CL, referred to as a 'static model'), more recent analyses have included a time-dependent pharmacokinetic (TDPK)

component for characterizing on-study changes in CL, with the intent of improving description of long-term pembrolizumab concentration-time data.

The description of pembrolizumab PK in the US prescribing information and the EU SmPC are based on these two different population PK model structures. The model supporting US prescribing information involves estimating a time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure, and the model supporting the EU SmPC assumes a static clearance (with no time-dependent changes).

To support the harmonization of pembrolizumab PK information in the EU SmPC and US prescribing information, a final rerun of the TDPK parameterization and covariate search has been conducted, again using the current SmPC dataset (n=2993; table below).

Table 8: Population PK Parameters From the Existing Label Models Versus the Proposed Updated PK Model

	Static Model, Current SmPC Dataset (N=2993)			Time-Dependent Model, Current USPI Dataset (N=2841)			Proposed Updated Label Time-Dependent Model, N=2993		
Parts and Studies included in the analysis	**Melanoma/NSCLC; A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from P001, P002, P006, P010, P024**			**Melanoma/NSCLC; A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from P001, P002, P006, P010**			**Melanoma/NSCLC; A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from P001, P002, P006, P010, P024**		
Data cut-off date	**P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014 P010V01; 30-September-2015 P024V01; 09-May- 2016**			**P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014 P010V01;**			**P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014 P010V01; 30-September-2015 P024V01; 09-May- 2016**		
Parameter	**Value**	**%RSE**	**%CVa**	**Value**	**%RSE**	**%CVa**	**Value**	**%RSE**	**%CV**
CL (L/day)	**0.229**	**1.67**	**36.8**	**0.257**	**2.19**	**31.8**	**0.281**	**1.84**	**31.4**
Vc (L)	**3.52**	**0.938**	**20.0**	**3.48**	**0.713**	**19.6**	**3.53**	**0.924**	**19.3**
Q (L/day)	**0.769**	**3.08**	**36.8**	**0.894**	**4.07**	**31.8**	**0.889**	**4.04**	**31.4**
Vp (L)	**3.96**	**1.72**	**20.0**	**2.84**	**4.72**	**19.6**	**2.75**	**4.47**	**19.3**
IMAX	**NA**	**NA**		**-0.204**	**-8.53**	**17.8**	**-0.218**	**-8.26**	**17.5**
TI50 (day)	**NA**	**NA**		**67.4**	**11.1**		**65.5**	**10.3**	
Hill	**NA**	**NA**		**3.1**	**2.18**		**2.99**	**6.79**	
α for CL and Q	**0.595**	**6.12**		**0.567**	**5.882**		**0.534**	**5.66**	
α for Vc and Vpc	**0.51**	**4.86**		**0.547**	**4.22**		**0.514**	**4.61**	
Albumin on CL	**-0.902**	**6.78**		**-0.851**	**-6.78**		**-0.849**	**-6.67**	
eGFR on CL	**0.132**	**18.9**		**0.121**	**17.7**		**0.123**	**17.4**	
GENDER on CL	**-0.151**	**8.81**		**-0.159**	**-8.11**		**-0.162**	**-6.98**	
Cancer Type (NSCLC vs Mel +other) on CL	**0.0745**	**22.4**		**0.0529**	**29.5**		**NA**	**NA**	
Baseline ECOG on CL	**-0.0666**	**22.1**		**0.0651**	**22.7**		**-0.0697**	**-17.5**	
Baseline tumor size on CL	**0.102**	**9.37**		**0.0982**	**9.08**		**0.0933**	**9.17**	
Bilirubin on CL	**NA**	**NA**		**-0.0485**	**-28.7**		**-0.0488**	**-28.5**	
Albumin on Vc	**-0.224**	**17.6**		**-0.226**	**-16.6**		**-0.233**	**-16**	
GENDER Vc	**-0.129**	**8.06**		**-0.129**	**-8.22**		**-0.131**	**-7.44**	
Cancer Type (NSCLC vs Mel +other) on Vc	**-0.0532**	**19**		**NA**	**NA**		**-0.059**	**-16.7**	
Residual error	**-0.261**	**1.81**		**-0.251**	**-1.86**		**-0.249**	**-1.85**	

a %CV of residual error is related to estimate of between-subject variability on this parameter
Presented population parameter estimates exclude effects of covariates; therefore apply to a hypothetical typical patient with average characteristics. CL: clearance; Vc: central volume of distribution; Q: intercompartmental clearance; Vp: peripheral volume of distribution; %RSE: relative standard error (%); 95% CI: 95% confidence interval of parameter estimate based on bootstrap results; %CV: coefficient of variation of between-subject distributions of parameters; NA: not applicable.
Peer Reviewed per SOP QP2-005.

Present Time-Dependent Model

General model development procedures, described in the original reports 04FYYY and 04FFLX, were followed with the new expanded dataset used in this analysis (16800 pembrolizumab concentration from 2993 subjects).

In brief, the population PK analysis was performed using a non-linear mixed effects modelling approach. Model selection was based on the Log- Likelihood Criterion, goodness of fit plots and scientific plausibility.

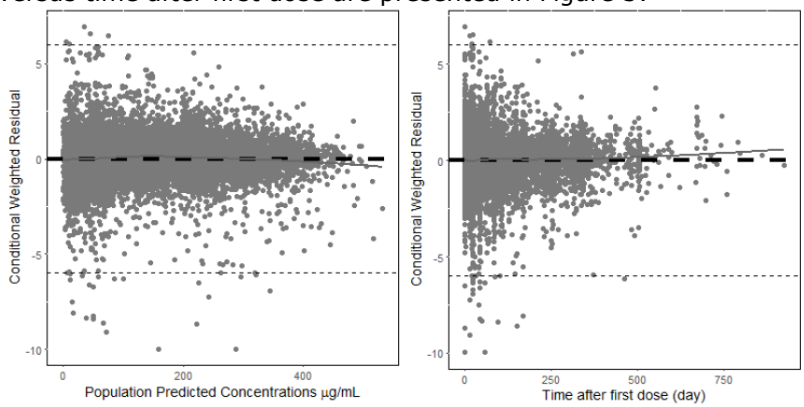
Identification of covariates was done using automated stepwise covariate model building. The covariate was retained in the model during the forward addition step if there was a reduction in the objective value, i.e. OFV, of 6.63 or more ($P < 0.01$, degree of freedom [df] = 1). In the subsequent backward deletion step, an OFV increase greater than 10.8 ($P \leq .001$, df = 1) was required for a covariate to be retained in the model.

Table 9: Results of the covariate evaluation

Covariates	CL	Central Volume
Age	No[a]	No
Gender	**Yes**	**Yes**
eGFR	**Yes**	No
AST	No	No
Albumin	**Yes**[b]	**Yes**
Bilirubin	Yes	No
Race	No	No
Cancer type	No	**Yes**
Use of glucocorticoids	No	No
BSLD	**Yes**	No
Baseline ECOG performance	**Yes**	No
PDL1	No	No
Smoking status	No	No

[a]No means covariate was not found statistically significant according to SCM algorithm
[b]Yes means covariate was retained by SCM algorithm

Reliability of the present TDPK model was checked with a range of goodness of fit plots as well as a bootstrap evaluation and visual predictive checks.
Plots of conditional weighted residuals versus population predictions and of conditional weighted residuals versus time after first dose are presented in Figure 5:



Dots are individual data. Dashes line is zero line whilst the solid line is the smooth line.

Figure 5: Conditional weighted residual diagnostic plots of the present time-dependant PK model

The present TDPK model parameter estimates and bootstrap estimates are presented in

Table 10. The covariate model was fitted to 1000 bootstrap replicate datasets to evaluate its stability and performance. Among the 1000 runs, 137 (13.7%) reported 'minimization terminated' errors, and thus, were skipped when calculating the bootstrap results. The 95% CIs calculated from bootstrap for all of parameter estimates obtained from successfully converged bootstrapping runs are summarized in the table below.

Table 10: Comparison of present time-dependant model estimates and bootstrap estimates

Parameters	Estimates	Mean Bootstrap	95% CI	% RSE	Shrinkage
CL (L/day) [a]	0.281	0.281	[0.268, 0.291]	1.84	
Vc (L) [b]	3.53	3.53	[3.47, 3.6]	0.924	
Q (L/day)	0.889	0.887	[0.822, 0.959]	4.04	
Vp (L)	2.75	2.76	[2.53, 3.14]	4.47	
α for CL and Q[c]	0.534	0.533	[0.473, 0.59]	5.66	
α for Vc or Vp[c]	0.514	0.513	[0.466, 0.562]	4.61	
IMAX	-0.218	-0.216	[-0.254, -0.157]	8.26	
TI50 (day)	65.5	66.6	[54.2, 88.6]	10.3	
Hill	2.99	3.26	[2.44, 4.48]	6.79	
Albumin on CL	-0.849	-0.852	[-0.959, -0.749]	6.67	
Bilirubin on CL	-0.0488	-0.0488	[-0.0766, -0.0212]	28.5	
BSLD on CL	0.0933	0.0935	[0.0772, 0.111]	9.17	
eGFR on CL	0.123	0.123	[0.0809, 0.165]	17.4	
Gender on CL	-0.162	-0.162	[-0.185, -0.138]	6.98	
Baseline ECOG on CL	-0.0697	-0.0695	[-0.0951, -0.0438]	17.5	
Albumin on Vc	-0.233	-0.234	[-0.311, -0.154]	16	
Gender on Vc	-0.131	-0.131	[-0.15, -0.111]	7.44	
Caner type on Vc	-0.0590	-0.0593	[-0.0797, -0.0394]	16.7	
Random Effect	**Estimates**	**Mean Bootstrap**	**95% CI**	**%RSE (%CV) [d]**	**Shrinkage**
IIV on CL or Q*	0.0939	0.0937	[0.082, 0.11]	6.59 (31.4%)	15.5
IIV on Vc or Vp*	0.0364	0.0361	[0.0303, 0.0422]	7.86 (19.3%)	27.6
IIV on IMAX[f]	0.0300	0.0304	[0.0242, 0.0381]	11.8 (79.5%)	48.5
Residual Error	**Estimates**	**Mean Bootstrap**	**95% CI**	**% RSE**	**Shrinkage**
	-0.249	-0.248	[-0.257, -0.24]	1.85	13.5

RSE: Relative standard error;
IIV: inter-individual variability
[a] $CL=0.281x(WGT/74.872)^{0.534}x(ALB/39.0)^{(-0.849)}x(BIL/8.90)^{(-0.0488)}x(BSLD/90.10)^{0.0933}$ $x(eGFR/88.71)^{0.123}x[(1-0.162)$ if female] $x[(1-0.0697)$ if BECOGN=0]
[b] $Vc=3.48(WGT/74.872)^{0.514}$ $x(ALB/39.0)^{(-0.233)}$ $x[(1-0.131)$ if female] $x[(1-0.0590)$ if NSCLC]
[c] α= power value for weight-based scaling
[d] Percentage of coefficient of variation (%CV)
* %CV= square root (exp(OMEGA) -1) *100, [f] %CV=(square root (OMEGA)/ THETA) *100

VPC stratified by dose and dose regimen (200 mg Q3W) of trough samples is presented in Figure 6:

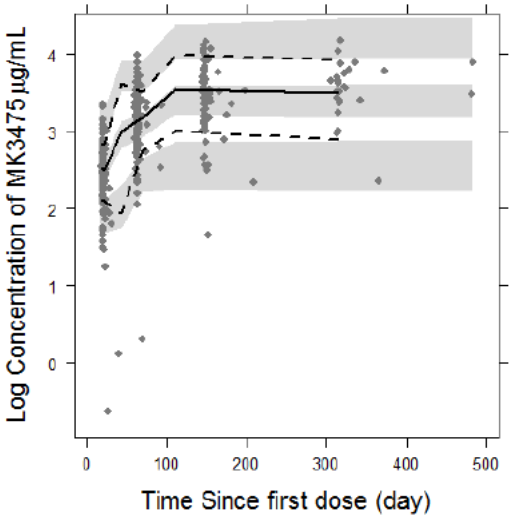
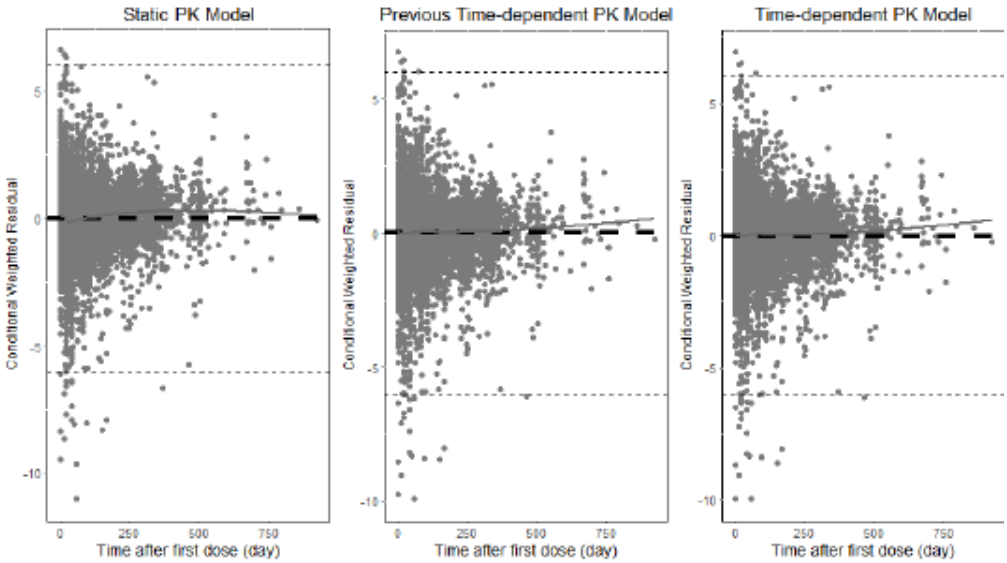


Figure 6: Visual predictive check for trough sample concentrations of the 200 mg Q3W dosing group from the present time-dependent PK model

Comparison To Prior PK Analyses Supporting Product Labeling

The results and performance of the static PK and TDPK models using KN001,-002,-006,-010, and -024 (04FFLX) as well as the TDPK model from KN001,-002,-006, and -010 reference dataset (04FYYY) are compared with results of the present analysis. Plots of conditional weighted residuals versus time after first dose of the previous static (04FFLX), previous TDPK (04FYYY), and present TDPK model are shown in **Figure 7**.



Dots are individual data. Dashes line is zero line whilst the solid line is the smooth line.

Figure 7: Comparison of conditional weighted residuals between static PK model from p1p2p6p10p24, time-dependant PK model from p1p2p6p10 and present TDPK model from p1p2p6p10p24

A comparison of parameter estimates between Static PK Model (04FFLX), previous Time-Dependent PK Model (04FYYY) and Present TDPK Model was provided in **Table 8** (reported above).

Consistent with prior findings, this TDPK model indicates that on-study changes in CL with time are small in magnitude (~20% average reduction) relative to the clinical dose range evaluated (~500% from 2 mg/kg to 10 mg/kg). The covariate analysis was repeated and a similar set of covariates as selected for the original static PK model were identified for the TDPK model. In general, the PK parameter values, including magnitudes of these covariate effects were similar between the TD and current SmPC static PK models, suggesting no clinically significant impact of these new results.

Estimation of derived pharmacokinetic parameters

The population TDPK model described in this report was used to estimate secondary PK parameters of pembrolizumab for inclusion in product labelling:

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] at steady state than that after the first dose [252mL/day (37%)]. The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%) and for terminal half-life (t1/2) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing.

The systemic accumulation of pembrolizumab at steady-state is 2.1 fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

2.3.2. Discussion on clinical pharmacology

Clinical pharmacology results for pembrolizumab specific to support approval in the treatment of adult patients with recurrent or metastatic HNSCC on or after platinum containing chemotherapy are available from study KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012 Cohort B and KEYNOTE-055).

The approach taken by the applicant was to compare the observed PK data for the current indication, HNSCC, with the predictions from the reference model.

The reference pharmacokinetic model for this submission was the TDPK model instead of the previous Static PK model (Report 04DDV3). In fact, over the course of recent clinical development, pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies. While earlier population PK analyses were conducted using a two-compartment PK structural model with static clearance (CL) (i.e. no time-dependent changes in CL, referred to as a 'static model'), more recent analyses have included a time-dependent pharmacokinetic (TDPK) component for characterizing on-study changes in CL, with the intent of improving description of long-term pembrolizumab concentration-time data.

Pembrolizumab serum concentrations in cycle 1, 2 and 8 observed at 200 mg Q3W in HNSCC patients are comparable to the range of concentrations at the same dose levels observed in patients with other type of cancer (Melanoma, NSCLC, UC…), and as general consideration, slight differences are considered unlikely to be clinically relevant in light of the flat relationship between dose and exposure.

The observed concentrations in HNSCC generally fall within the range of predicted concentrations, both after first dose and at steady state (at and after cycle 8) indicating that the definitive population TDPK model provides an adequate representation of the pembrolizumab pharmacokinetics in HNSCC, in addition to melanoma and NSCLC.

Further to the CHMP request, the MAH provided a direct comparison of the observed PK data (trough and peak concentrations at each cycle) with those obtained with the 200 mg Q3W flat dose for other tumour types (data not shown). Boxplots showed that concentrations from KEYNOTE-040 were comparable with the concentrations at the same time points for the same 200 mg Q3W dose from across multiple protocols/tumour types.

The MAH took the opportunity of this extension of indication to include in SmPC section 5.2 the description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure.

The magnitude of on-study change in clearance with the TDPK model is about 20%, therefore it is not considered clinically meaningful. The proposed final dataset is based on the EU SmPC dataset consisting of PK data from KEYNOTE-001,-002, -006, -010 and -024 (n=2993).

An increment of roughly 20% and 15%, for CL and Q respectively, as well as a decrement of the %CV values from 36.8% to 31.4% for both CL and Q parameters has been observed in the proposed updated label time dependent model (TDPK).

Overall, the MAH's proposal to implement a TDPK model structure is endorsed as well as the proposed update of PK parameters obtained from this model in EU SmPC section 5.2.

No dose finding study was conducted for pembrolizumab monotherapy for treatment of HNSCC. The recommended dose and schedule of pembrolizumab monotherapy for treatment of HNSCC is the same as that approved for 1L NSCLC, cHL and urothelial carcinoma monotherapy: 200 mg IV infusion over 60 minutes Q3W. This is considered acceptable.

Regarding immunogenicity, no new data are available for this submission since no more data are collected respect to the previous immunogenicity dataset. The existing immunogenicity assessment for pembrolizumab is based on a sufficiently large dataset of 3268 patients, with a very low observed rate of treatment emergent ADA (1.8%) and no demonstrated impact on efficacy or safety. This percentage was consistent across tumor type.

Bioanalytical methods and assay validation

The 3rd generation assay at PPD was transferred and cross-validated at Wuxi AppTec laboratories in Shanghai, China (Report 04RYSL) and (Report 04P467), due to the logistical difficulties in shipping clinical serum samples collected in China from China to PPD laboratories in USA.

The validated method at Wuxi is utilized to support Pembrolizumab drug concentration analysis for study protocols where Chinese subjects are enrolled through clinical sites in China. The methods' main characteristics were correctly investigated, and resulted within the required specifications. The two methods were then compared through cross-validation.

A cross-validation exercise between the 3rd generation assay at PPD and method developed at Wuxi was performed with 30 clinical samples to determine the methods' result comparability. The MAH concluded that the cross lab reproducibility (PPD-Wuxi) on the same set of 30 pooled study samples was demonstrated considering that 29 out of 30 of tested samples were within the 30% relative bias.

However, these results are not compliant with the acceptance criteria reported in the relevant Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) section 4.3 Cross validation: […] For study samples, the difference between the two values obtained should be within 20% of the mean for at least 67% of the repeats.[…]. In the submitted cross-validation method, the difference between the two values were within 20% only for 17 pooled study samples out of 30 (56,7%). Data demonstrate that the concentration data obtained at Wuxi AppTec laboratories were lower when compared to the concentration data obtained at PPD.

Considering that "*the outcome of the cross validation is critical in determining whether the obtained data are reliable and whether they can be compared and used",* the MAH was requested to discuss on this issue and extensively justify deviation from relevant guideline.

The MAH clarified that all pembrolizumab serum concentration submitted in this extension of indication (PK data from KEYNOTE-040, and from KEYNOTE-012/KEYNOTE-055) were generated at PPD laboratories while analysis of pembrolizumab serum concentrations at Wuxi AppTec laboratories (located in Shanghai, China) is limited to clinical sample collections from clinics in China.

Regarding the cross validation per se, the MAH will consider the cross-validation data in a manner consistent with the relevant guideline prior to the submission of future marketing applications, which may include pembrolizumab serum concentration data generated at multiple laboratories.

2.3.3. Conclusions on clinical pharmacology

Overall**,** the pharmacokinetics and immunogenicity of pembrolizumab has been sufficiently investigated for the extension of the indication of pembrolizumab 200 mg every 3 weeks for treatment of HNSCC.

2.4. Clinical efficacy

To support the Keytruda extension of indication as treatment of patients with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy, the MAH submitted the results of the pivotal trial KEYNOTE-040 study (KN040), an open-label, Phase 3, randomized, multicenter, active-controlled clinical trial

evaluating the efficacy and safety of pembrolizumab (200 mg every 3 weeks [Q3W]) versus the choice of 3 different standard treatment options (ie, methotrexate, docetaxel, or cetuximab) in subjects with disease progression occurring during or after a platinum-containing chemotherapy regimen (eg, carboplatin or cisplatin) administered either as 1L or 2L treatment (eg, R/M setting), or recurrence/disease progression within 3 to 6 months following combination therapy with platinum-containing chemotherapy (eg, locally advanced setting).

In addition, data derived from two supportive studies KEYNOTE-012 (KN012) and KEYNOTE-055 (KN055) have been provided. KN012 is an open-label, multicohort, multicenter, non-randomized Phase 1b trial of pembrolizumab in subjects with advanced solid tumors. Cohort B (10 mg/kg Q2W) enrolled subjects with PD-L1 positive (based on a prototype IHC assay ≥1% PD-L1 membrane staining of tumor cells or the presence of a stromal banding pattern) HNSCC and Cohort B2 (200 mg Q3W) is an "all comers" cohort (enrolling HNSCC subjects regardless of PD-L1 tumor status). Data from Cohorts B and B2 have been pooled and presented here. KN055 is an open-label, single-cohort, multicenter, non-randomized Phase 2 trial of pembrolizumab (200 mg Q3W) in subjects with R/M HNSCC regardless of PD-L1 or HPV status and whose disease had progressed on or after platinum-containing chemotherapy and cetuximab therapy.

2.4.1. Dose response study(ies)

No specific dose-response studies have been performed for HNSCC population. Pembrolizumab has been administered in R/M HNSCC at a fixed dose regimen of 200 mg Q3W to subjects in all three trials, with the exception of cohort B in KN012 (including 61 patients PD-L1 positive) who received pembrolizumab at 10 mg/kg Q2W.

Pembrolizumab was initially approved for advanced melanoma at 2 mg/kg Q3W. Subsequent approvals for adult subjects were at 200 mg Q3W dosing regimens for multiple other indications. The choice of the switch to the flat dose was based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

2.4.2. Main study

KEYNOTE-040 - A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer

Methods

Study participants

Main inclusion criteria

- Age ≥ 18 years
- Histologically or cytologically-confirmed recurrent (recurrent disease that is not amenable to curative treatment with local and/or systemic therapies) or metastatic (disseminated) head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx that is considered incurable by local therapies. Subjects may not have any other primary tumor site (e.g. nasopharynx).
- Prior platinum failure as defined by, either:

a. Disease progression after treatment with a platinum-containing regimen for recurrent (disease not amenable to curative treatment)/metastatic disease. Note: Disease progression may occur at any time during or after a platinum-containing regimen (e.g. carboplatin or cisplatin) which was administered in either 1L or 2L in the recurrent/metastatic setting

OR

b. Recurrence/progression within 6 months of prior multimodal therapy using platinum (e.g. locally advanced setting)

- Have results from local testing of HPV positivity for oropharyngeal cancer defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point. Note: HPV stratification in this trial will be performed using local or central testing of HPV status in patients with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative.
- Have provided tissue for PD-L1 biomarker analysis – and received the PD-L1 results – (PD-L1 analysis will be blinded to both site and sponsor) from a newly obtained core or excisional biopsy. Note: Patients for whom newly obtained samples cannot be obtained (e.g. inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the Sponsor. Note: If emerging data indicate a high concordance in PD-L1 expression scores between newly obtained and archival samples, archived samples may be acceptable.
- Have radiographically measurable disease based on RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
- ECOG PS of 0 or 1
- Adequate organ function

<u>Main exclusion criteria</u>

- disease suitable for local therapy administered with curative intent.
- progressive disease within 3 months of completion of curatively intended treatment for locoregionally advanced or recurrent HNSCC. Note: This exclusion criterion is only applicable for subjects who have not had treatment in the metastatic/recurrent setting.
- previously treated with 3 or more systemic regimens given for recurrent and/or metastatic disease.
- Patients previously treated in the recurrent/metastatic setting or resistant in the locally advanced setting to one of the 3 standard of care agents in this trial (i.e. docetaxel, methotrexate, or cetuximab) may not receive the same agent if randomized to the standard treatment arm
- diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
- prior anti-cancer monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a

previously administered agent. Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

- received an investigational study therapy or used an investigational device within 4 weeks prior to randomization.
- additional malignancy within 5 years prior to randomization with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or curatively resected in situ cervical and/or breast cancers.
- known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
- active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted.
- active, non-infectious pneumonitis; active infection requiring systemic therapy; known history of HIV, known active Hepatitis B or Hepatitis C
- pregnant or breastfeeding

Treatments

Drug	Dose/Regimen	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle (3 week cycles)	Experimental
Methotrexate	40 mg/m2 (maximum of 60 mg/m2 weekly in the absence of toxicity)	QW	IV infusion	Days 1, 8, and 15 of each cycle (3 week cycles)	Active-comparator
Docetaxel	75 mg/m2	Q3W	IV infusion	Day 1 of each cycle (3 week cycles)	Active-comparator
Cetuximab	400 mg/m2 loading dose followed by 250 mg/m2	QW	IV infusion	Days 1, 8 and 15 of each cycle (3 week cycles)	Active-comparator

QW = Every week; Q3W = every 3 weeks

The choice of standard therapy for a subject must be identified and documented prior to randomization.

Patients randomized to standard therapy who discontinue will not be crossed-over to pembrolizumab.

Subjects resistant to one of the 3 standard treatments in this trial (ie, methotrexate, docetaxel, or cetuximab) could not receive the same agent if randomized to the standard treatment group.

Administration of trial treatments continued until any of the following occurred: documented disease progression (i.e. radiographic PD confirmed by the site at least 28 days after verification of progression by central imaging vendor, with the option of continuing treatment in patient is clinically stable while awaiting radiologic confirmation of progression), unacceptable AEs, intercurrent illness that prevented further administration of treatment, investigator's decision to withdraw the subject, subject (or legally

acceptable representative) requested treatment discontinuation, pregnancy, subject noncompliance, completion of 24 months of treatment with pembrolizumab, subject lost to follow-up, or administrative reasons.

Discontinuation of treatment may be considered for subjects with confirmed CR treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

The first on-study imaging was at 9 weeks after first dose of study treatment and then every 6 weeks thereafter or more frequently if clinically indicated. After 1 year, imaging time point will occur every 9 weeks.

In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window).

Objectives

Primary Objective

- To compare the OS in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment in all subjects

Key Secondary Objectives

- To compare OS in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment in subjects with PD-L1 Positive Tumor Expression (CPS ≥1)
- To compare ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment in subjects with PD-L1 Positive Tumor Expression (CPS ≥1)
- To compare progression-free survival (PFS) per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment in subjects with PD-L1 Positive Tumor Expression (CPS ≥1)
- To compare ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment in all subjects
- To compare PFS per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment in all subjects

Other Secondary Objectives

The following objectives were evaluated separately among (1) Subjects with CPS ≥ 1 and (2) All subjects regardless of PD-L1 expression:

- To evaluate the safety and tolerability profile of pembrolizumab.
- To evaluate Time to Progression (TTP) and Duration of Response (DOR) per RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.
- To evaluate PFS per modified RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Exploratory Objectives

- To compare OS and PFS and ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with strongly positive PD-L1 expression defined by Tumor Proportion Score (TPS) ≥ 50% in R/M HNSCC treated with pembrolizumab compared to standard treatment.
- To evaluate changes in health-related quality of life assessments from baseline in subjects with R/M HNSCC using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-H&N35.
- To characterize utilities in previously-treated subjects with R/M HNSCC cancer using the European Quality of Life Five-Dimensions Questionnaire (EuroQoL EQ-5D™).
- To investigate the relationship between pembrolizumab treatment and biomarkers expression in predicting disease response (eg, PD-L1, genetic variation, serum PD-L1) from newly obtained or archival tumor tissue and blood, including serum and plasma.
- To evaluate PFS by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to standard treatment.

All subjects **=** Subjects regardless PD-L1 expression

Subjects with PD-L1 Positive Tumour Expression = Subjects with Combined Positive Score (CPS) ≥1 (PD-L1 positive expression henceforth abbreviated as CPS ≥ 1). CPS is defined as the number of PD-L1 staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

Outcomes/endpoints

Endpoints		**Analysis Populations**	**Definitions**
Primary	OS	ITT all-comers	Time from randomization to death due to any cause
Key Secondary	OS	PD-L1 by CPS ≥1	Time from randomization to death due to any cause
	PFS	ITT all-comers and PD-L1 by CPS ≥1	Time from randomization to first PD (per RECIST 1.1 based on central radiology review) or death due to any cause
	ORR	ITT all-comers and PD-L1 by CPS ≥1	Proportion of subjects who had CR or PR (per RECIST 1.1 based on central radiology assessment)
Other Secondary	DOR	ITT all-comers and PD-L1 by CPS ≥1	Time from first documented evidence of CR or PR until PD (per RECIST 1.1 based on central radiology assessment) or death
Exploratory	OS	PD-L1 by TPS ≥50%	Time from randomization to death due to any cause
	PFS	PD-L1 by TPS ≥50%	Time from randomization to first PD per RECIST 1.1 based on central radiology review or death due to any cause
	PFS mRECIST	ITT	Per mRECIST based on central radiology assessment in ITT population
	ORR	PD-L1 by TPS ≥50%	Proportion of subjects in analysis population who had CR or PR per RECIST 1.1 based on central radiology assessment
	PFS2	ITT	Evaluation of PFS by Investigator review in the next line of therapy
	EORTC QLQ-C30	FAS	Cancer specific standard instruments for measuring HRQOL
	EORTC QLQ-H&N35	FAS	Standard instruments for measuring QOL in subjects with head and neck cancer
	EuroQoL EQ-5D	FAS	Standardized instrument for measuring patient-reported health outcomes

Abbreviations: CPS=Combined Positive Score; CR=Complete response; DOR=Duration of response; EORTC= European Organisation for the Research and Treatment of Cancer; EuroQoL EQ-5D=European Quality of Life Five-Dimensions Questionnaire; HPV=Human papillomavirus; HRQOL=Health-related quality of life; ITT=Intention to Treat; mRECIST=Modified RECIST; ORR=Objective response rate; OS=Overall Survival; PD=Progressive disease; PD-L1=Programmed cell death ligand 1; PFS=Progression-free survival; PFS2=Progression-free survival in the next line of therapy; PR=Partial response; QLQ-C30=Quality of Life Core Questionnaire, Version 3.0; QLQ-H&N35=Quality of Life Questionnaire, Head and Neck Module 35; QOL=Quality of life; FAS = Full Analysis Set; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; TPS=Tumor Proportion Score.

Censoring rules for OS: Censored at date last known alive.

Censoring rules for PFS:

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

Rationale for Changing the PD-L1 Scoring Method and Cutoff from Tumour Proportion Score (TPS) ≥ 50% to Combined Positive Score (CPS) ≥ 1 in KEYNOTE-040

TPS is defined as the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. TPS ≥ 50% has been used as the initial pre-specified scoring method and cutoff to assess PD-L1 status and as stratification factor in KN040.

However, evidence on literature and data for pembrolizumab in HNSCC from KN012 and in other solid tumours showed that PDL1 expression on Tumour Infiltrating Immune Cells significantly contributes to clinical outcome upon treatment with pembrolizumab. Therefore a new scoring system called Combined Positive Score (CPS) was developed by the MAH. CPS is defined as the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100. This scoring system with ≥ 1 cutoff has been selected as the primary biomarker in Gastric, Bladder and TNBC pembrolizumab trials.

To understand the role of PDL1 expression on infiltrating inflammatory cells in HNSCC in predicting outcome with pembrolizumab, a retrospective evaluation of 190 HNSCC patients with IHC scoring in KN012 Cohorts B (61 pts, PD-L1 ≥1%, 10 mg/kg pembrolizumab) and B2 (132 pts, any PD-L1 status, 200 mg) was performed. ROC curves for CPS and TPS showed statistically significant difference (p=0.004 2 sided) in the AUC.

Cohort B2 (with any PD-L1 status) was analysed alone. The incorporation of inflammatory cell staining improved sensitivity for detecting responders.

Table 11: Clinical utility statistics for CPS and TPS cutoffs: KN012 Cohort B2 only (N=132)

	CPS Cutoff			TPS Cutoff	
Performance Estimate	**1**	**1**	**2**	**1%**	**50%**
% PPV | NPV	21.5 | 96.0	23.4 | 89.1	23.1 | 86.6	19.1 | 83.7	22.0 | 83.5
% Sensitivity | Specificity	95.8 | 22.2	75.0 | 45.4	62.5 | 53.7	70.8 | 33.3	37.5 | 70.4
% Prevalence	81.1	58.3	49.2	67.4	31.1

PPV: positive predictive value, the response rate above the cutoff
NPV: negative predictive value, the non-response rate below the cutoff
Prevalence: the percentage of patients with CPS scores above the cutoff

Clinical KN012 results ORR, PFS and OS were analysed according to both TPS and CPS score in all population (cohort B + B2, n=190). Curves for PFS according to TPS at cutoff <1% or ≥1% were overlapping, as well as for OS.

Based on the results from KN012, the KN040 clinical protocol was amended, prior to data analysis, to include CPS ≥ 1 as the primary PD-L1 scoring method and cutoff. TPS ≥ 50% was also assessed, but as a pre-defined exploratory objective.

Sample size

Approximately 466 subjects were to be randomized in a 1:1 ratio into the pembrolizumab group or the standard treatment group.

This was an event driven trial. The final OS analysis in all subjects was to be conducted after ~340 deaths occurred between the pembrolizumab group and the standard treatment group. Under the proportional hazard assumption with 340 events at the final analysis, the study provided 90% power to demonstrate superiority in OS of pembrolizumab relative to standard treatment at the alpha = 2.5% (one-sided) level with a true hazard ratio (HR) of 0.7. Success for OS at the final analysis approximately corresponded to an observed hazard ratio of <0.80.

The sample size calculation was based on the following assumptions: (1) OS follows an exponential distribution with a median of 6.2 months in the standard treatment group; (2) hazard ratio between MK-3475 and standard treatment is 0.7; (3) an enrollment period of 16 months; and (4) a yearly discontinuation from trial rate of 5%.

Randomisation

Randomization occurred centrally using an IVRS/IWRS. Subjects were randomized in a 1:1 ratio to pembrolizumab or standard treatment in an unblinded fashion using centrally randomized blocks.

Randomization was stratified according to the following factors:

- ECOG Performance Status (0 versus 1)
- HPV status (positive vs negative)
- PD-L1 expression status (PD-L1 strongly positive [TPS ≥50% TPS] versus PD-L1 not strongly positive [TPS <50%] or not able to be determined for any level)

HPV stratification in this trial was performed using local or central testing of HPV status in subjects with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer were not required to undergo HPV testing by p16 IHC as by convention they were assumed to be HPV negative. Results from local testing of HPV positivity for oropharyngeal cancer were defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point.

Blinding (masking)

This was an open-label trial.

Statistical methods

The intention-to-treat (ITT) population was used for the analysis of efficacy data.

The Kaplan-Meier method was used to estimate the survival curves. The treatment difference in survival was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference. The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate were reported. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model for all subject population as well as PD-L1 1% CPS subject population. For the primary OS analysis in all subjects, an additional sensitivity analysis replacing the PD-L1 Strong Positive vs. Not Strong Positive by the PD-L1 1% CPS vs. Not 1% CPS in the stratified analysis was performed.

Subjects in the standard therapy arm were expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm and might switch to another anti PD-1 treatment following verification of progressive disease by central review. As an exploratory analysis, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1991) [49] was used to adjust for the effect of crossover to other PD-1 therapies on OS.

The 95% confidence intervals of the hazard ratio for OS after adjustment of the cross-over effect were provided. The Kaplan-Meier estimates of the OS rate at 9 weeks, 27 weeks (when most cross-overs are likely to occur) and other time points of interest were compared between the two treatment groups to explore the confounding effect of subsequent treatments.

For PFS endpoint the same analysis defined for OS endpoint and based on Kaplan Meier method and Cox proportional hazard model were applied. The proportional hazard assumption was tested at the 0.05 significance level by including treatment*function(time) as a factor in the model; nonsignificance ($p>0.05$) of this factor suggested proportionality. A kernel-based estimate of log-hazard vs. time was used to identify the appropriate functional form of the treatment effect-by-time interaction in a Cox PH model. Further, a visual examination of the plot of the differences in the log versus time for each level of treatment group was examined. To account for the possible non-proportional hazards effect associated with immunotherapies, a supportive analysis was conducted using a test for the restricted mean survival time (RMST) proposed by Uno, Tian, et al for equality of two survival functions based on weighted differences of Kaplan-Meier curves. Thus, the PFS within each treatment group was estimated using this approach, the 95% confidence intervals for the difference were computed, and a test for differences between treatment groups were performed. The cutoff for determining the RMST was the last month for which at least 30 subjects within each treatment group were still at risk.

One key assumption for the stratified Cox proportional hazard model is that the hazard ratio (HR) is constant across strata. If strong departures from constant HR are observed in the stratified PFS analysis for all subjects, a sensitivity analysis may be performed using the twostep weighted Cox model approach by Mehrotra et al [52]. In this approach, the treatment effect is estimated within each stratum and the stratum-specific estimates are subsequently combined using sample size weights.

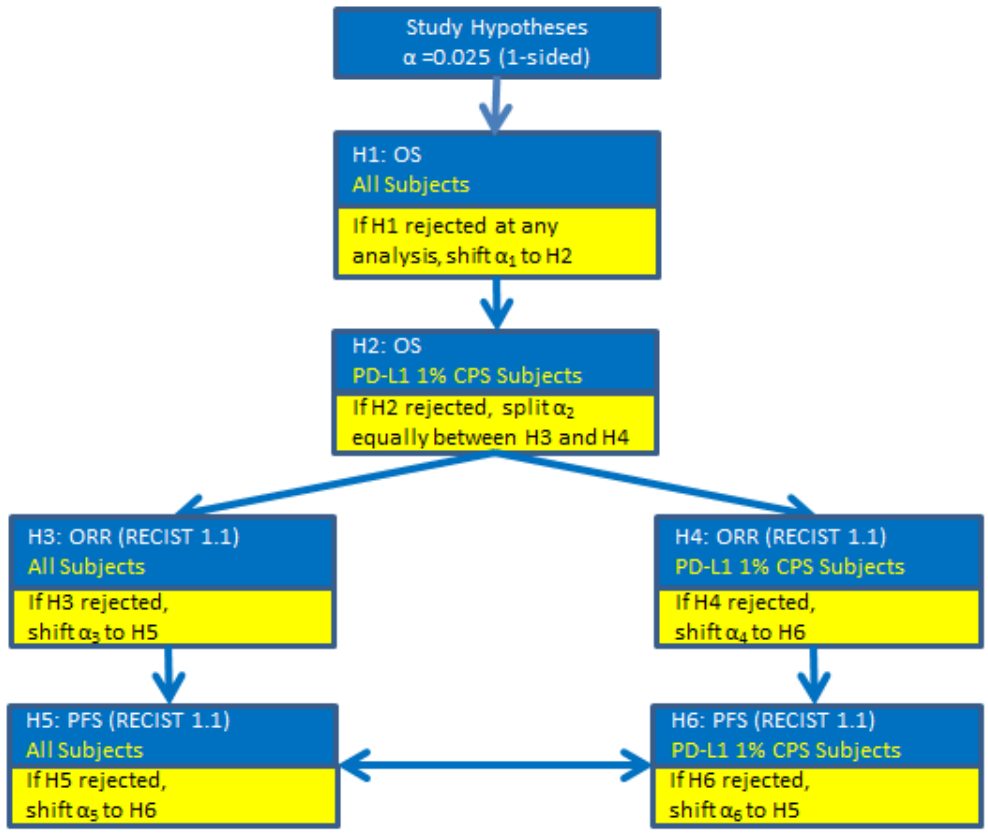
The family-wise type I error rate for this study was controlled at 2.5% (one-sided) with full alpha allocated to the OS hypothesis in all subjects (H1). A Hwang-Shih-DeCani alpha spending function with the gamma parameter (-4) and beta-spending function with the gamma parameter (-16) were constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis. Two interim analyses for OS in all subjects were planned in this trial and further details of the interim analysis strategy can be found in following table.

Table 12:Interim analyses for OS in all subjects:

Analysis	OS Events (Alpha Spent)		Boundary	
			p value (1-sided)	~Observed HR at boundary
IA 1: OS in all subjects (H1)	160 (0.0038§)	Efficacy	0.0038	0.65
		Futility†	0.92	1.2
IA 2: OS in all subjects (H1)	245 (0.0097§)	Efficacy	0.0120	0.75
		Futility†	0.277	0.93
Final Analysis: OS in all subjects (H1)	340‡ (0.0114)	Efficacy	0.0186	0.80
		Futility	0.0186	0.80

IA = Interim Analysis.
†: Futility boundary is non-binding.
‡: Expected to occur approximately 12 months after the last subject was enrolled to ensure adequate survival follow-up
§: Actual alpha spent at each interim analyses

The following figure shows the hierarchical order for testing key secondary endpoints and alpha spending scheme according to the method of Maurer and Bretz.



Stratified Miettinen and Nurminen's method with strata weighting by sample size were used for comparison of the objective response rates between the treatment groups. A 95% confidence interval for the difference in response rates between the pembrolizumab arm and the standard therapy arm were provided. The same stratification factors used for randomization were applied to the analysis. ORR by site radiology assessment and ORR in the subgroup of subjects with PD-L1 1% CPS were analyzed using the same approach as the primary ORR analysis.

Response duration was summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who showed a complete response or partial response were included in this analysis.

An exploratory analysis of PFS2 was conducted using the same methods as for the secondary analysis of PFS.

Exploratory analyses of the treatment effect comparing pembrolizumab to standard treatment for OS, PFS, and ORR using RECIST 1.1 as assessed by blinded independent radiology review in the subgroup of subjects with strongly positive PD-L1 expression defined by ≥50% TPS were carried out.

EORTC QLQ-C30, EORTC QLQ H&N35, and EQ-5D were summarized as part of the exploratory analysis. Longitudinal and descriptive data analysis were used to evaluate patient-reported outcomes. Several approaches were considered to address the issue of informative missing data: (i) truncating the analysis observation period at the visit closest to median duration of treatment in the comparator arm, (ii) hierarchical pattern mixture models incorporating reason for missingness (a model that treats disease progression as a time varying covariate) and (iii) multiple imputation methods. The difference in PRO score for progressed patients compared to patients with no radiographic evidence of tumor progression was evaluated within each treatment arm. For HEA, descriptive statistics by treatment group were includes total counts of each type of healthcare contact, as well as the total number of hospital days.

Results

Participant flow

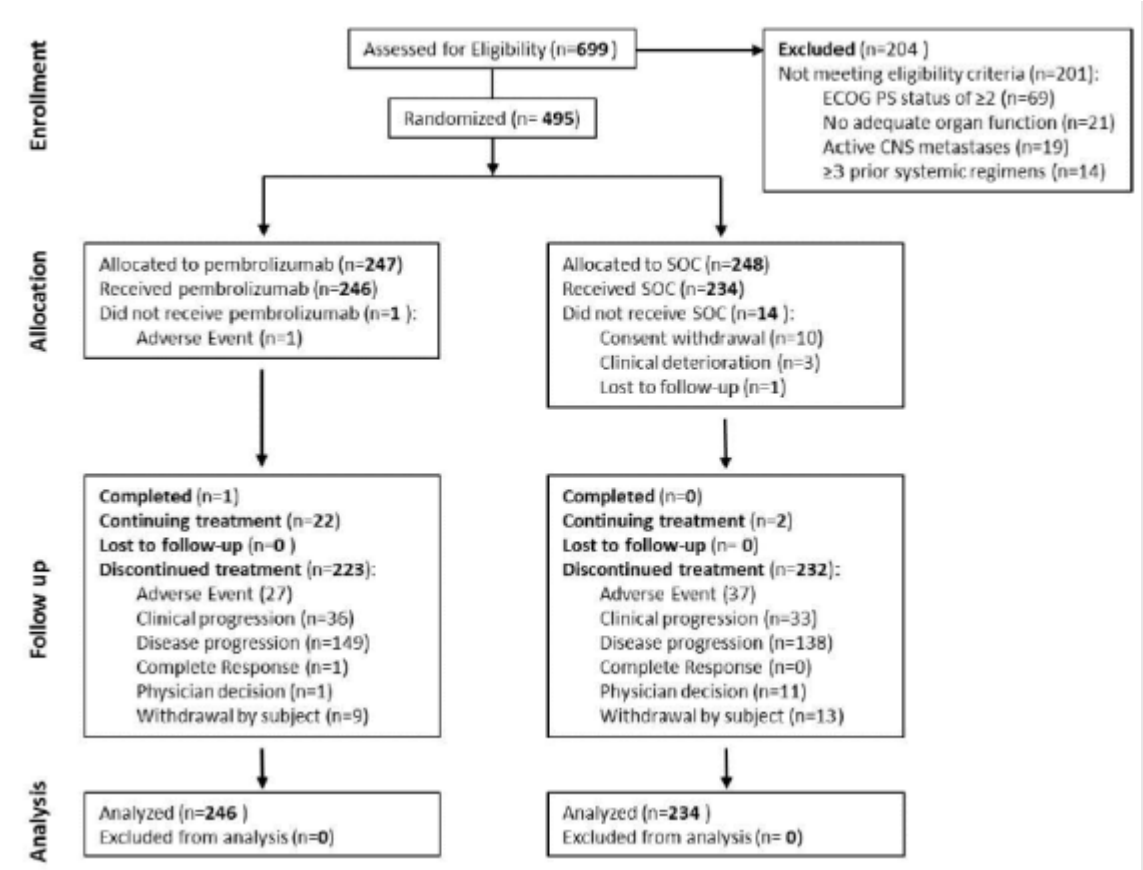


Table 13: Consort Diagram KN040

	MK-3475 200 mg Q3W	Standard Treatment	Total
Subjects screened			699
Subjects randomized	247	248	495
Subjects who died	181	207	388
Subjects who did not receive treatment	1	9	10
Subjects who received treatment	180	198	378
Subjects who are alive and on study	63	35	98
Subjects who have not received treatment	0	0	0
Subjects who received treatment and are on treatment	22	2	24
Subjects who discontinued study treatment and are in follow-up	41	33	74
Subjects who are alive but off study*	3	6	9
Subjects who did not receive treatment	0	5	5
Subjects who received treatment	3	1	4
* Subjects are off study treatment and no longer in study follow up.			
Database Cutoff Date: 15MAY2017.			

The main reason for subjects not being randomized was not meeting the trial eligibility criteria (201 subjects, 98.5%).

Table 14: Disposition of Subjects KN040 (ASaT Population)

	MK-3475 200 mg Q3W	Standard Treatment	Total
	N (%)	N (%)	N (%)
Subjects in population	246	234	480
Status for Study medication in Trial			
Started	246	234	480
Completed	1 (0.4)	0 (0.0)	1 (0.2)
Discontinued	223 (90.7)	232 (99.1)	455 (94.8)
Adverse Event	27 (11.0)	37 (15.8)	64 (13.3)
Clinical Progression	36 (14.6)	33 (14.1)	69 (14.4)
Complete Response	1 (0.4)	0 (0.0)	1 (0.2)
Physician Decision	1 (0.4)	11 (4.7)	12 (2.5)
Progressive Disease	149 (60.6)	138 (59.0)	287 (59.8)
Withdrawal By Subject	9 (3.7)	13 (5.6)	22 (4.6)
Subjects Ongoing	22 (8.9)	2 (0.9)	24 (5.0)
Status for Trial			
Discontinued	182 (74.0)	199 (85.0)	381 (79.4)
Death	169 (68.7)	189 (80.8)	358 (74.6)
Withdrawal By Subject	13 (5.3)	10 (4.3)	23 (4.8)
Subjects Ongoing	64 (26.0)	35 (15.0)	99 (20.6)
Database Cutoff Date: 15MAY2017			

Recruitment

A total of 699 subjects were screened. Overall, 495 subjects (247 versus 248) were randomized in 100 centers worldwide (21 countries, 97 centers randomized subjects to trial treatment: Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Lithuania, Mexico, Netherlands, Poland, Portugal, Puerto Rico, Russia, South Korea, Spain, Sweden, Switzerland, the United Kingdom, United States) and were included in the ITT population. Enrollment was from 03-DEC-2014 to 13-MAY-2016 (~17 months).

The data cut-off for the analysis was 15-MAY-2017 (one year after the last patient was enrolled).

Conduct of the study

Protocol amendments:

A total of 11 protocol amendments to the original protocol, including 3 global and 8 country-specific, were implemented during the study. Main changes are summarized below:

Table 15: Global amendments to the protocol

Protocol or Amendment	Main changes
Protocol (01-AUG-2014)	Original protocol (PFS and OS as co-primary objectives in all subjects)
Amendment 01 (27-FEB-2015)	Increased number from 466 to 600; added hypotheses for PFS and OS in the PD-L1 Strong Positive population (TPS ≥50%) as primary objectives (4 primary hypotheses); added hypotheses for PFS and OS in the CPS ≥1 PD-L1 positive population as secondary objectives
Amendment 10 (10-MAR-2016)	Decreased the sample size from 600 to 466 subjects; kept OS in all subjects as the single primary hypothesis and downgraded OS and PFS in the PD-L1 positive subjects from primary hypotheses to key secondary hypotheses; replaced hypotheses on the PD-L1 population with hypotheses on the CPS ≥1 population; promoted ORR to a key secondary endpoints; updated language to include PD-L1 status masking and included the role of unblinded Sponsor personnel.
Amendment 11 (02-NOV-2016)	Updated, in the Statistical Analysis Plan, the alpha-spending language, power calculation, and timing of the final analysis to reflect the change to the number of death events at the final analysis.

Protocol deviations:

The medical monitoring process included a review of all major deviations documented as of 13-NOV-2017 (n=90) to identify a subgroup of subjects with deviations that were considered clinically relevant (n=11). Clinically relevant major deviations included one subject who received prohibited medication while on study treatment (1) and subjects who did not meet entry criteria (10) as below:

- 1 patient was enrolled without having been treated with failed platinum therapy.
- 4 subjects received three or more lines of therapy prior to screening
- 3 subjects did not meet inclusion criteria 4b: Recurrence/progression within 6 months of prior multimodal therapy using platinum (e.g. locally advanced setting)
- 1 patient with a tumour lesion situated in a previously irradiated area not being progressive (=not measurable per inclusion criteria)
- 1 subject did not meet entry criteria due to prior chemo specifics not obtained through medical records from Mexico.

The remaining deviations were minor and/or not clinically relevant and did not affect subject safety or the interpretation of trial results.

Baseline data

Table 16: baseline characteristics (ITT Population)

	MK-3475 200 mg Q3W		**Standard Treatment**		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	**247**		**248**		495	
Gender						
Male	207	(83.8)	205	(82.7)	412	(83.2)
Female	40	(16.2)	43	(17.3)	83	(16.8)
Age (Years)						
<65	165	(66.8)	167	(67.3)	332	(67.1)
>=65	82	(33.2)	81	(32.7)	163	(32.9)
Age (Years)						
<75	228	(92.3)	236	(95.2)	464	(93.7)
>=75	19	(7.7)	12	(4.8)	31	(6.3)
Age (Years)						
Mean	60.3		60.2		60.2	
SD	9.8		8.6		9.2	
Median	60.0		60.0		60.0	
Range	19 to 85		34 to 78		19 to 85	
Race						
American Indian or Alaska Native	2	(0.8)	0	(0.0)	2	(0.4)
Black or African American	3	(1.2)	7	(2.8)	10	(2.0)
White	207	(83.8)	207	(83.5)	414	(83.6)
Asian	15	(6.1)	16	(6.5)	31	(6.3)
Multi-racial	4	(1.6)	3	(1.2)	7	(1.4)
Unknown	16	(6.5)	15	(6.0)	31	(6.3)
Region						
EU	147	(59.5)	158	(63.7)	305	(61.6)
NA	73	(29.6)	60	(24.2)	133	(26.9)
ROW	27	(10.9)	30	(12.1)	57	(11.5)
Smoking Status						
Never Smoked	68	(27.5)	66	(26.6)	134	(27.1)
Former Smoker	147	(59.5)	146	(58.9)	293	(59.2)
Current Smoker	32	(13.0)	36	(14.5)	68	(13.7)
Investigators Choice of Standard Therapy Identified Prior to Randomization						
Methotrexate	70	(28.3)	65	(26.2)	135	(27.3)
Docetaxel	123	(49.8)	110	(44.4)	233	(47.1)
Cetuximab	54	(21.9)	73	(29.4)	127	(25.7)
ECOG PS						
0	71	(28.7)	67	(27.0)	138	(27.9)
1	176	(71.3)	180	(72.6)	356	(71.9)
2	0	(0.0)	1	(0.4)	1	(0.2)
HPV Status						
Positive	61	(24.7)	58	(23.4)	119	(24.0)
Negative	186	(75.3)	190	(76.6)	376	(76.0)
PD-L1 TPS Status						
TPS = 0%	103	(41.7)	93	(37.5)	196	(39.6)
1% <= TPS < 50%	79	(32.0)	87	(35.1)	166	(33.5)
TPS >= 50%	64	(25.9)	65	(26.2)	129	(26.1)
Missing	1	(0.4)	3	(1.2)	4	(0.8)
PD-L1 CPS Status						

CPS < 1	50	(20.2)	54	(21.8)	104	(21.0)
CPS >= 1	196	(79.4)	191	(77.0)	387	(78.2)
Missing	1	(0.4)	3	(1.2)	4	(0.8)
Current Disease Brain Metastases						
Yes	0	(0.0)	3	(1.2)	3	(0.6)
No	247	(100.0)	245	(98.8)	492	(99.4)
Liver Metastases at Baseline						
Yes	30	(12.1)	27	(10.9)	57	(11.5)
No	217	(87.9)	221	(89.1)	438	(88.5)
Current Disease Primary Tumor						
T0, Tis	11	(4.5)	15	(6.0)	26	(5.3)
T1	16	(6.5)	16	(6.5)	32	(6.5)
T2	49	(19.8)	61	(24.6)	110	(22.2)
T3	44	(17.8)	48	(19.4)	92	(18.6)
T4	49	(19.8)	43	(17.3)	92	(18.6)
T4a	31	(12.6)	27	(10.9)	58	(11.7)
T4b	12	(4.9)	9	(3.6)	21	(4.2)
Tx	35	(14.2)	29	(11.7)	64	(12.9)
Current Disease Nodal Involvement						
NX	30	(12.1)	28	(11.3)	58	(11.7)
N0	57	(23.1)	50	(20.2)	107	(21.6)
N1	25	(10.1)	33	(13.3)	58	(11.7)
N2	110	(44.5)	119	(48.0)	229	(46.3)
N3	25	(10.1)	18	(7.3)	43	(8.7)
Current Disease Metastasis						
MX	7	(2.8)	6	(2.4)	13	(2.6)
M0	56	(22.7)	75	(30.2)	131	(26.5)
M1	184	(74.5)	167	(67.3)	351	(70.9)
Current Disease Overall Stage						
Stage II	5	(2.0)	7	(2.8)	12	(2.4)
Stage III	9	(3.6)	17	(6.9)	26	(5.3)
Stage IV	84	(34.0)	77	(31.0)	161	(32.5)
Stage IV A	22	(8.9)	30	(12.1)	52	(10.5)
Stage IV B	11	(4.5)	12	(4.8)	23	(4.6)
Stage IV C	116	(47.0)	105	(42.3)	221	(44.6)
Baseline Tumor Size (mm)						
Subjects with data	241		240		481	
Mean	65.2		77.2		71.2	
SD	41.3		72.3		59.0	
Median	57.0		63.0		59.0	
Range	15 to 276		12 to 825		12 to 825	
Interquartile range of tumour size (Q1, Q3)	(36,83)		(40.5, 92.5)			
Interquartile range (Q3-Q1)	47		52			
Prior Lines of Therapy						
Adjuvant, Neoadjuvant, or Definitive	34	(13.8)	40	(16.1)	74	(14.9)
First Line	141	(57.1)	141	(56.9)	282	(57.0)
Second Line	69	(27.9)	64	(25.8)	133	(26.9)
Third Line	3	(1.2)	3	(1.2)	6	(1.2)
Time from Most Recent Prior Systemic Therapy						
>=3 months	225	(91.1)	229	(92.3)	454	(91.7)
<3 months	22	(8.9)	19	(7.7)	41	(8.3)
Time from Most Recent Prior Platinum Therapy						
>=3 months	233	(94.3)	233	(94.0)	466	(94.1)
<3 months	13	(5.3)	14	(5.6)	27	(5.5)
No Prior Systemic Platinum Therapy	1	(0.4)	1	(0.4)	2	(0.4)
Progression on Prior Systemic Therapy						

Yes	246	(99.6)	245	(98.8)	491	(99.2)
No	1	(0.4)	3	(1.2)	4	(0.8)
Most Recent Prior Oncologic Radiation						
Neoadjuvant	22	(8.9)	29	(11.7)	51	(10.3)
Adjuvant	122	(49.4)	132	(53.2)	254	(51.3)
In Combination With First Line Treatment	29	(11.7)	16	(6.5)	45	(9.1)
In Combination With Second Line Treatment	3	(1.2)	3	(1.2)	6	(1.2)
Control Of Metastatic Or Recurrent Disease Or Refractory	14	(5.7)	12	(4.8)	26	(5.3)
Palliative Treatment Or Symptom Control	27	(10.9)	21	(8.5)	48	(9.7)
No Radiation	30	(12.1)	35	(14.1)	65	(13.1)
Oncologic Surgery						
Yes	137	(55.5)	148	(59.7)	285	(57.6)
No	110	(44.5)	100	(40.3)	210	(42.4)
Database Cutoff Date: 15MAY2017						

Table 17: Subjects With Specific Concomitant Medications (ASaT Population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
With one or more concomitant medications	103	(41.9)	161	(68.8)
With no concomitant medication	143	(58.1)	73	(31.2)

Table 18: baseline characteristics (ITT Population) TPS ≥ 50%

	MK-3475 200 mg Q3W		Standard Treatment		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	64		65		129	
Gender						
Male	53	(82.8)	51	(78.5)	104	(80.6)
Female	11	(17.2)	14	(21.5)	25	(19.4)
Age (Years)						
<65	40	(62.5)	37	(56.9)	77	(59.7)
>=65	24	(37.5)	28	(43.1)	52	(40.3)
<75	59	(92.2)	59	(90.8)	118	(91.5)
>=75	5	(7.8)	6	(9.2)	11	(8.5)
Subjects with data	64		65		129	
Mean	61.3		62.5		61.9	
SD	9.9		9.0		9.4	
Median	61.0		63.0		62.0	
Range	31 to 83		34 to 77		31 to 83	
Race						
American Indian or Alaska Native	1	(1.6)	0	(0.0)	1	(0.8)
Black or African American	1	(1.6)	1	(1.5)	2	(1.6)
White	52	(81.3)	48	(73.8)	100	(77.5)
Asian	5	(7.8)	9	(13.8)	14	(10.9)
Multi-racial	0	(0.0)	1	(1.5)	1	(0.8)
Unknown	5	(7.8)	6	(9.2)	11	(8.5)
Race Group						
White	52	(81.3)	48	(73.8)	100	(77.5)
Non-White	7	(10.9)	11	(16.9)	18	(14.0)
Unknown	5	(7.8)	6	(9.2)	11	(8.5)
Ethnicity						
Hispanic or Latino	4	(6.3)	3	(4.6)	7	(5.4)
Not Hispanic or Latino	48	(75.0)	43	(66.2)	91	(70.5)
Not Reported	6	(9.4)	9	(13.8)	15	(11.6)
Unknown	6	(9.4)	10	(15.4)	16	(12.4)

Region						
EU	39	(60.9)	43	(66.2)	82	(63.6)
NA	18	(28.1)	17	(26.2)	35	(27.1)
ROW	7	(10.9)	5	(7.7)	12	(9.3)
Smoking Status						
Never Smoked	17	(26.6)	23	(35.4)	40	(31.0)
Former Smoker	39	(60.9)	39	(60.0)	78	(60.5)
Current Smoker	8	(12.5)	3	(4.6)	11	(8.5)
Investigators Choice of Standard Therapy Identified Prior to Randomization						
Methotrexate	16	(25.0)	21	(32.3)	37	(28.7)
Docetaxel	32	(50.0)	20	(30.8)	52	(40.3)
Cetuximab	16	(25.0)	24	(36.9)	40	(31.0)
ECOG PS						
0	19	(29.7)	11	(16.9)	30	(23.3)
1	45	(70.3)	54	(83.1)	99	(76.7)
HPV Status						
Positive	13	(20.3)	12	(18.5)	25	(19.4)
Negative	51	(79.7)	53	(81.5)	104	(80.6)
Current Disease Brain Metastases						
Yes	0	(0.0)	1	(1.5)	1	(0.8)
No	64	(100.0)	64	(98.5)	128	(99.2)
Liver Metastases at Baseline						
Yes	5	(7.8)	9	(13.8)	14	(10.9)
No	59	(92.2)	56	(86.2)	115	(89.1)
Current Disease Overall Stage						
Stage II	0	(0.0)	1	(1.5)	1	(0.8)
Stage III	3	(4.7)	4	(6.2)	7	(5.4)
Stage IV	22	(34.4)	19	(29.2)	41	(31.8)
Stage IV A	7	(10.9)	11	(16.9)	18	(14.0)
Stage IV B	2	(3.1)	3	(4.6)	5	(3.9)

Stage IV C	30	(46.9)	27	(41.5)	57	(44.2)
Current Disease Primary Tumor						
T0, Tis	3	(4.7)	3	(4.6)	6	(4.7)
T1	8	(12.5)	4	(6.2)	12	(9.3)
T2	11	(17.2)	17	(26.2)	28	(21.7)
T3	11	(17.2)	11	(16.9)	22	(17.1)
T4	12	(18.8)	15	(23.1)	27	(20.9)
T4a	8	(12.5)	6	(9.2)	14	(10.9)
T4b	2	(3.1)	2	(3.1)	4	(3.1)
Tx	9	(14.1)	7	(10.8)	16	(12.4)
Current Disease Nodal Involvement						
NX	7	(10.9)	7	(10.8)	14	(10.9)
N0	18	(28.1)	10	(15.4)	28	(21.7)
N1	6	(9.4)	8	(12.3)	14	(10.9)
N2	29	(45.3)	34	(52.3)	63	(48.8)
N3	4	(6.3)	6	(9.2)	10	(7.8)
Current Disease Metastasis						
MX	2	(3.1)	1	(1.5)	3	(2.3)
M0	16	(25.0)	23	(35.4)	39	(30.2)
M1	46	(71.9)	41	(63.1)	87	(67.4)
Baseline Tumor Size (mm)						
Subjects with data	62		61		123	
Mean	58.2		72.7		65.4	
SD	36.1		44.9		41.2	
Median	51.5		60.0		58.0	
Range	15 to 185		12 to 236		12 to 236	
Prior Lines of Therapy						
Adjuvant, Neoadjuvant, or Definitive	12	(18.8)	8	(12.3)	20	(15.5)
First Line	36	(56.3)	40	(61.5)	76	(58.9)
Second Line	16	(25.0)	17	(26.2)	33	(25.6)
Time from Most Recent Prior Systemic Therapy						
>=3 months	55	(85.9)	62	(95.4)	117	(90.7)
<3 months	9	(14.1)	3	(4.6)	12	(9.3)
Time from Most Recent Prior Platinum Therapy						
>=3 months	59	(92.2)	61	(93.8)	120	(93.0)
<3 months	5	(7.8)	3	(4.6)	8	(6.2)
No Prior Systemic Platinum Therapy	0	(0.0)	1	(1.5)	1	(0.8)
Progression on Prior Systemic Therapy						
Yes	64	(100.0)	64	(98.5)	128	(99.2)
No	0	(0.0)	1	(1.5)	1	(0.8)
Most Recent Prior Oncologic Radiation						
Neoadjuvant	4	(6.3)	9	(13.8)	13	(10.1)
Adjuvant	30	(46.9)	35	(53.8)	65	(50.4)
In Combination With First Line Treatment	11	(17.2)	3	(4.6)	14	(10.9)
In Combination With Second Line Treatment	2	(3.1)	0	(0.0)	2	(1.6)
Control Of Metastatic Or Recurrent Disease Or Refractory	5	(7.8)	3	(4.6)	8	(6.2)
Palliative Treatment Or Symptom Control	5	(7.8)	5	(7.7)	10	(7.8)
No Radiation	7	(10.9)	10	(15.4)	17	(13.2)
Oncologic Surgery						
Yes	41	(64.1)	41	(63.1)	82	(63.6)
No	23	(35.9)	24	(36.9)	47	(36.4)
Database Cutoff Date: 15MAY2017						

Numbers analysed

Efficacy analyses were based on ITT population (randomized subjects were included regardless of whether or not they received trial treatment) which include 495 subjects (247 in the pembrolizumab treatment group and 248 in the standard treatment group).

Outcomes and estimation

The primary analysis was based on a data cut-off date of 15-MAY-2017 and a database lock date of 04-JUN-2017; however, the database did not fully capture data on all subjects who had died as of the data cutoff date of 15-MAY-2017 as there was incomplete collection of survival data on 12/388 subjects (11 deaths and 1 confirmed alive status). Critical changes to the database were made to capture all death events on 3 occasions (26-AUG-2017, 25-SEP-2017, and 13-OCT-2017) permitting the entry of survival data that had not been captured in the database lock of 04-JUN-2017.

Unless specifically noted otherwise, all efficacy results provided are based on a database lock date of 13-OCT-2017, at which time data on all subjects who had died as of the data cut-off date of 15-MAY-2017 were included in the database.

The only p-value provided for statistical inference is the one for the primary OS analysis in all subjects based on the 04-JUN-2017 database lock. All other p-values, including those based on the 13-OCT-2017 database update, are considered nominal and are not adjusted for multiplicity.

Table 19: database lock and updates for KN040

DBL/Database Update dates	Rationale	Cumulative Percentage of Events[a]
04-JUN-2017	DBL	97.2%
26-AUG-2017	Database update, to add new data regarding time to death for select patients that were missing at the time of the initial DBL	98.0%
25-SEP-2017	Database update to add death and survival follow-up eCRFs missing at the time of the 04-JUN-2017 DBL	99.0%
13-OCT-2017	Database update to add death and survival follow-up eCRFs missing at the time of the 04-JUN-2017 DBL	100%

[a] Subjects who had died as of the 15-MAY-2017 data cutoff date (n=388) DBL = database lock; eCRF = electronic case report form

Primary endpoint: OS (DBL 04-JUN-2017)

At the time of the database lock on 04-JUN-2017, data on 377 (97.2%) of 388 subjects who had died as of the data cutoff date of 15-MAY-2017 were included in the database. This is the only p-value provided for statistical inference. The OS boundary of 0.0316 narrowly missed the primary statistical hypothesis of a p-value OS boundary of 0.0175 for 377 events (deaths). Median follow-up for OS was 7.8 months (range, 0.1, 28.6 months).

Table 20: Analysis of overall survival (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 6 in %[†] (95% CI)	vs. Standard Treatment	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
MK-3475 200 mg Q3W	247	179 (72.5)	2226.8	8.0	8.4 (6.5, 9.4)	59.0 (52.6, 64.8)	0.82 (0.67, 1.01)	0.03160
Standard Treatment	248	198 (79.8)	1977.1	10.0	7.1 (5.9, 8.1)	56.3 (49.8, 62.3)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

Table 21: Overall survival rate (ITT population)

	MK-3475 200 mg Q3W (N=247)	Standard Treatment (N=248)
OS rate at 6 Months in (95% CI)[†]	59.0 (52.6, 64.8)	56.3 (49.8, 62.3)
OS rate at 9 Months in (95% CI)[†]	46.2 (39.9, 52.3)	41.5 (35.2, 47.7)
OS rate at 12 Months in (95% CI)[†]	37.1 (31.0, 43.1)	28.0 (22.4, 33.8)

[†] From the product-limit (Kaplan-Meier) method for censored data.
(Database Cutoff Date: 15MAY2017).

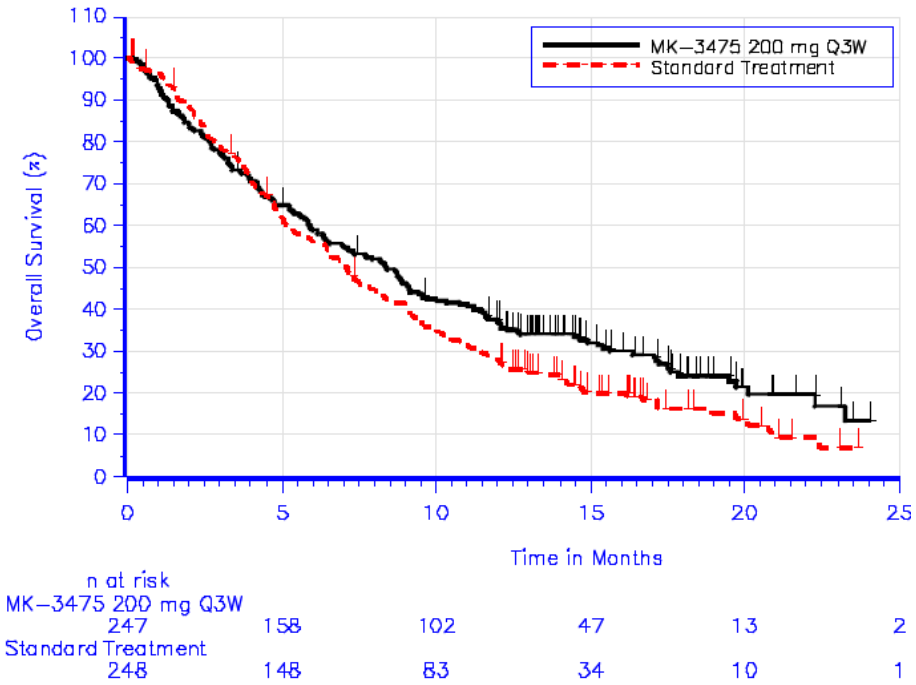


Figure 8: Kaplan-Meier of overall survival (ITT population)

OS (DBL 13-OCT-2017)

At the DBL of 13-OCT-2017, median duration of follow-up for OS was 7.5 months (range, 0.1 to 28.6 months).

Table 22: Analysis of overall survival (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in % [†] (95% CI)	vs. Standard Treatment	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
MK-3475 200 mg Q3W	247	181 (73.3)	2247.4	8.1	8.4 (6.4, 9.4)	37.0 (31.0, 43.1)	0.80 (0.65, 0.98)	0.01605
Standard Treatment	248	207 (83.5)	1997.2	10.4	6.9 (5.9, 8.0)	26.5 (21.2, 32.2)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

Table 23: Overall survival rate (ITT population)

	MK-3475 200 mg Q3W (N=247)	Standard Treatment (N=248)
OS rate at 6 Months in (95% CI)[†]	58.7 (52.3, 64.6)	55.9 (49.5, 61.9)
OS rate at 9 Months in (95% CI)[†]	46.1 (39.8, 52.2)	40.8 (34.6, 46.9)
OS rate at 12 Months in (95% CI)[†]	37.0 (31.0, 43.1)	26.5 (21.2, 32.2)

[†] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 15MAY2017

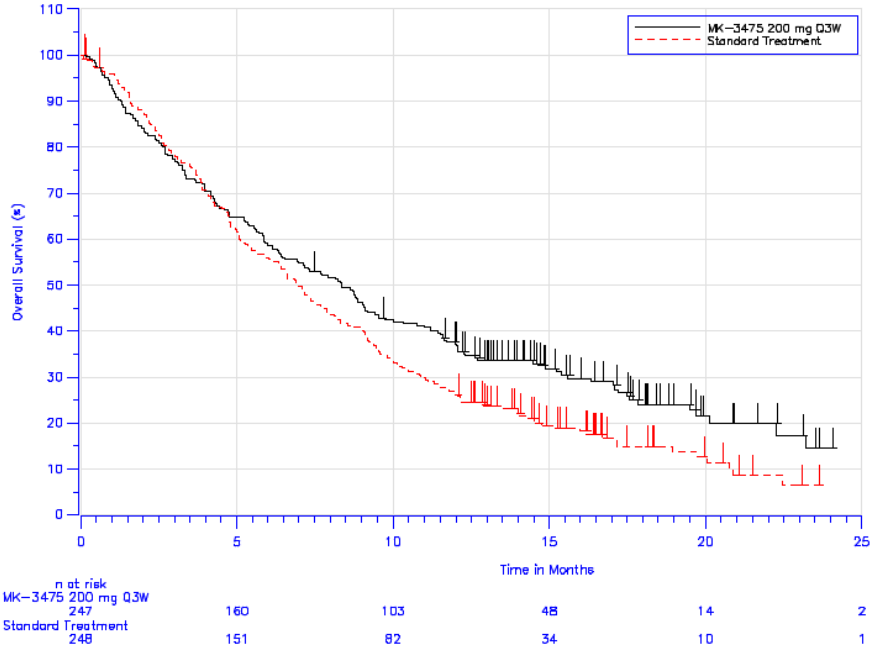


Figure 9: Kaplan-Meier of overall survival (ITT population)

OS analyses by treatment

Table 24: Analysis of overall survival by treatment (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in % [†] (95% CI)	vs. Chemotherapy	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
MK-3475 200mg Q3W	247	181 (73.3)	2247.4	8.1	8.4 (6.4, 9.4)	37.0 (31.0, 43.1)	---	---
Methotrexate	65	54 (83.1)	486.8	11.1	6.0 (4.5, 8.3)	27.7 (17.5, 38.8)	0.81 (0.59, 1.11)	0.09414
Cetuximab	73	62 (84.9)	576.6	10.8	7.1 (4.8, 8.2)	22.2 (13.5, 32.4)	0.77 (0.57, 1.03)	0.03754
Docetaxel	110	91 (82.7)	933.9	9.7	7.7 (5.7, 9.6)	28.7 (20.5, 37.4)	0.81 (0.62, 1.05)	0.05776

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

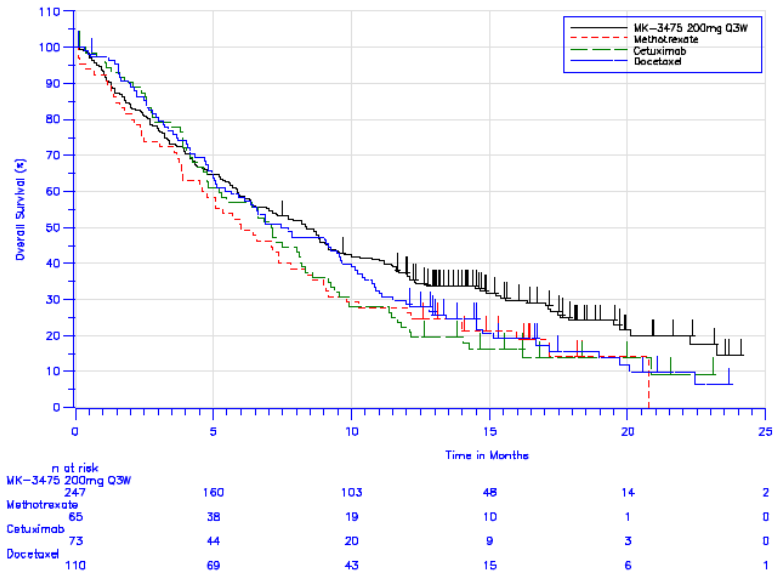


Figure 10: Kaplan-Meier of overall survival by treatment

Secondary endpoint: PFS

Table 25: Analysis of PFS based on BICR assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS[†] (Months) (95% CI)	PFS Rate at Month 6 in %[†] (95% CI)	vs. Standard Treatment	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
MK-3475 200 mg Q3W	247	218 (88.3)	1092.1	20.0	2.1 (2.1, 2.3)	25.6 (20.3, 31.2)	0.96 (0.79, 1.16)	0.32504
Standard Treatment	248	224 (90.3)	965.1	23.2	2.3 (2.1, 2.8)	20.0 (15.1, 25.3)	---	---

BICR = Blinded Independent Central Review
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

PFS rate for the overall population was 12.5% and 8.1% at 12 months for subjects receiving pembrolizumab and standard treatment, respectively.

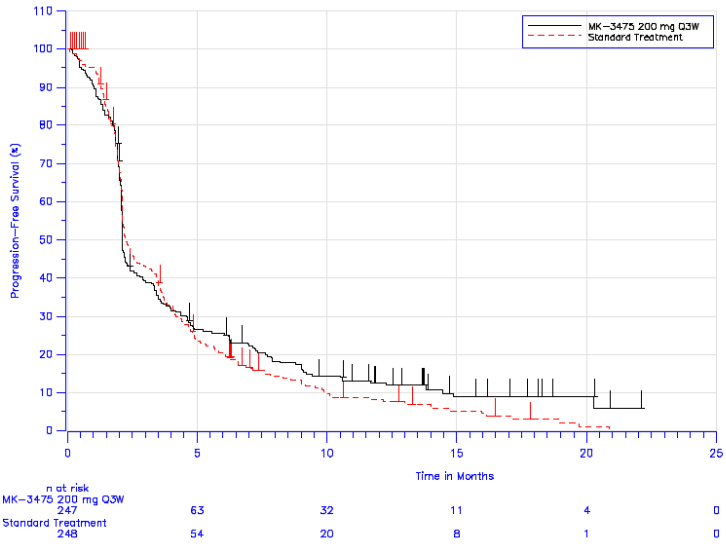


Figure 11: Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1 (ITT population)

PFS per modified RECIST

Modified RECIST 1.1, which takes into account the unique tumor response patterns seen with pembrolizumab treatment (eg, tumour flare), was also used by investigators for making treatment decisions. PFS per modified RECIST was assessed at least 4 weeks after confirmation of PD per RECIST 1.1.

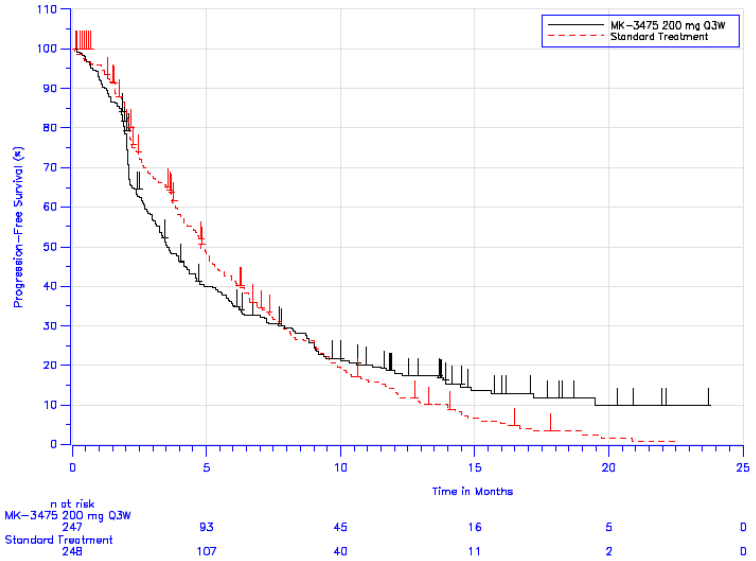


Figure 12: Kaplan-Meier estimates of PFS based on BICR per modified RECIST (ITT population)

Median PFS according to modified RECIST 1.1 was 3.5 vs 4.8 months in pembrolizumab vs standard treatment arm, respectively, (HR = 1.04 [95% CI: 0.86, 1.27]). PFS rate at 6 months was 35.3% and 41.1%, at 9 months was 25.8% and 26.1%, and at 12 months was 18.7 and 13.7% by KM estimation.

An updated analysis was conducted in which the initial PD date was used as the PD event date per mRECIST for subjects who had disease progression per RECIST 1.1 without confirmation. In this corrected analysis, the median PFS per modified RECIST (pembrolizumab:2.1 months, 95% CI: (2.1, 2.4); standard treatment: 2.3 months, 95% CI: 2.1, 2.9) is largely the same as that per RECIST 1.1.

Secondary endpoint: ORR

Table 26: Analysis of Objective response based on BICR assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Standard Treatment	
				Estimate (95% CI)[†]	p-Value[††]
MK-3475 200 mg Q3W	247	36	14.6 (10.4,19.6)	4.6 (-1.2,10.6)	0.0610
Standard Treatment	248	25	10.1 (6.6,14.5)		

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with and without confirmation.

[†] Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive) ; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

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

Database Cutoff Date: 15May2017

Table 27: Summary of best objective response BICR per RECIST 1.1 (ITT population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Number of Subjects in Population	247		248	
Complete Response (CR)	4	(1.6)	1	(0.4)
Partial Response (PR)	32	(13.0)	24	(9.7)
Objective Response (CR+PR)	**36**	**(14.6)**	**25**	**(10.1)**
Stable Disease (SD)	56	(22.7)	65	(26.2)
Progressive Disease (PD)	108	(43.7)	97	(39.1)
Non-CR/Non-PD (NN)	2	(0.8)	1	(0.4)
Not Evaluable (NE)	3	(1.2)	6	(2.4)
No Assessment	42	(17.0)	54	(21.8)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with and without confirmation.
Database Cutoff Date: 15MAY2017

Confirmed responses were 26 (10.5%) and 18 (7.3%) in pembrolizumab and standard treatment group respectively (the scan for confirmation of response was performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (e.g. 6 weeks later), whichever clinically indicated).

ORR by investigator assessment per RECIST 1.1 was consistent with the ORR according to BICR: pembrolizumab 16.2% (95%CI 11.8, 21.4) vs standard treatment 10.1% (95%CI 6.6, 14.5), with the exception of 4 additional CRs recorded in the pembrolizumab group.

ORR results by treatment are presented below:

Table 28: Analysis of objective response by treatment based on BICR assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Standard Treatment	
				Estimate (95% CI)[†]	p-Value[††]
MK-3475 200mg Q3W	247	36	14.6 (10.4,19.6)		
Cetuximab	73	8	11.0 (4.9,20.5)	4.5 (-5.4,12.0)	0.1631
Docetaxel	110	13	11.8 (6.4,19.4)	3.4 (-5.0,10.5)	0.2021
Methotrexate	65	4	6.2 (1.7,15.0)	8.7 (-1.4,15.8)	0.0398

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with and without confirmation.
[†] Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive) ; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 15May2017

Table 29: Summary of best objective response by treatment based on BICR per RECIST 1.1 (ITT population)

	MK-3475 200mg Q3W		Methotrexate		Cetuximab		Docetaxel	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of Subjects in Population	247		65		73		110	
Complete Response (CR)	4	(1.6)	0	(0.0)	0	(0.0)	1	(0.9)
Partial Response (PR)	32	(13.0)	4	(6.2)	8	(11.0)	12	(10.9)
Objective Response (CR+PR)	**36**	**(14.6)**	**4**	**(6.2)**	**8**	**(11.0)**	**13**	**(11.8)**
Stable Disease (SD)	56	(22.7)	17	(26.2)	22	(30.1)	26	(23.6)
Progressive Disease (PD)	108	(43.7)	22	(33.8)	34	(46.6)	41	(37.3)
Non-CR/Non-PD (NN)	2	(0.8)	0	(0.0)	0	(0.0)	1	(0.9)
Not Evaluable (NE)	3	(1.2)	3	(4.6)	1	(1.4)	2	(1.8)
No Assessment	42	(17.0)	19	(29.2)	8	(11.0)	27	(24.5)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with and without confirmation.
Database Cutoff Date: 15MAY2017

Duration of response (DOR)

DOR was calculated based on confirmed responses by BICR according to RECIST 1.1.

Table 30: Summary of time to response and duration of response for subjects with confirmed response based on BICR per RECIST 1.1 (ITT population)

	MK-3475 200 mg Q3W (N=247)	Standard Treatment (N=248)
Number of subjects with response[†]	26	18
Time to Response[†] (months)		
Mean (SD)	5.1 (3.0)	3.3 (2.1)
Median (Range)	4.5 (1.9-13.8)	2.2 (1.6-9.3)
Response Duration[‡] (months)		
Median (Range)	18.4 (2.7 - 18.4)	5.0 (1.4+ - 18.8)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	16 (71.5)	6 (47.1)

[†] Response: Best objective response as confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 15MAY2017

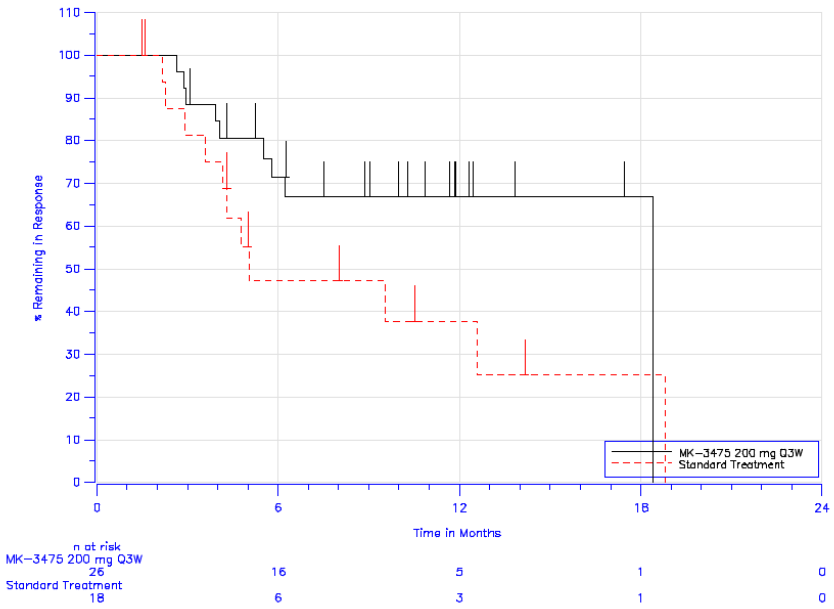


Figure 13: Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per RECIST 1.1 (ITT population)

Health-related Quality of Life (Exploratory Endpoint)

Electronic patient reported outcomes (ePROs) were administered prior to all study procedures, and were to be performed prior to Cycle 1,2,3,4 and every 2 cycles thereafter (e.g., Cycle 6,8,10) up to a year or End of Treatment, whichever occurs first, and the 30-day safety follow-up visit. The primary analysis for PRO was based on a quality-of-life-related full analysis set (FAS) population, which consists of all randomized subjects who received at least one dose of study treatment, and had completed at least one PRO assessment.

Changes from baseline in the EORTC QLQ-C30 and EORTC QLQ-H&N35 were primarily evaluated at Week 9 and at Week 15. Supportive analyses on the mean change from baseline to Week 21 and 27.

Compliance for both questionnaires C30 and H&N35 was approximately 95% in both arms at baseline, 88% vs 80% in pembrolizumab vs control arm at Week 9, 75% in both arms at Week 15, 84% vs 69% at Week 21, 86% vs 64% at Week 27.

EORTC QLQ-C30:

Baseline global health status/QOL scores were similar between treatment arms in EORTC QLQ-C30.

Over 15 weeks of follow-up, subjects receiving pembrolizumab had stable global health status/QOL, while those treated with standard treatment had a decline of global health status/QOL.

Subjects in the pembrolizumab arm exhibited stable scores at Week 9/Week 15 relative to baseline in most of the functioning and symptom domains of the EORTC QLQ-C30 (i.e. 95% CIs mostly included zero), except for the physical and cognitive functioning score which exhibited a decline from baseline to Week 15.

Table 31: Analysis of change from baseline of EORTC QLQ-C30 global health status/QoL scales at week 9 (FAS population)

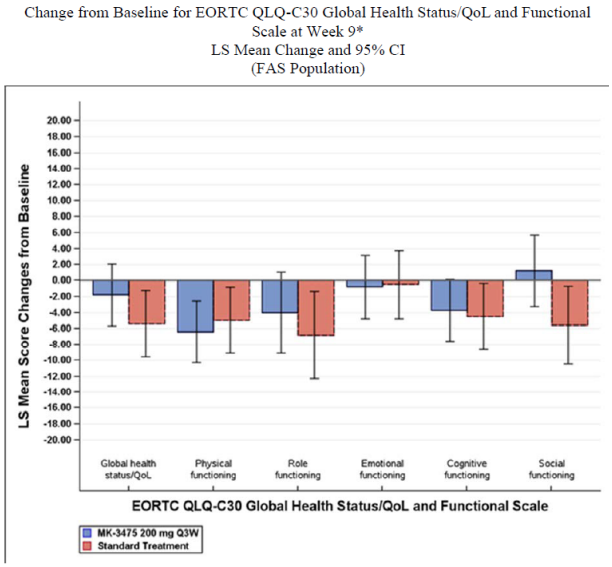
	Baseline		Week 9		Change from Baseline at Week 9	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
MK-3475 200 mg Q3W	231	56.02 (21.241)	162	59.10 (20.408)	241	-0.69 (-3.58, 2.19)
Standard Treatment	215	55.81 (21.627)	137	55.60 (21.841)	228	-3.50 (-6.58, -0.43)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg Q3W vs. Standard Treatment					2.81 (-1.21, 6.82)	0.170

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.
For baseline and Week 9, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff: 15MAY2017

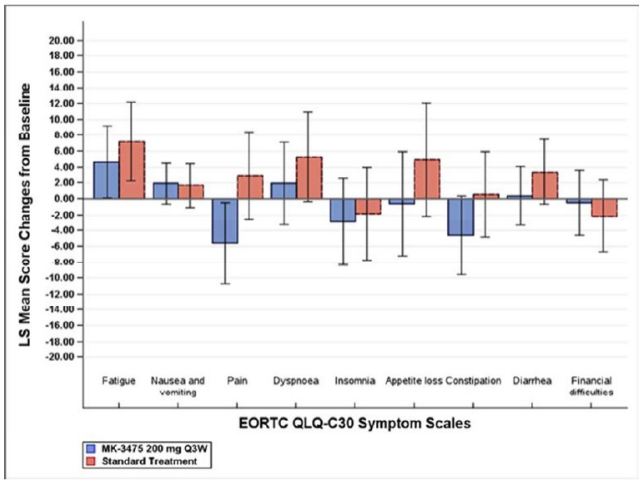
Table 32: Analysis of change from baseline of EORTC QLQ-C30 global health status/QoL scales at week 15 (FAS population)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
MK-3475 200 mg Q3W	231	56.02 (21.241)	116	61.71 (19.720)	241	0.39 (-3.00, 3.78)
Standard Treatment	215	55.81 (21.627)	85	55.69 (22.018)	228	-5.86 (-9.68, -2.04)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
MK-3475 200 mg Q3W vs. Standard Treatment					6.25 (1.32, 11.18)	0.013

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.
For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff: 15MAY2017



* For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function. For symptoms scales,
a higher score denotes worse symptoms.



* For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function. For symptoms scales,
a higher score denotes worse symptoms.

Figure 14: Change from baseline for EORTC QLQ-C30

EORTC QLQ-H&N35:

Subjects in the pembrolizumab and standard treatment arms generally exhibited stable or slight numerical worsening from baseline to Week 9/Week 15 in most of the symptom domains of the EORTC QLQ-H&N35 (i.e. 95% CIs mostly included zero). As an exception, dry mouth at Week 15 remained stable relative to baseline in the pembrolizumab arm and improved relative to baseline in the standard treatment arm. At Week 9/Week 15, the proportions of subjects with "deteriorated" status for the symptom domains of the EORTC QLQ-H&N35 in the pembrolizumab arm were generally smaller or similar to the standard treatment arm with few exceptions (dry mouth at Week 15).

EQ-5D:

Subjects in both the pembrolizumab and standard treatment arms exhibited stable or slight numerical worsening from baseline to Week 9/Week 15 in the EQ-5D visual analog scale and utility scores.

Ancillary analyses

OS analyses

Proportional hazards (PH) assumption

The PH assumption for OS was examined using both graphical and analytical methods.

- Plot of log(-log(survival)) against log(time) was generated. If the PH assumption was satisfied then the curves should be approximately parallel to each other.
- Plot of Schoenfeld residuals versus survival time was generated. If the PH assumption was satisfied then the plot of scaled residuals over time should be randomly distributed at either side of the "zero" line.

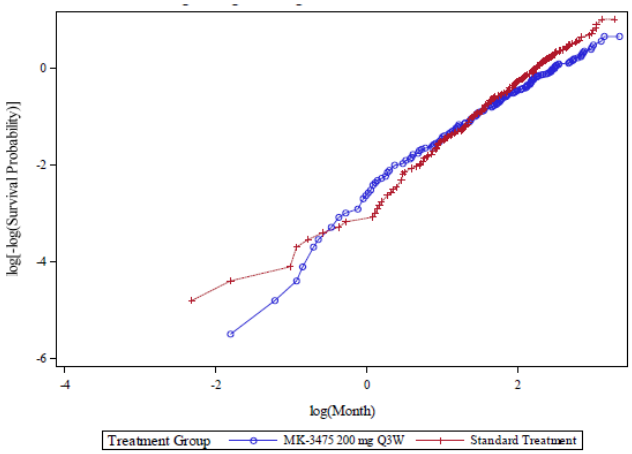


Figure 15: Log of negative Log of estimated survivor functions

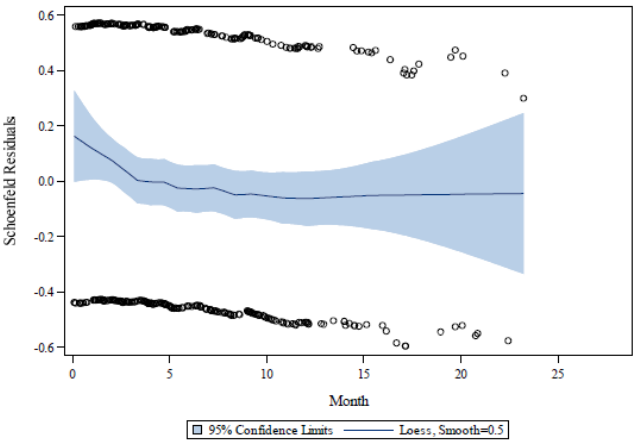


Figure 16: Overall survival (ITT population)

Table 33: Analysis of Overall Survival† Including treatment*time Interaction (ITT Population)

Covariate in the Cox Regression Model	p-Value§
Treatment: MK-3475 200 mg Q3W vs. Standard Treatment Treatment*Time Interaction	0.9604 0.0602
† Including Treatment*Time Interaction in the Cox regression model. § Two-sided p-value based on Wald chi-square test. Database Cutoff Date: 15MAY2017	

Restricted mean survival time (RMST) analyses

Table 34: Summary of restricted mean survival times (RMST) of overall survival (ITT population)

	MK-3475 200 mg Q3W (N=247)		Standard Treatment (N=248)		Difference (95% CI) vs. Standard Treatment
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	56	2.66	53	2.72	-0.05 (-0.18 , 0.07)
RMST based on 6 months of follow up	102	4.70	108	4.72	-0.02 (-0.34 , 0.31)
RMST based on 9 months of follow up	133	6.29	145	6.13	0.16 (-0.38 , 0.70)
RMST based on 12 months of follow up	155	7.53	180	7.09	0.44 (-0.29 , 1.18)
RMST based on 15 months of follow up	166	8.54	195	7.77	0.77 (-0.15 , 1.69)
RMST based on 18 months of follow up	176	9.40	201	8.29	1.11 (0.02 , 2.20)
RMST:Restricted mean survival time. Database Cutoff Date: 15MAY2017					

Table 35: Summary of restricted mean survival times (RMST) of overall survival (ITT population – CPS ≥1)

	MK-3475 200 mg Q3W (N=196)		Standard Treatment (N=191)		Difference (95% CI) vs. Standard Treatment
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	41	2.68	41	2.70	-0.03 (-0.17 , 0.11)
RMST based on 6 months of follow up	78	4.77	83	4.70	0.07 (-0.30 , 0.44)
RMST based on 9 months of follow up	101	6.41	110	6.12	0.30 (-0.31 , 0.91)
RMST based on 12 months of follow up	117	7.74	139	7.07	0.67 (-0.17 , 1.51)
RMST based on 15 months of follow up	127	8.84	150	7.74	1.10 (0.05 , 2.14)
RMST based on 18 months of follow up	134	9.78	156	8.24	1.53 (0.29 , 2.78)
RMST:Restricted mean survival time. Database Cutoff Date: 15MAY2017					

OS Sensitivity analyses - 2-step Cox model of OS

A sensitivity analysis using the two-step weighted Cox model approach was performed to adjust for non-constant hazard ratio across strata for OS (PD-L1 50%, HPV status, and ECOG status). In this approach, the treatment effect is estimated within each stratum and the stratum-specific estimates are subsequently combined using sample size weights.

Table 36: Analysis of Overall Survival† Two-Step Weighted Cox Model (ITT Population)

Treatment Effect: MK-3475 200 mg Q3W vs. Standard Treatment	Hazard Ratio† (95% CI)‡	p-Value§
MK-3475 200 mg Q3W vs. Standard Treatment	0.79 (0.65, 0.97)	0.0135
† Two-step weighted Cox model approach by Mehrotra et al. ‡ Based on Cox regression model with treatment as a covariate. § One-sided p-value based on Wald chi-square test. Database Cutoff Date: 15MAY2017		

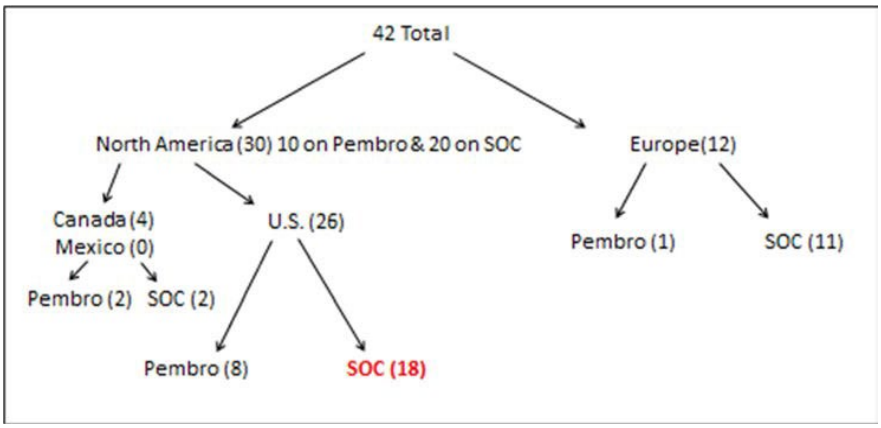
OS sensitivity analyses with regard to subsequent immunotherapy use

No pre-specified crossover of subjects from standard treatment to immunotherapy was defined in the protocol. However, unplanned crossover was reported and analysed. Subsequent immunotherapies used

by subjects in the KN040 trial included: nivolumab, anti-OX40 monoclonal antibody (unspecified), anti-PDL1 monoclonal antibody (unspecified), pembrolizumab, avelumab, tremelimumab, durvalumab, utomilumab, durvalumab (+) tremelimumab.

In the ITT population, 42 subjects crossed over to subsequent immunotherapy (checkpoint inhibitors or immunotherapy) post-randomization; 30 (23%) in North America (NA) and 12 (4.0%) in European Union (EU). There were no subjects who crossed over to subsequent immunotherapy in the Rest of World (ROW).

Table 37: Post-randomization Subsequent Medication (Crossover to Checkpoint Inhibitors or Immunotherapy at any Time) (ITT Population)



To examine the impact of crossover to subsequent immunotherapy, three sensitivity analyses were conducted:

1. subjects with subsequent immunotherapy were censored at the initiation of subsequent immunotherapy: → *HR = 0.72 (95%CI 0.58, 0.88), p-value 0.00075*
2. subjects with subsequent immunotherapy were excluded: → *HR = 0.66 (95%CI 0.54, 0.82), p-value 0.00005*
3. the time of the first initiation of subsequent immunotherapy was included in a Cox regression model as a time varying adjustment covariate along with the pembrolizumab treatment effect: → *HR = 0.73 (95%CI 0.60, 0.90), p-value 0.0015* (CSR KN040 table 11-6) (The same analysis in all subjects using time-varying adjustment covariate method performed at the initial DBL of 04-JUN-2017 yielded an HR = 0.76 [95%CI 0.62, 0.93], p-value = 0.0045).

Table 38: Analysis of Overall Survival† Initiation of Subsequent Checkpoint Immunotherapy as Time Varying Covariate (ITT Population)

Covariate in the Cox Regression Model	Hazard Ratio† (95% CI)‡	p-Value§
Treatment Effect: MK-3475 200 mg Q3W vs. Standard Treatment	0.73 (0.60, 0.90)	0.0015
Effect of initiation of subsequent checkpoint immunotherapy	0.54 (0.34, 0.85)	0.0036

† Including initiation of subsequent IO therapy as a time varying covariate in the Cox regression model.
‡ Based on Cox regression model with treatment and initiation of subsequent IO therapy as a time varying covariate.
§ One-sided p-value based on Wald chi-square test.
Database Cutoff Date: 15MAY2017

OS according to subgroups

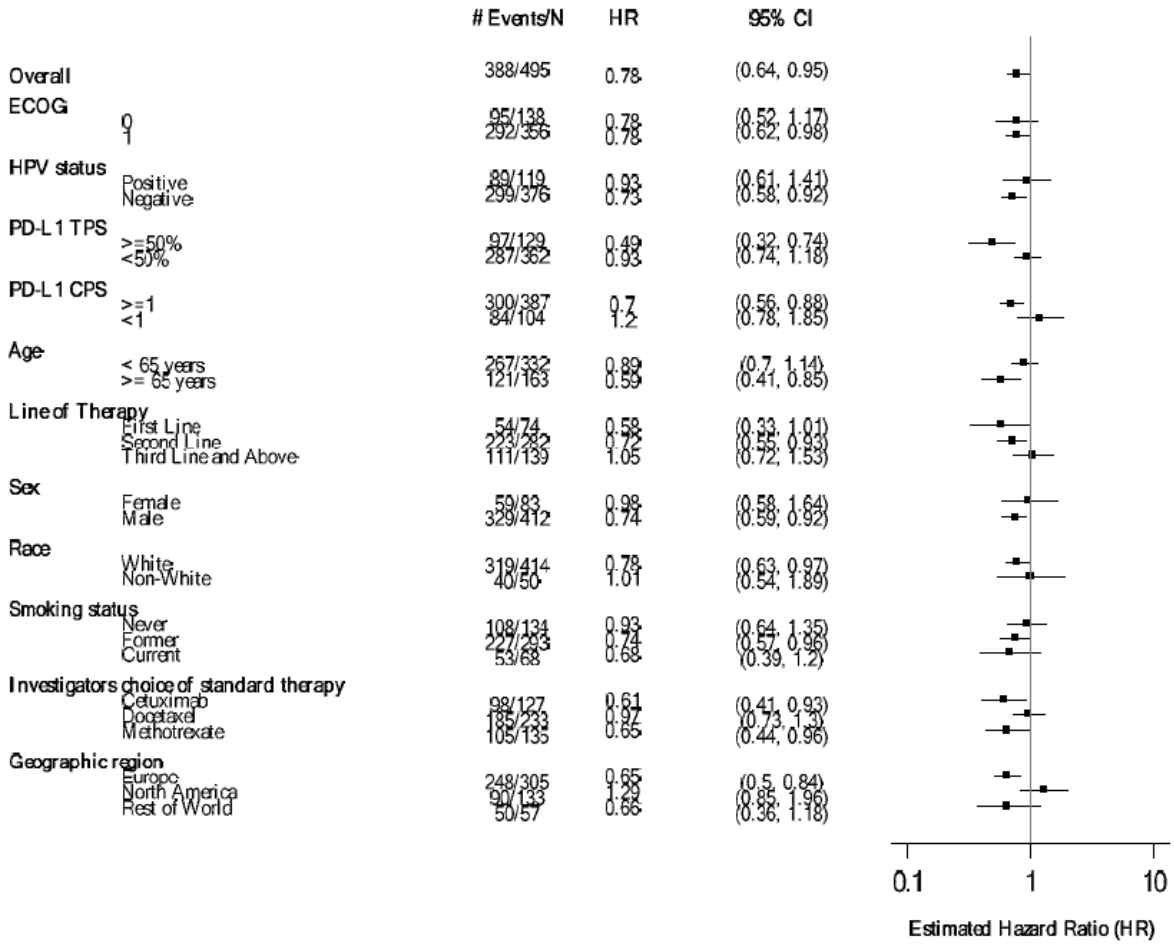
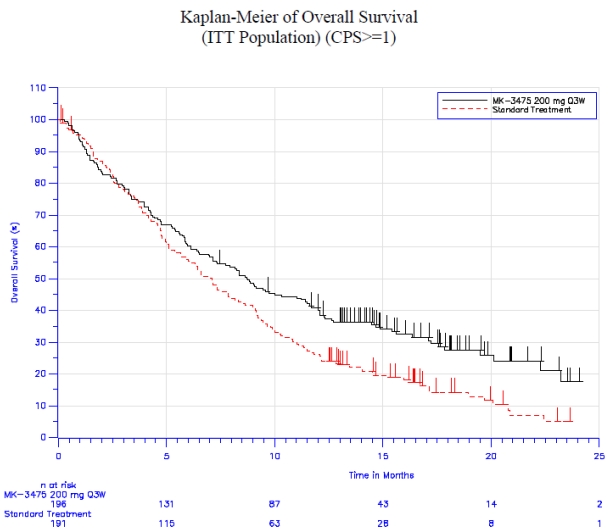


Figure 17: Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population)

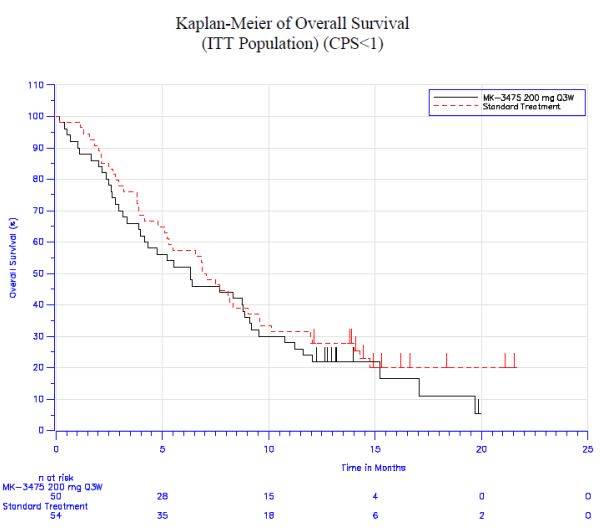
OS according to PD-L1

CPS ≥1



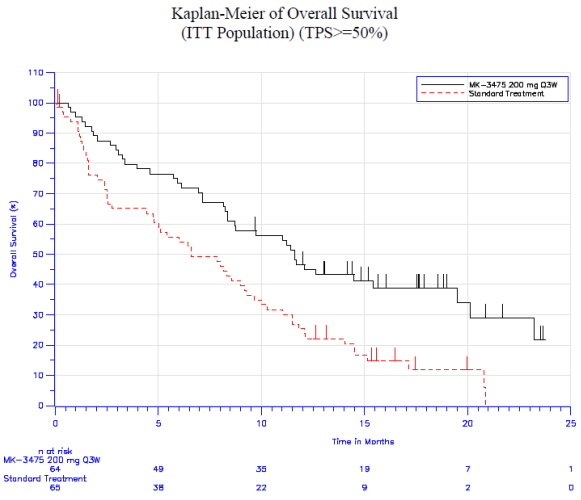
CPS≥1: HR=0.74 (95%CI 0.58, 0.93), p=0.00493

CPS<1



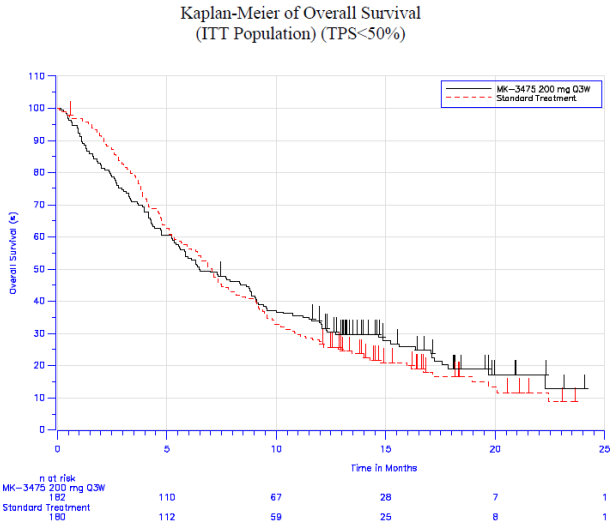
CPS<1: HR=1.28 (95%CI 0.80, 2.07), p=0.848

TPS ≥50%



TPS≥50%: HR=0.53 (95%CI 0.35, 0.81), p=0.00136

TPS<50%



TPS<50%: HR=0.93 (95%CI 0.73, 1.17), p= 0.267

Table 39: OS results according to PD-L1 status (CPS cut-off 1)

	CPS ≥ 1		**CPS < 1**	
	pembrolizumab	**standard treatment**	**pembrolizumab**	**standard treatment**
nb pts	196	191	50	54
nb events (%)	138 (70.4)	162 (84.8)	42 (84.0)	42 (77.8)
median OS[†] (95%CI) months	8.7 (6.9 , 11.4)	7.1 (5.7, 8.3)	6.3 (3.9, 8.9)	7.0 (5.1, 9.0)
HR (95%CI) [‡]	0.74 (0.58, 0.93)		1.28 (0.80, 2.07)	
p-value[§]	0.00493		0.84762	
OS rate at 6 Months (95% CI)†	60.2 (53.0, 66.7)	55.9 (48.5, 62.6)	52.0 (37.4, 64.7)	57.4 (43.2, 69.3)
OS rate at 12 Months (95% CI)†	40.1 (33.2, 46.9)	26.1 (20.0, 32.5)	24.0 (13.3, 36.4)	29.6 (18.2, 42.0)
	TPS ≥ 50%		**TPS < 50%**	
	pembrolizumab	**standard treatment**	**pembrolizumab**	**standard treatment**
nb pts	64	65	182	180
nb events (%)	41 (64.1)	56 (86.2)	139 (76.4)	148 (82.2)
median OS[†] (95%CI) months	11.6 (8.3, 19.5)	6.6 (4.8, 9.2)	6.5 (5.6, 8.8)	7.1 (5.7, 8.1)
HR (95%CI) [*]	0.53 (0.35, 0.81)		0.93 (0.73, 1.17)	
p-value[§]	0.00136		0.26752	
OS rate at 6 Months (95% CI)†	73.4 (60.8, 82.6)	55.6 (42.5, 66.8)	53.3 (45.8, 60.2)	56.4 (48.8, 63.3)
OS rate at 12 Months (95% CI)†	46.6 (34.0, 58.2)	25.4 (15.5, 36.6)	33.3 (26.6, 40.2)	27.4 (21.1, 34.0)

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)
[*] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1) and HPV status (Positive vs. Negative)
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

The MAH provided an adjusted sensitivity analysis of OS in which TPS≥50% versus TPS<50% has been replaced PD-L1 CPS≥1 versus CPS<1 in the stratified analysis, showed almost the same results compared to the ITT OS analysis.

Table 40: Analysis of Overall Survival Using CPS 1 as the Stratification Variable (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	vs. Standard Treatment	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[ʃ]
MK-3475 200 mg Q3W	247	181 (73.3)	2247.4	8.1	8.4 (6.4, 9.4)	37.0 (31.0, 43.1)	0.80 (0.65, 0.99)	0.01766
Standard Treatment	248	207 (83.5)	1997.2	10.4	6.9 (5.9, 8.0)	26.5 (21.2, 32.2)	---	---

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (CPS>=1 vs. CPS<1)
[ʃ] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

Table 41: Key Efficacy Results CPS <10/CPS ≥10 and CPS <1/CPS ≥1 Population Findings KEYNOTE-040

	ITT (All Subjects)		PD-L1 CPS <10		PD-L1 CPS ≥10		PD-L1 CPS <1		PD-L1 CPS ≥1	
	Pembrolizumab N=247	Std Treatment N=248	Pembrolizumab N=125	Std Treatment N=121	Pembrolizumab N=121	Std Treatment N=124	Pembrolizumab N=50	Std Treatment N=54	Pembrolizumab N=196	Std Treatment N=191
OS										
Number of events (%)	181 (73.3)	207 (83.5)	92 (73.6)	97 (80.2)	88 (72.7)	107 (86.3)	42 (84.0)	42 (77.8)	138 (70.4)	162 (84.8)
Median in month (95% CI)	8.4 (6.4, 9.4)	6.9 (5.9, 8.0)	6.4 (5.3, 9.1)	7.1 (5.5, 9.0)	8.7 (7.2, 11.7)	6.6 (5.0, 8.6)	6.3 (3.9, 8.9)	7.0 (5.1, 9.0)	8.7 (6.9, 11.4)	7.1 (5.7, 8.3)
HR (95% CI)	0.80 (0.65, 0.98)		0.95 (0.71, 1.28)		0.70 (0.52, 0.93)		1.28 (0.8, 2.07)		0.74 (0.58, 0.93)	
P-value	0.01605		0.37020		0.00695		0.84762		0.00493	
OS rate at 12 months (95% CI)	37.0 (31.0, 43.1)	26.5 (21.2, 32.2)	33.6 (25.5, 41.9)	30.0 (22.1, 38.3)	40.1 (31.3, 48.8)	23.8 (16.7, 31.6)	24.0 (13.3, 36.4)	29.6 (18.2, 42.0)	40.1 (33.2, 46.9)	26.1 (20.0, 32.5)
PFS (BICR per RECIST 1.1)										
Number of events (%)	218 (88.3)	224 (90.3)	111 (88.8)	110 (90.9)	106 (87.6)	111 (89.5)	47 (94.0)	51 (94.4)	170 (86.7)	170 (89.0)
Median in months (95% CI)	2.1 (2.1, 2.3)	2.3 (2.1, 2.8)	2.1 (2.0, 2.1)	2.3 (2.1, 3.4)	2.6 (2.1, 3.5)	2.3 (2.1, 3.5)	2.0 (1.9, 2.1)	2.3 (2.1, 3.5)	2.2 (2.1, 3.0)	2.3 (2.1, 3.0)
HR (95% CI)[b]	0.96 (0.79, 1.16)		1.10 (0.84, 1.44)		0.87 (0.66, 1.15)		1.33(0.86, 2.07)		0.86 (0.69, 1.06)	
P-value	0.32504		0.74564		0.15722		0.89904		0.07736	
PFS rate at 6 months (95% CI)	25.6 (20.3, 31.2	20.0 (15.1, 25.3)	19.7 (13.2, 27.1)	19.9 (13.2, 27.5)	31.9 (23.8, 40.3)	20.6 (13.8, 28.4)	14.0 (6.2, 25.0)	19.3 (9.9, 30.9)	28.7 (22.5, 35.2)	20.5 (15.0, 26.7)
PFS rate at 12 months (95% CI)	12.5 (8.6, 17.1)	8.1 (4.9, 12.3)	12.5 (7.3, 19.2)	8.7 (4.2, 15.1)	12.7 (7.4, 19.5)	7.9 (3.8, 14.0)	8.0 (2.6, 17.5)	4.3 (0.8, 12.9)	13.7 (9.2, 19.1)	9.3 (5.5, 14.4)
ORR (BICR per RECIST 1.1)										
% (95% CI)	14.6 (10.4,	10.1 (6.6, 14.5)	9.6 (5.1, 16.2)	9.9 (5.2,16.7)	19.8 (13.1, 28.1)	10.5 (5.7, 17.3)	4.0 (0.5, 13.7)	11.1 (4.2, 22.6)	17.3 (12.3, 23.4)	9.9 (6.1, 15.1)
Difference (95% CI)	4.6 (-1.2, 10.6)		0.1 (-7.8, 8.0)		9.4 (0.2, 18.8)		-6.6 (-18.9, 5.1)		7.5 (0.6, 14.6)	
P-value[e]	0.0610		0.4849		0.0221		0.8910		0.0171	
DOR (Confirmed CR or PR, BICR per RECIST 1.1)										
Median in months (range)	18.4 (2.7 to 18.4)	5.0 (1.4+ to 18.8)	18.4 (3.0+ to 18.4)	12.6 (1.4+ to 14.1+)	NR (2.7 to 13.8+)	5.0 (2.3 to 18.8)	-	4.8 (3.6 to 12.6)	18.4 (2.7 to 18.4)	9.6 (1.4+ to 18.8)
Number (Kaplan Meier %) With Confirmed Response Duration (≥6 months)	16 (71.5)	6 (47.1)	5 (100)	3 (57.1)	11 (62.3)	3 (40.0)	0	1 (33.3)	16 (71.5)	5 (50.5)

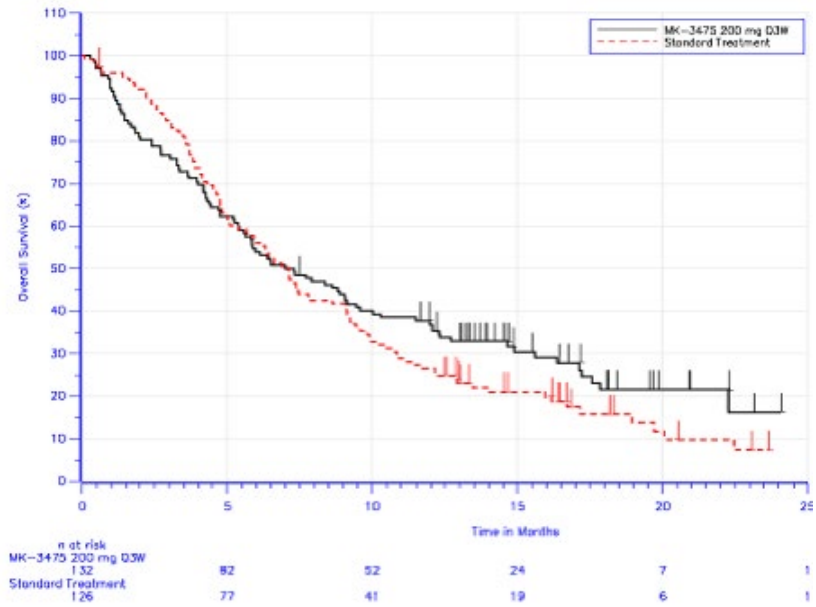
Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CPS=Combined positive score; CR=Complete response; DOR=Duration of response; HR=Hazard ratio; ITT=Intention to treat; NR=Not reached; ORR=Objective response rate; OS=Overall survival; PD-L1=Programmed cell death ligand 1; PFS=Progression-free survival; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1; Std=Standard Database cutoff date: 15-MAY-2017

The MAH has provided the results for the post-hoc exploratory subgroup of subjects with CPS≥1 and TPS<50% population. KEYNOTE-040 was not designed to be adequately powered to test subjects with CPS ≥1 and TPS <50%, thus evaluation of OS in this underpowered subgroup should be considered hypothesis generating.

Table 42: Key Efficacy Results CPS ≥1 and TPS <50% Population Findings KEYNOTE-040

	CPS ≥1		PD-L1 CPS ≥1 & TPS <50%	
	Pembrolizumab N=196	**Std Treatment N=191**	**Pembrolizumab N=132**	**Std Treatment N=126**
OS				
Number of events (%)	138 (70.4)	162 (84.8)	97 (73.5)	106 (84.1)
Median in month (95% CI)	8.7 (6.9, 11.4)	7.1 (5.7, 8.3)	7.1 (5.6, 9.1)	7.1 (5.7, 9.1)
HR (95% CI)	0.74 (0.58, 0.93)		0.85 (0.64, 1.12)	
P-value	0.00493		0.11747	
OS rate at 12 months (95% CI)	40.1 (33.2, 46.9)	26.1 (20.0, 32.5)	36.9 (28.7, 45.1)	26.4 (19.0, 34.3)
PFS (BICR per RECIST 1.1)				
Number of events (%)	170 (86.7)	170 (89.0)	118 (89.4)	112 (88.9)
Median in months (95% CI)	2.2 (2.1, 3.0)	2.3 (2.1, 3.0)	2.1 (2.1, 2.4)	2.6 (2.1, 3.7)
HR (95% CI)	0.86 (0.69, 1.06)		1.08 (0.84, 1.41)	
P-value	0.07736		0.72108	
PFS rate at 6 months (95% CI)	28.7 (22.5, 35.2)	20.5 (15.0, 26.7)	23.2 (16.4, 30.8)	22.1 (15.2, 29.9)
PFS rate at 12 months (95% CI)	13.7 (9.2, 19.1)	9.3 (5.5, 14.4)	10.8 (6.1, 17.0)	12.1 (6.8, 19.0)
ORR (BICR per RECIST 1.1)				
% (95% CI)	17.3 (12.3, 23.4)	9.9 (6.1, 15.1)	12.9 (7.7, 19.8)	10.3 (5.6, 17.0)
Difference (95% CI)	7.5 (0.6,14.6)		2.6 (-5.5, 10.6)	
P-value	0.0171		0.2610	
DOR (BICR per RECIST 1.1)				
Median in months (range)	18.4 (2.7 to 18.4)	9.6 (1.4+ to 18.8)	18.4 (2.9 - 18.4)	Not reached (1.4+ - 14.1+)
Number (Kaplan Meier %) With Confirmed Response Duration (≥6 months)	16 (71.5)	5 (50.5)	7 (81.8)	3 (50.0)

Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CPS=Combined positive score;
DOR=Duration of response; HR=Hazard ratio; ITT=Intention to treat; ORR=Objective response rate; OS=Overall survival; PD-L1=Programmed cell death ligand 1; PFS=Progression-free survival; RECIST 1.1=Response Evaluation
Criteria in Solid Tumors Version 1.1; Std=Standard; TPS=Tumor proportion score.
NOTE: Database cutoff date: 15-MAY-2017

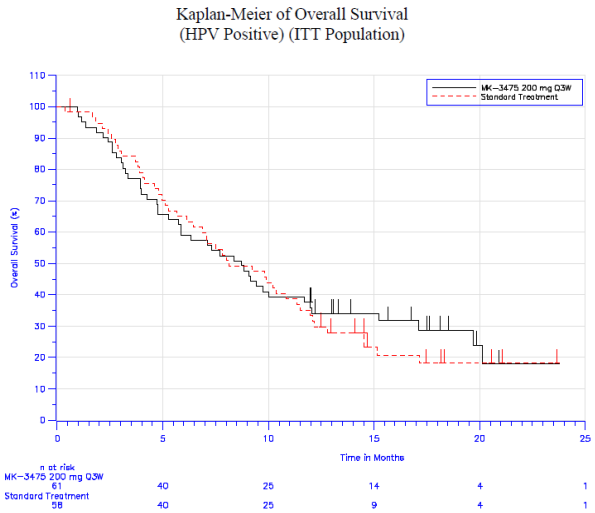


Database Cutoff Date: 15MAY2017

Figure 18: Kaplan-Meier of overall survival (ITT population) (CPS≥1 and TPS<50%)

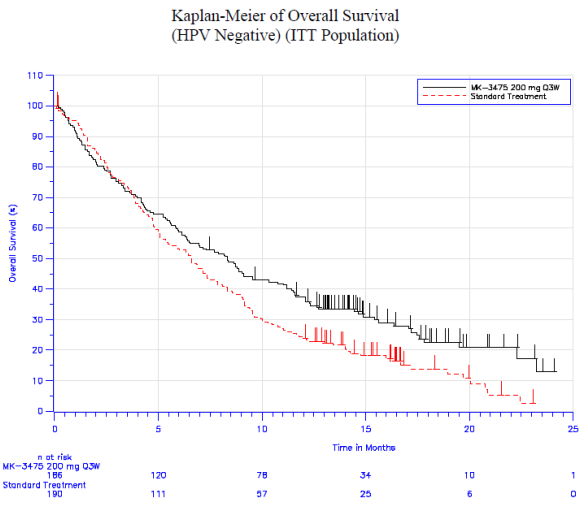
OS according to HPV

HPV positive



HPV+: HR=0.93 (95%CI 0.61, 1.41), p=0.362

HPV negative



HPV-: HR=0.73 (95%CI 0.58, 0.92), p=0.0039

Table 43: Numbers (proportion) of patients by HPV- and PDL-1 status in pembrolizumab arm

	ITT N=247	CPS <1 N=50	CPS ≥1 N=196	CPS <10 N=125	CPS ≥10 N=121
HPV pos.	61/247 (25%)	14/50 (28%)	47/196 (24%)	31/125 (25%)	30/121 (25%)
HPV neg.	186/247 (75%)	36/50 (72%)	149/196 (76%)	94/125 (75%)	91/121 (75%)

Table 44: Key efficacy results HPV positive and PD-L1 status (CPS<1/CPS≥1) population findings KEYNOTE-040

	ITT (HPV Positive)		HPV Positive & PD-L1 CPS <1		HPV Positive & PD-L1 CPS ≥1	
	Pembrolizumab N=61	Std Treatment N=58	Pembrolizumab N=14	Std Treatment N=10	Pembrolizumab N=47	Std Treatment N=48
OS						
Number of events (%)	44 (72.1)	45 (77.6)	13 (92.9)	8 (80.0)	31 (66.0)	37 (77.1)
Median in month (95% CI)	8.7 (5.7, 11.7)	8.1 (6.1, 11.3)	5.1 (2.6, 12.0)	6.2 (1.8, 12.0)	9.1 (5.8, 17.1)	9.8 (6.4, 11.5)
HR (95% CI)	0.93 (0.61, 1.41)		1.12 (0.46, 2.71)		0.84 (0.52, 1.35)	
P-value	0.36234		0.59579		0.23810	
OS rate at 12 months (95% CI)	35.9 (24.1, 47.8)	33.3 (21.6, 45.6)	28.6 (8.8, 52.4)	20.0 (3.1, 47.5)	38.0 (24.4, 51.6)	36.2 (22.8, 49.7)
PFS (BICR per RECIST 1.1)						
Number of events (%)	54 (88.5)	51 (87.9)	14 (100.0)	10 (100.0)	40 (85.1)	41 (85.4)
Median in months (95% CI)	2.1 (2.1, 2.4)	2.2 (2.1, 3.7)	2.1 (1.8, 2.2)	2.1 (1.5, 3.5)	2.1 (2.1, 3.4)	2.3 (2.1, 4.1)
HR (95% CI)	0.95 (0.65, 1.40)		1.11 (0.47, 2.60)		0.91 (0.59, 1.41)	
P-value	0.38661		0.58598		0.32724	
PFS rate at 6 months (95% CI)	26.0 (15.8, 37.5)	19.0 (9.9, 30.5)	14.3 (2.3, 36.6)	0	29.5 (17.3, 42.8)	23.5 (12.3, 36.7)
ORR (BICR per RECIST 1.1)						
% (95% CI)	11.5 (4.7, 22.2)	6.9 (1.9, 16.7)	0.0 (0.0,23.2)	10.0 (0.3,44.5)	14.9 (6.2, 28.3)	6.3 (1.3, 17.2)
Difference (95% CI)	4.6 (-6.6, 16.1)		-10.0 (-41.2,13.6)		8.6 (-4.2, 22.5)	
P-value	0.1953		0.8816		0.0861	
DOR (Confirmed Responses, BICR per RECIST 1.1)						
Median in months (range)	3.5 (2.0 – 10.0)	2.3 (20. – 6.3)	-	-	NR (5.5 to 17.4+)	NR (2.9 to 10.4+)
Number (Kaplan Meier %) With Confirmed Response Duration (≥6 months)	4 (66.7)	1 (66.7)	0 (0.0)	0 (0.0)	4 (66.7)	1 (66.7)

Table 45: Key efficacy results HPV negative and PD-L1 status (CPS<1/CPS≥1) population findings KEYNOTE-040

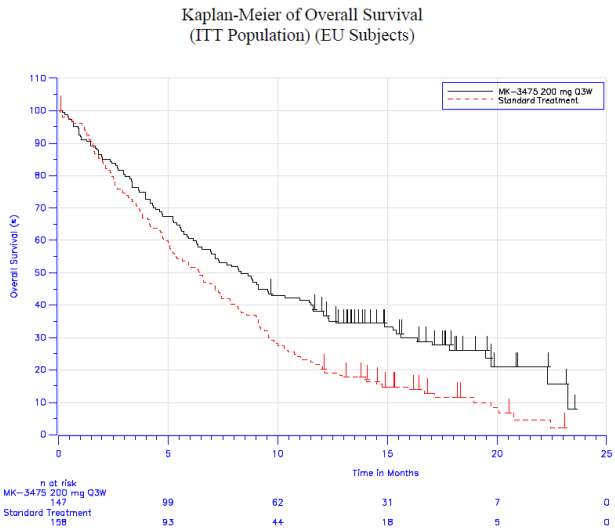
	ITT (HPV Negative)		HPV Negative & PD-L1 CPS <1		HPV Negative & PD-L1 CPS ≥1	
	Pembrolizumab N=186	Std Treatment N=190	Pembrolizumab N=36	Std Treatment N=44	Pembrolizumab N=149	Std Treatment N=143
OS						
Number of events (%)	137 (73.7)	162 (85.3)	29 (80.6)	34 (77.3)	107 (71.8)	125 (87.4)
Median in month (95% CI)	8.3 (6.3, 9.6)	6.6 (5.1, 7.7)	6.4 (3.9, 9.1)	7.3 (4.1, 9.6)	8.6 (6.4, 11.5)	6.4 (4.8, 7.4)
HR (95% CI)	0.73 (0.58, 0.92)		1.24 (0.75, 2.04)		0.66 (0.51, 0.85)	
P-value	0.00390		0.79652		0.00072	
OS rate at 12 months (95% CI)	37.4 (30.5, 44.3)	24.5 (18.6, 30.8)	22.2 (10.5, 36.7)	31.8 (18.8, 45.6)	40.7 (32.8, 48.5)	22.7 (16.2, 29.9)
PFS (BICR per RECIST 1.1)						
Number of events (%)	164 (88.2)	173 (91.1)	33 (91.7)	41 (93.2)	130 (87.2)	129 (90.2)
Median in months (95% CI)	2.1 (2.1, 2.6)	2.3 (2.1, 3.2)	2.0 (1.9, 2.2)	2.7 (2.1, 3.6)	2.2 (2.1, 3.4)	2.3 (2.1, 3.4)
HR (95% CI)	0.91 (0.73, 1.13)		1.40 (0.88, 2.22)		0.85 (0.67, 1.09)	
P-value	0.18902		0.91819		0.09366	
PFS rate at 6 months (95% CI)	25.4 (19.4, 31.9)	20.3 (14.8, 26.4)	13.9 (5.1, 27.1)	23.9 (12.4, 37.5)	28.4 (21.4, 35.9)	19.6 (13.4, 26.7)
ORR (BICR per RECIST 1.1)						
% (95% CI)	15.6 (10.7, 21.6)	11.1 (7.0, 16.4)	5.6 (0.7, 18.7)	11.4 (3.8, 24.6)	18.1 (12.3, 25.3)	11.2 (6.5, 17.5)
Difference (95% CI)	4.5 (-2.4, 11.6)		-5.8 (-19.5,8.4)		6.9 (-1.2, 15.2)	
P-value	0.0978		0.8183		0.0476	
DOR (Confirmed Responses, BICR per RECIST 1.1)						
Median in months (range)	18.4 (2.7 – 18.4)	5.0 (1.4+ – 18.8)	-	4.8 (3.6 – 12.6)	18.4 (2.7 – 18.4)	5.0 (1.4+ - 18.8)
Number (Kaplan Meier %) With Confirmed Response Duration (≥6 months)	12 (74.4)	5 (44.9)	0 (0.0)	1 (33.3)	12 (74.4)	4 (48.0)

OS by Region

Overall, of the ITT population, patients enrolled in the EU region were 62%, and 27% were enrolled in North America (NA), corresponding to 305 subjects (147 pembrolizumab and 158 standard treatment) in EU, and 133 (73 pembrolizumab and 60 standard treatment) in NA.

OS outcome according to region is presented below:

Europe (EU)



North America (NA)

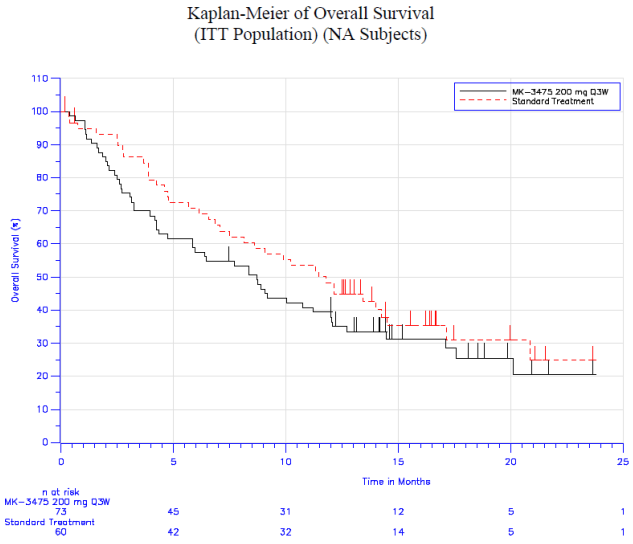
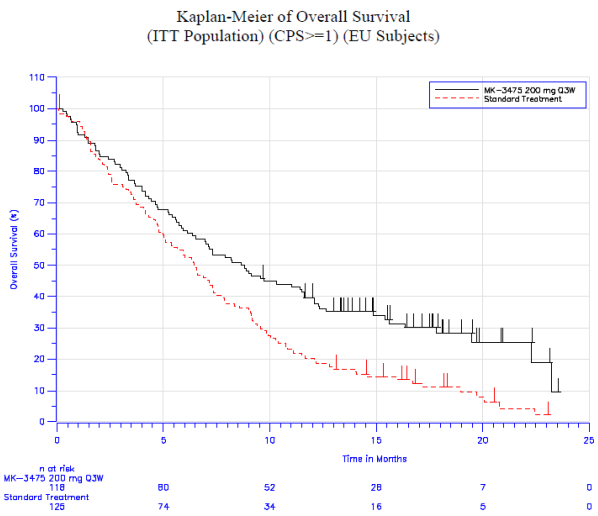


Table 46: OS analysis by region (all subjects ITT) (made by Assessor)

	ITT (all subjects)		EU (ITT)		NA (North Amerika) (ITT)		ROW (Rest of World) (ITT)	
	Pembro N=247	SOC N=248	Pembro N=147	SOC N=158	Pembro N=73	SOC N=60	Pembro N=27	SOC N=30
OS								
Median, mo (95% CI)	8.4 (6.4, 9.4)	6.9 (5.9, 8.0)	8.3 (6.4, 10.3)	6.4 (5.1, 7.5)	8.7 (4.8, 12.0)	11.8 (7.5, 14.5)	6.1 (1.4, 11.7)	5.3 (4.0, 7.7)
HR (95% CI)	0.80 (0.65, 0.98)		0.65 (0.5, 0.84)		1.29 (0.85, 1.96)		0.66 (0.36, 1.18)	
P-value	0.01605*		0.00038*		0.88410*		0.07880*	
12m (%)	37.0 (31.0, 43.1)	26.5 (21.2, 32.2)	38.0 (30.2, 45.8)	21.0 (15.0, 27.7)	37.9 (27, 49)	48.3 (35, 60.4)	29.6 (14.1, 47.0)	13.3 (4.2, 27.8)

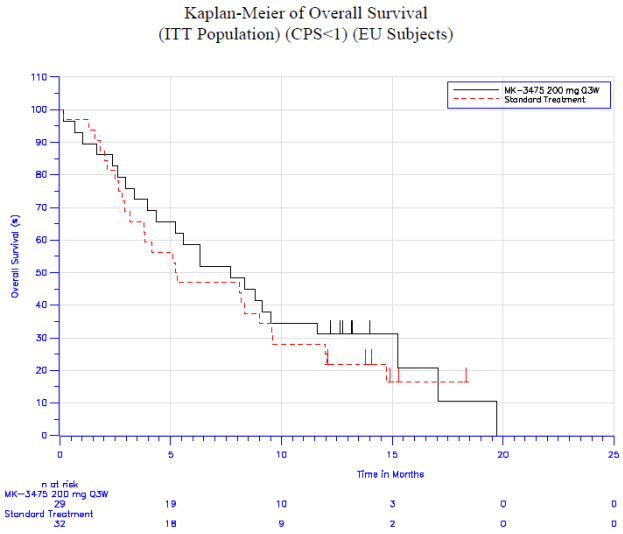
<u>OS in EU region according to PD-L1 expression</u>

CPS ≥1



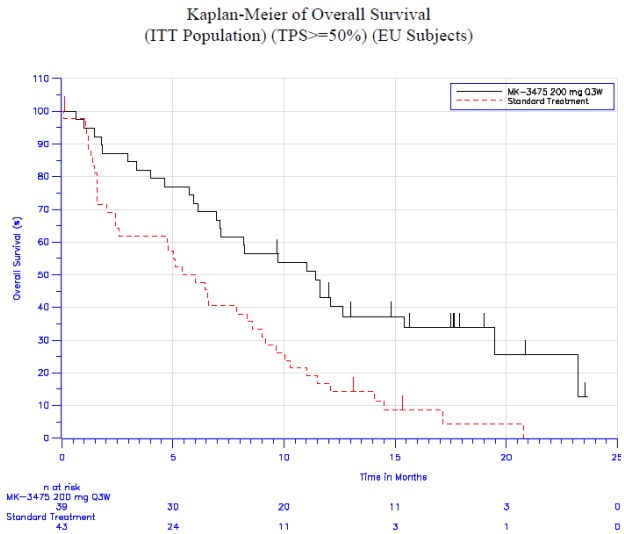
EU CPS≥1: HR=0.61 (95%CI 0.46, 0.81)

CPS<1



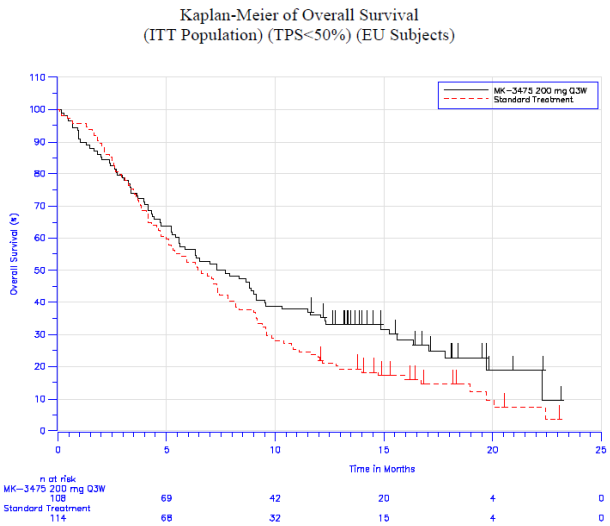
EU CPS<1: HR=0.82 (95%CI 0.46, 1.45)

TPS ≥50%



EU TPS≥50%: HR=0.43 (95%CI 0.26, 0.70)

TPS<50%



EU TPS<50%: HR=0.76 (95%CI 0.57, 1.01)

Evaluation of the first part of the OS curves

Table 47: Summary of death reasons – subjects who died within 2 months of randomisation

	MK-3475 200 mg Q3W (N=247) n(%)	Standard Treatment (N=248) n(%)	Total (N=495) n(%)
Subjects who died	41 (16.6)	31 (12.5)	72 (14.5)
Progressive Disease	**23 (9.3)**	**18 (7.3)**	**41 (8.3)**
Adverse Event	**12 (4.9)**	**10 (4.0)**	**22 (4.4)**
Not Related	11 (4.5)	10 (4.0)	21 (4.2)
Related	1 (0.4)	0 (0.0)	1 (0.2)
Unknown	**6 (2.4)**	**3 (1.2)**	**9 (1.8)**
Withdrawal By Subject	2 (0.8)	1 (0.4)	3 (0.6)
Other	4 (1.6)	2 (0.8)	6 (1.2)
Database Cutoff Date: 15MAY2017			

Table 48: Summary of deaths reasons – Subjects who died within 3 months of randomisation

	MK-3475 200 mg Q3W (N=247) n(%)	Standard Treatment (N=248) n(%)	Total (N=495) n(%)
Subjects who died	57 (23.1)	54 (21.8)	111 (22.4)
Progressive Disease	**34 (13.8)**	**36 (14.5)**	**70 (14.1)**
Adverse Event	**17 (6.9)**	**15 (6.0)**	**32 (6.5)**
Not Related	15 (6.1)	13 (5.2)	28 (5.7)
Related	2 (0.8)	2 (0.8)	4 (0.8)
Unknown	**6 (2.4)**	**3 (1.2)**	**9 (1.8)**
Withdrawal By Subject	2 (0.8)	1 (0.4)	3 (0.6)
Other	4 (1.6)	2 (0.8)	6 (1.2)
Database Cutoff Date: 15MAY2017			

Table 49: Summary of death reasons – subjects who died within 5 months of randomisation

	MK-3475 200 mg Q3W (N=247) n(%)	Standard Treatment (N=248) n(%)	Total (N=495) n(%)
Subjects who died	87 (35.2)	95 (38.3)	182 (36.8)
Progressive Disease	**59 (23.9)**	**66 (26.6)**	**125 (25.3)**
Adverse Event	**19 (7.7)**	**20 (8.1)**	**39 (7.9)**
Not Related	17 (6.9)	16 (6.5)	33 (6.7)
Related	2 (0.8)	4 (1.6)	6 (1.2)
Unknown	**9 (3.6)**	**9 (3.6)**	**18 (3.6)**
Withdrawal By Subject	3 (1.2)	3 (1.2)	6 (1.2)
Other	6 (2.4)	6 (2.4)	12 (2.4)
Database Cutoff Date: 15MAY2017			

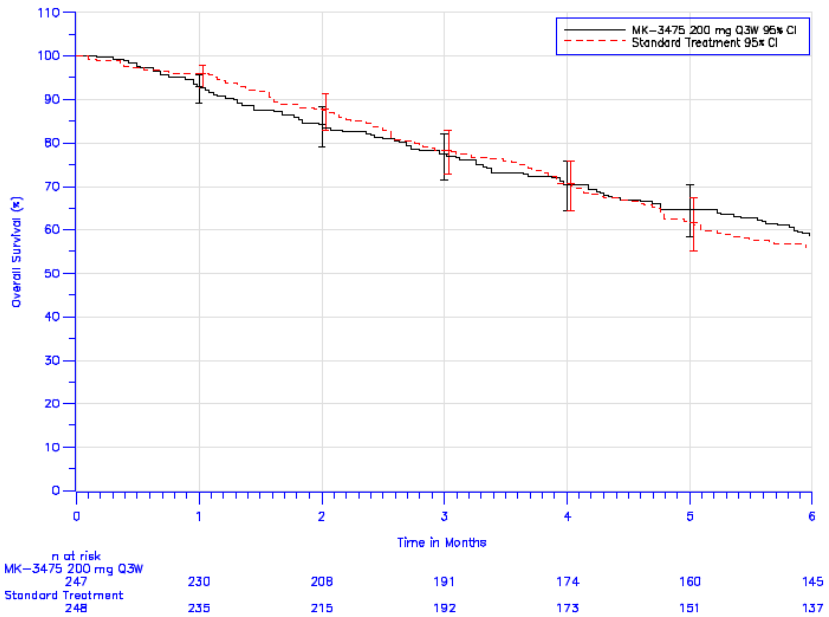


Figure 19: Kaplan-Meier of overall survival (ITT population) (first 6 months)

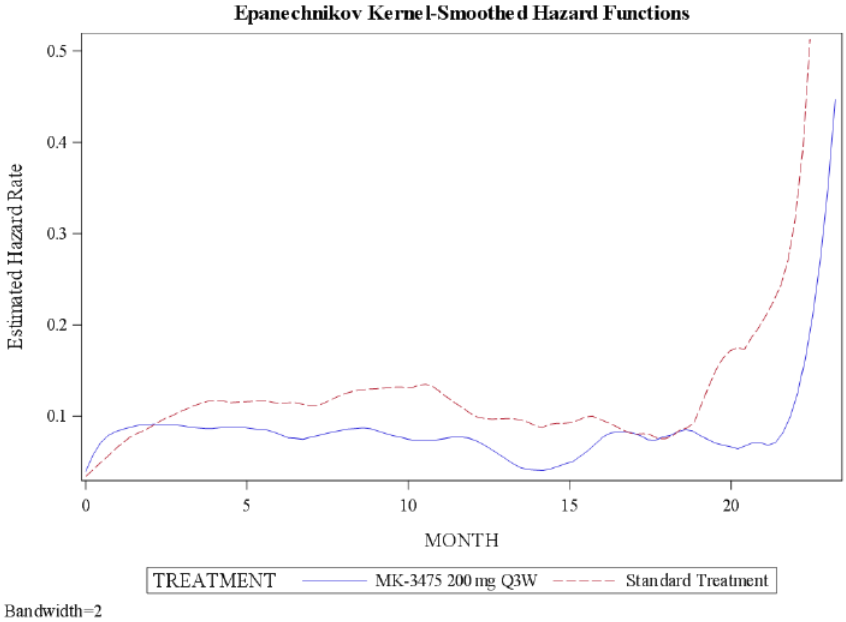


Figure 20: : Overall survival – Kernel smoothing hazard function – All subjects (ITT)

Table 50: Subject Characteristics - Subjects Who Died Within 2 Months of Randomization (ITT Population)

	MK-3475 200 mg Q3W		Standard Treatment		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	41		31		72	
Gender						
Male	32	(78.0)	24	(77.4)	56	(77.8)
Female	9	(22.0)	7	(22.6)	16	(22.2)
Age (Years)						
<65	34	(82.9)	16	(51.6)	50	(69.4)
>=65	7	(17.1)	15	(48.4)	22	(30.6)
<75	39	(95.1)	28	(90.3)	67	(93.1)
>=75	2	(4.9)	3	(9.7)	5	(6.9)
Subjects with data	41		31		72	
Mean	57.3		62.0		59.3	
SD	10.3		9.3		10.1	
Median	58.0		64.0		60.0	
Range	19 to 83		34 to 76		19 to 83	
Race						
Black or African American	1	(2.4)	0	(0.0)	1	(1.4)
White	29	(70.7)	24	(77.4)	53	(73.6)
Asian	7	(17.1)	3	(9.7)	10	(13.9)
Multi-racial	2	(4.9)	2	(6.5)	4	(5.6)
Unknown	2	(4.9)	2	(6.5)	4	(5.6)
Race Group						
White	29	(70.7)	24	(77.4)	53	(73.6)
Non-White	10	(24.4)	5	(16.1)	15	(20.8)
Unknown	2	(4.9)	2	(6.5)	4	(5.6)
Ethnicity						
Hispanic or Latino	6	(14.6)	3	(9.7)	9	(12.5)
Not Hispanic or Latino	31	(75.6)	23	(74.2)	54	(75.0)
Not Reported	1	(2.4)	2	(6.5)	3	(4.2)
Unknown	3	(7.3)	3	(9.7)	6	(8.3)
Region						
EU	22	(53.7)	25	(80.6)	47	(65.3)
NA	11	(26.8)	4	(12.9)	15	(20.8)
ROW	8	(19.5)	2	(6.5)	10	(13.9)
Smoking Status						
Never Smoked	12	(29.3)	11	(35.5)	23	(31.9)
Former Smoker	21	(51.2)	15	(48.4)	36	(50.0)

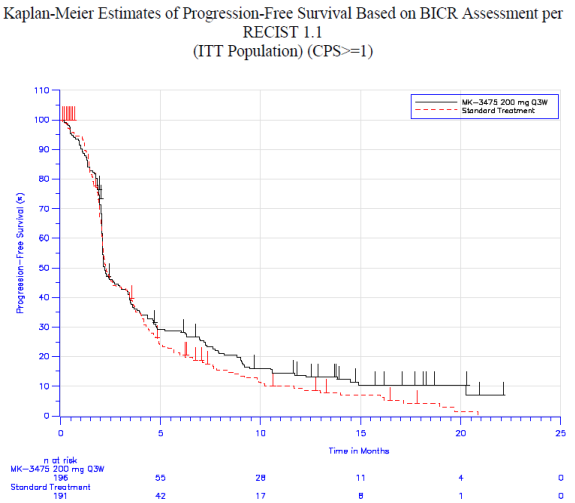
Current Smoker	8	(19.5)	5	(16.1)	13	(18.1)
Investigators Choice of Standard Therapy Identified Prior to Randomization						
Methotrexate	9	(22.0)	12	(38.7)	21	(29.2)
Docetaxel	29	(70.7)	12	(38.7)	41	(56.9)
Cetuximab	3	(7.3)	7	(22.6)	10	(13.9)
ECOG PS						
0	7	(17.1)	0	(0.0)	7	(9.7)
1	34	(82.9)	31	(100.0)	65	(90.3)
HPV Status						
Positive	5	(12.2)	3	(9.7)	8	(11.1)
Negative	36	(87.8)	28	(90.3)	64	(88.9)
PD-L1 TPS Status						
TPS = 0%	17	(41.5)	9	(29.0)	26	(36.1)
1% <= TPS < 50%	17	(41.5)	7	(22.6)	24	(33.3)
TPS >= 50%	7	(17.1)	15	(48.4)	22	(30.6)
PD-L1 CPS Status						
CPS < 1	8	(19.5)	6	(19.4)	14	(19.4)
CPS >= 1	33	(80.5)	25	(80.6)	58	(80.6)
Current Disease Brain Metastases						
Yes	0	(0.0)	1	(3.2)	1	(1.4)
No	41	(100.0)	30	(96.8)	71	(98.6)
Liver Metastases at Baseline						
Yes	5	(12.2)	5	(16.1)	10	(13.9)
No	36	(87.8)	26	(83.9)	62	(86.1)
Current Disease Overall Stage						
Stage II	1	(2.4)	1	(3.2)	2	(2.8)
Stage III	1	(2.4)	0	(0.0)	1	(1.4)
Stage IV	19	(46.3)	10	(32.3)	29	(40.3)
Stage IV A	5	(12.2)	7	(22.6)	12	(16.7)
Stage IV B	1	(2.4)	2	(6.5)	3	(4.2)
Stage IV C	14	(34.1)	11	(35.5)	25	(34.7)
Current Disease Primary Tumor						
T0, Tis	1	(2.4)	0	(0.0)	1	(1.4)
T1	1	(2.4)	2	(6.5)	3	(4.2)
T2	4	(9.8)	6	(19.4)	10	(13.9)
T3	7	(17.1)	7	(22.6)	14	(19.4)
T4	8	(19.5)	8	(25.8)	16	(22.2)
T4a	7	(17.1)	6	(19.4)	13	(18.1)
T4b	5	(12.2)	0	(0.0)	5	(6.9)
Tx	8	(19.5)	2	(6.5)	10	(13.9)
Current Disease Nodal Involvement						
NX	9	(22.0)	5	(16.1)	14	(19.4)
N0	5	(12.2)	5	(16.1)	10	(13.9)
N1	5	(12.2)	4	(12.9)	9	(12.5)
N2	17	(41.5)	16	(51.6)	33	(45.8)
N3	5	(12.2)	1	(3.2)	6	(8.3)
Current Disease Metastasis						
MX	2	(4.9)	1	(3.2)	3	(4.2)
M0	7	(17.1)	10	(32.3)	17	(23.6)
M1	32	(78.0)	20	(64.5)	52	(72.2)
Baseline Tumor Size (mm)						
Subjects with data	41		30		71	
Mean	77.9		79.0		78.4	
SD	45.5		44.6		44.8	
Median	62.0		71.5		67.0	
Range	23 to 207		19 to 224		19 to 224	
Prior Lines of Therapy						
Adjuvant, Neoadjuvant, or Definitive	5	(12.2)	3	(9.7)	8	(11.1)
First Line	24	(58.5)	22	(71.0)	46	(63.9)
Second Line	12	(29.3)	6	(19.4)	18	(25.0)
Time from Most Recent Prior Systemic Therapy						
>=3 months	36	(87.8)	30	(96.8)	66	(91.7)
<3 months	5	(12.2)	1	(3.2)	6	(8.3)
Time from Most Recent Prior Platinum Therapy						
>=3 months	37	(90.2)	30	(96.8)	67	(93.1)
<3 months	4	(9.8)	1	(3.2)	5	(6.9)
Progression on Prior Systemic Therapy						
Yes	40	(97.6)	31	(100.0)	71	(98.6)
No	1	(2.4)	0	(0.0)	1	(1.4)

Most Recent Prior Oncologic Radiation						
Neoadjuvant	5	(12.2)	3	(9.7)	8	(11.1)
Adjuvant	23	(56.1)	16	(51.6)	39	(54.2)
In Combination With First Line Treatment	3	(7.3)	2	(6.5)	5	(6.9)
Control Of Metastatic Or Recurrent Disease Or Refractory	1	(2.4)	2	(6.5)	3	(4.2)
Palliative Treatment Or Symptom Control	4	(9.8)	4	(12.9)	8	(11.1)
No Radiation	5	(12.2)	4	(12.9)	9	(12.5)
Oncologic Surgery						
Yes	23	(56.1)	20	(64.5)	43	(59.7)
No	18	(43.9)	11	(35.5)	29	(40.3)
Database Cutoff Date: 15MAY2017						

Secondary endpoints analyses

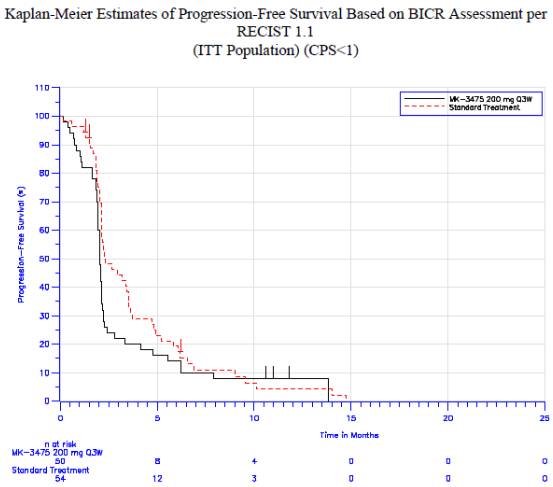
PFS according to PD-L1

CPS ≥1



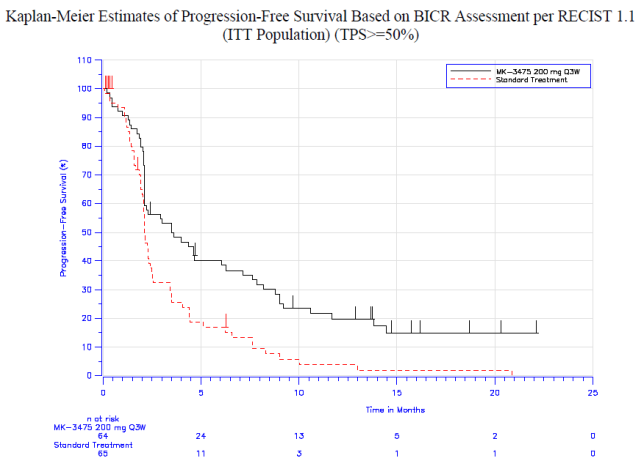
CPS≥1: HR=0.86 (95%CI 0.69, 1.06), p=0.077

CPS <1



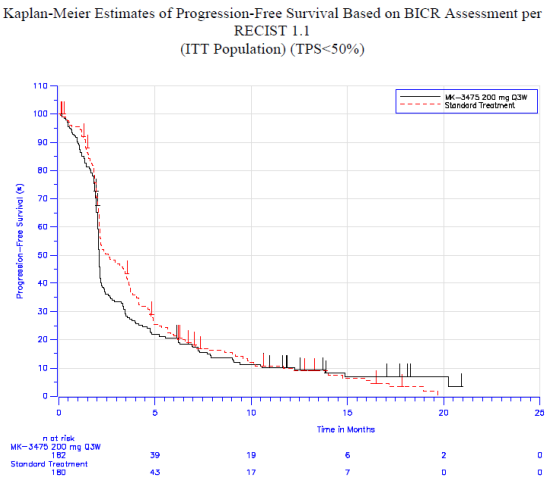
CPS<1: HR=1.33 (95%CI 0.86, 2.07), p=0.9

TPS ≥50%



TPS≥50%:HR=0.58 (95%CI 0.39, 0.86),p=0.0028

TPS <50%



TPS<50%: HR=1.14 (95%CI 0.92, 1.43), p=0.875

Table 51: PFS based on BICR assessment per RECIST 1.1 results according to PD-L1 status

	CPS ≥ 1		CPS < 1	
	pembrolizumab	**standard treatment**	**pembrolizumab**	**standard treatment**
nb pts	196	191	50	54
nb events (%)	170 (86.7)	170 (89.0)	47 (94.0)	51 (94.4)
median PFS[†] (95%CI) months	2.2 (2.1, 3.0)	2.3 (2.1, 3.0)	2.0 (1.9, 2.1)	2.3 (2.1, 3.5)
HR (95%CI)	0.86 (0.69, 1.06) [‡]		1.33 (0.86, 2.07) [**]	
p-value[§]	0.07736		0.89904	
PFS rate at 6 Months (95% CI)†	28.7 (22.5, 35.2)	20.5 (15.0, 26.7)	14.0 (6.2, 25.0)	19.3 (9.9, 30.9)
PFS rate at 12 Months (95% CI)†	13.7 (9.2, 19.1)	9.3 (5.5, 14.4)	8.0 (2.6, 17.5)	4.3 (0.8, 12.9)
	TPS ≥ 50%		**TPS < 50%**	
	pembrolizumab	**standard treatment**	**pembrolizumab**	**standard treatment**
nb pts	64	65	182	180
nb events (%)	52 (81.3)	58 (89.2)	165 (90.7)	163 (90.6)
median OS[†] (95%CI) months	3.5 (2.1, 6.3)	2.1 (2.0, 2.4)	2.1 (2.1, 2.1)	2.6 (2.1, 3.5)
HR (95%CI)	0.58 (0.39, 0.86) [*]		1.14 (0.92, 1.43) [*]	
p-value[§]	0.00277		0.87517	
PFS rate at 6 Months (95% CI)†	40.1 (28.1, 51.9)	17.1 (8.8, 27.7)	20.7 (15.1, 26.8)	21.3 (15.5, 27.7)
PFS rate at 12 Months (95% CI)†	19.8 (10.9, 30.6)	3.8 (0.7, 11.4)	10.0 (6.1, 15.1)	9.8 (5.7, 15.1)

BICR = Blinded Independent Central Review
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a single covariate
[*] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative).
[**] Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)
[§] One-sided p-value based on log-rank test.
Database Cutoff Date: 15MAY2017

Restricted mean survival time (RMST) analyses of PFS

Table 52: Summary of restricted mean survival times (RMST) of PFS based on BICR per RECIST 1.1 (ITT population)

	MK-3475 200 mg Q3W (N=247)		Standard Treatment (N=248)		Difference (95% CI) vs. Standard Treatment
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	149	2.23	135	2.31	-0.08 (-0.21 , 0.06)
RMST based on 6 months of follow up	182	3.14	189	3.19	-0.05 (-0.38 , 0.28)
RMST based on 9 months of follow up	201	3.76	203	3.66	0.09 (-0.41 , 0.60)
RMST based on 12 months of follow up	212	4.17	213	3.95	0.22 (-0.41 , 0.85)
RMST based on 15 months of follow up	217	4.51	218	4.15	0.35 (-0.40 , 1.11)
RMST:Restricted mean survival time. Database Cutoff Date: 15MAY2017					

Source: [P040V01MK3475: adam-adsl; adtte]

ORR and DOR according to PD-L1 expression

Table 53: ORR based on BICR per RECIST 1.1 according to PD-L1 expression, DOR for subjects with <u>confirmed</u> response based on BICR per RECIST 1.1

	CPS ≥ 1		**CPS < 1**	
	pembrolizumab	**standard treatment**	**pembrolizumab**	**standard treatment**
nb pts	196	191	50	54
CR (%)	4 (2)	1 (0.5)	0	0
SD (%)	46 (23.5)	53 (27.7)	9 (18.0)	12 (22.2)
ORR (95%CI)	17.3% (12.3,23.4)	9.9% (6.1,15.1)	4.0 (0.5,13.7)	11.1 (4.2,22.6)
p-value	0.0171		0.8910	
nb of objective responses	34	19	2	6
nb of confirmed objective responses	26	15	0	3
median DOR (range) months	18.4 (2.7 - 18.4)	9.6 (1.4+ - 18.8)	-	4.8 (3.6 - 12.6)
nb responses ≥6 months*	16 (71.5%)	5 (50.5%)	0	1 (33.3%)
	TPS ≥ 50%		**TPS < 50%**	
	pembrolizumab	**standard treatment**	**pembrolizumab**	**standard treatment**
nb pts	64	65	182	180
CR (%)	3 (4.7)	1 (1.5)	1 (0.5)	0
SD (%)	15 (23.4)	15 (23.1)	40 (22.0)	50 (27.8)
ORR (95%CI)	26.6% (16.3, 39.1)	9.2% (3.5, 19)	6.0% (3.1, 10.6)	7.8% (4.3, 12.7)
p-value	0.0009			
nb of objective responses	17	6	11	14
nb of confirmed objective responses	15	4	11	14
median DOR (range) months	NR (2.7 - 13.8+)	6.9 (4.2 - 18.8)	18.4 (2.9 - 18.4)	5.0 (1.4+ - 14.1+)
nb responses ≥6 months*	9 (65.5%)	2 (50.0%)	7 (81.8%)	4 (45.7%)

*From product-limit (Kaplan-Meier) method for censored data. NR= not reached

ORR according to HPV status

ORR according to HPV status was in HPV negative 15.6% (10.7,21.6) vs 11.1% (7.0,16.4) and in HPV positive 11.5% (4.7,22.2) vs 6.9% (1.9,16.7) for pembrolizumab vs standard treatment arm, respectively.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 54: Summary of Efficacy for trial KEYNOTE 040

Title: A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer (KEYNOTE-040)		
Study identifier	MK-3475-040	
Design	Randomized, multi-site, open-label, active-controlled, phase 3	
	Duration of main phase:	trial initiation date: 17-NOV-2014 trial ongoing, data cutoff: 15-MAY-2017
Hypothesis	Superiority	
Treatments groups	Pembrolizumab	200 mg IV every 3 weeks for up to 24 months or until disease progression or unacceptable toxicity 247 subjects randomized, 246 treated

	Standard treatment (Investigator's choice of methotrexate, docetaxel or cetuximab)		Investigator's choice: methotrexate 40 mg/m2 IV once weekly (with the option of a maximum increase to 60 mg/m2 IV weekly in the absence of toxicity), or docetaxel 75 mg/m2 IV every 3 weeks, or cetuximab 400 mg/m2 IV loading dose and then 250 mg/m2 IV once weekly, until disease progression or unacceptable toxicity 248 subjects randomized, 234 treated
Endpoints and definitions	Primary endpoint	OS in ITT	Time to death due to any cause
	Key secondary efficacy endpoint	OS in CPS ≥1	Time to death due to any cause
	Key secondary efficacy endpoint	PFS per RECIST 1.1 based on BICR in ITT and CPS ≥1	Time to the first documented disease progression or to death due to any cause
	Key secondary efficacy endpoint	ORR by BICR per RECIST 1.1 in ITT and CPS ≥1	Proportion of subjects who have a complete response (CR) or partial response (PR)
	Other secondary efficacy endpoints	TTP and DOR per RECIST 1.1 PFS per modified RECIST	TTP: time to the first documented disease progression DOR: time from first documented evidence of CR or PR until disease progression or death PFS per modified RECIST: assessed at least 4 weeks after confirmation of PD per RECIST 1.1
	Secondary safety endpoint	Tier 2 AEs Tier 3 AEs	Adverse events occurring in at least 4 subjects in any treatment group Specific AEs and changes from baseline results for laboratory tests, ECGs, vital signs
Data cut-off date	15-MAY-2017		
Database lock	13-OCT-2017 NOTE: all data are provided with a DBL date of 13-OCT-2017 (388 death events occurred at the cut-off date of 15-MAY -2017). The only p-value provided for statistical inference is the one for the primary OS analysis in all subjects based on the 04-JUN-2017 DBL (including information on 377/388 death events occurred at the cut-off date of 15-MAY -2017). All other p-values, including those based on the 13-OCT-2017 database update, are considered nominal and are not adjusted for multiplicity.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability, Effect estimate per comparison	Treatment group	**Pembrolizumab**	**Standard treatment**
	Number of subject	247	248
	OS (ITT) N. with events (%)	181 (73.3)	207 (83.5)
	Median OS months (95% CI)	8.4 (6.4, 9.4)	6.9 (5.9, 8.0)
	HR (95% CI)	0.80 (0.65, 0.98)	
	p-value	0.01605	
	OS rate at 6 months	58.7 (52.3, 64.6)	55.9 (49.5, 61.9)
	OS rate at 12 months	37.0 (31.0, 43.1)	26.5 (21.2, 32.2)
	OS (CPS ≥1) N. pts N. with events (%)	 196 138 (70.4)	 191 162 (84.8)
	Median OS months (95% CI)	8.7 (6.9 , 11.4)	7.1 (5.7, 8.3)
	HR (95% CI)	0.74 (0.58, 0.93)	
	p-value	0.00493	

	OS (TPS ≥ 50%) N. pts N. with events	64 41 (64.1)	65 56 (86.2)
	Median OS months (95% CI)	11.6 (8.3, 19.5)	6.6 (4.8, 9.2)
	HR (95% CI)	0.53 (0.35, 0.81)	
	p-value	0.00136	
	PFS (ITT) N. with events (%)	218 (88.3)	224 (90.3)
	Median PFS months (95% CI)	2.1 (2.1, 2.3)	2.3 (2.1, 2.8)
	HR (95% CI)	0.96 (0.79, 1.16)	
	p-value	0.32504	
	ORR by BICR (%) (95%CI)	14.6 (10.4, 19.6)	10.1 (6.6, 14.5)
	DOR based on confirmed response by BICR in months median (range)	18.4 (2.7, 18.4)	5.0 (1.4+, 18.8)
Notes	OS at the database lock of 04-JUN-2017: HR 0.82, 95%CI 0.67-1.01, p=0.03160, median OS 8.4 vs 7.1 months (the OS boundary of 0.0186 missed the primary statistical hypothesis of a p-value OS boundary of 0.0175 for 377 deaths)		

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

Not applicable

Clinical studies in special populations

No specific clinical studies have been performed in special population.

OS data by age group in the pivotal Keynote 040 study are depicted in the below table. In the age group of 75-84 years OS HR is 1.01; however the 95% CI is wide and a small number of subjects were enrolled in this age group. Only one subject was ≥85 years of age at baseline.

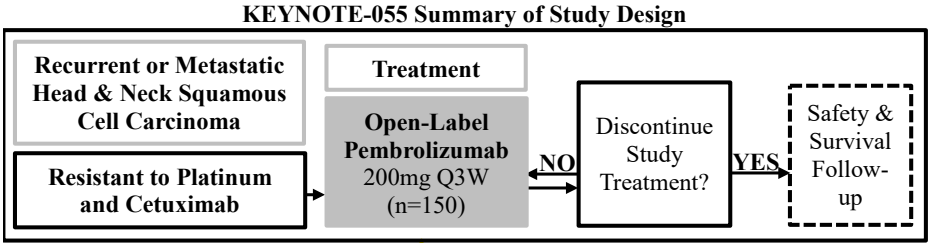
Table 55: OS by age (table made by Assessor)

	ITT (all subjects)		Age <65 years		65-74 years		75-84 years	
	Pembro N=247	SOC N=248	Pembro N=165	SOC N=167	Pembro N=63	SOC N=69	Pembro N=18	SOC N=12
OS								
Median, mo (95% CI)	8.4 (6.4, 9.4)	6.9 (5.9, 8.0)	7.2 (5.2, 8.8)	7.1 (6.0, 8.6)	11.6 (8.7, 15.2)	6.4 (3.9, 8.3))	6.8 (3.3, 11.5)	5.7 (1.4, .)
HR (95% CI)	0.80 (0.65, 0.98)		0.89 (0.70, 1.14)		0.51 (0.34, 0.77)		1.01 (0.42, 2.42)	
P-value	0.01605*		0.17942*		0.00049*		0.50817*	
12m (%)	37.0 (31.0, 43.1)	26.5 (21.2, 32.2)	33.3 (26.3, 40.5)	28.5 (21.8, 35.5)	48.5 (36, 60)	20.3 (11.8, 30.4)	27.8 (10.1, 48.9)	36.4 (11.2, 62.7)

Supportive study(ies)

KEYNOTE-055

Title: A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab



Methods

Study participant

The trial enrolled male/female subjects of at least 18 years of age, ECOG 0-1 and adequate organ functions. Subjects must have had histologically or cytologically-confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx that was considered incurable by local therapies (subjects with oropharynx cancer must have had an assessment of HPV status from tumor tissue).

Subjects must have been resistant to both platinum (either cisplatin or carboplatin) and cetuximab-based therapy, i.e. tumor progression or recurrence within 6 months of the last dose of platinum and cetuximab therapy in the adjuvant (eg, with radiation after surgery), primary (eg, with radiation), recurrent, or metastatic setting. Platinum and cetuximab did not need to be given concurrently; however, subjects must have recurred within 6 months of the last dose for each of these therapies. Any number of previous systemic regimens given for recurrent and/or metastatic disease was allowed.

Subjects must have provided tissue for PD-L1 biomarker analysis from a newly obtained core or excisional biopsy (archived specimen may be submitted upon agreement from the Sponsor).

Subjects must have had measurable disease based on RECIST 1.1 as determined by central review. Tumor lesions situated in a previously irradiated area were considered measurable if progression had been demonstrated in such lesions.

Subject with known active central nervous system metastases and/or carcinomatous meningitis, chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1, active autoimmune disease that required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs), prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent active infection, active non infectious pneumonitis, HIV, HBV, HCV were excluded.

Treatments

All patients received 200 mg of pembrolizumab every 3 weeks (Q3W).

The first imaging assessment was performed at 9 weeks, then every 6 weeks to complete the first year of treatment, then every 9 weeks for subjects who remained on treatment for the 2nd year of pembrolizumab.

RECIST 1.1 response rate as assessed by the independent central radiology vendor was used as the primary efficacy endpoint.

If radiologic imaging showed PD, tumor assessment might be repeated ≥4 weeks later at the site in order to confirm PD with the option of continuing treatment for clinically stable subjects.

Subjects who attained an investigator-determined confirmed CR might have considered stopping trial treatment after receiving at least 24 weeks of treatment.

Objectives

Primary objective: To determine the safety and tolerability of 200 mg Q3W dose of pembrolizumab in subjects with R/M HNSCC who have progressed on platinum and cetuximab therapy.

Primary objectives: To evaluate antitumor activity of pembrolizumab by ORR using RECIST 1.1 assessed by independent central radiology review in all subjects and in PD-L1 strong positive (i.e. TPS ≥50%) subjects with R/M HNSCC who have progressed on platinum and cetuximab therapy.

Secondary objectives: To evaluate antitumor activity of pembrolizumab by ORR in PD-L1 positive subjects, and to estimate the duration of response, PFS and OS in all subjects, PD-L1 strong positive, and PD-L1 positive subjects.

Outcomes/endpoints

Endpoints	Abbreviations	Populations	Definitions
Primary	ORR	ASaT	Proportion of subjects in analysis population who had confirmed CR or confirmed PR per RECIST 1.1 based on central radiology assessment
	ORR	PD-L1 by TPS status	Proportion of subjects in analysis population who had confirmed CR or confirmed PR per RECIST 1.1 based on central radiology assessment
Key Secondary	DOR	ASaT	Time from first RECIST 1.1 response to confirmed PD in subjects who achieved a PR or better
	ORR by mRECIST	ASaT	Proportion of subjects with CR or PR at any time during the trial, including a confirmed CR or confirmed PR that occurred after a RECIST 1.1 PD assessment
	ORR	HPV+	Proportion of subjects with an HPV-positive tumor who achieved a confirmed CR or confirmed PR according to RECIST 1.1
	PFS	ASaT	Time from allocation to the first documented confirmed PD according to RECIST 1.1 or death due to any cause, whichever occurred first
	OS	ASaT	Time from allocation to death due to any cause

Abbreviations: ASaT=All Subjects as Treated; CR=Complete response; DOR=Duration of response; HPV=Human papilloma virus; mRECIST=modified RECIST; ORR=Objective response rate; OS=Overall survival; PD=Progressive disease; PD-L1=Programmed cell death-1 ligand 1; PFS=Progression free survival; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; TPS=Tumor proportion score.

Sample size

Assuming that approximately 135 of the 150 enrolled subjects with recurrent and/or metastatic head and neck cancer will be evaluable for the primary efficacy analysis in the FAS population, the study has approximately 85% power to demonstrate that the ORR is >5% with a type I error rate of 1.25% if the true ORR in all subjects is 13%. Success for this hypothesis requires at least 14/135 responses. Assuming that the prevalence of PD-L1 strong positive subjects with recurrent and/or metastatic head and neck cancer is 20%~30%, then among the 150 enrolled subjects approximately 30~45 PD-L1 strong positive subjects would be expected. The study has approximately 92% to 99% power to demonstrate that the

ORR >5% with a type I error rate of 1.25% if the true ORR in PD-L1 strong positive subjects is 30%. Success for this hypothesis requires at least 6 responses out of 30~39 PD-L1 strong positive subjects, and at least 7 responses out of 40~45 PD-L1 strong positive subjects.

Statistical methods

The ORR was evaluated for the primary efficacy hypothesis and estimated separately for all subjects and for subjects with strongly positive PD-L1 expression based on TPS ≥50%. A 97.5% CI along with a one-sided p-value for testing the null hypothesis based on the binomial distribution was provided for ORR. The trial was considered to have met the efficacy endpoint if the one-sided p-value for testing the primary hypothesis in all subjects was less than 1.25%, OR if the one-sided p-value for testing the primary hypothesis in PD-L1 strongly positive subjects was less than 1.25%. A step-down procedure controlled Type I error between the primary PD-L1 strongly positive hypothesis and the secondary PD-L1 positive (defined as TPS >0% by IHC) hypothesis.

Results

Patient disposition

A total of 172 subjects were enrolled. 1 subject was not dosed, therefore excluded from efficacy and safety analyses. As a result, ASaT population included 171 subjects.

Table 56: Subject Disposition (ASaT Population) KN055

	MK-3475 n (%)
Subjects in population	171
Status for Study Medication	
Started	171
Discontinued	135 (78.9)
Adverse Event	24 (14.0)
Clinical Progression	23 (13.5)
Complete Response	1 (0.6)
Death	2 (1.2)
Excluded Medication	1 (0.6)
Lost To Follow-Up	1 (0.6)
Physician Decision	1 (0.6)
Progressive Disease	80 (46.8)
Withdrawal By Subject	2 (1.2)
Treatment Ongoing	36 (21.1)
Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record. Abbreviations: ASaT = All Subjects as Treated (Database Cutoff Date: 22APR2016).	

Recruitment

Trial was conducted at 41 centers, of which 33 allocated subjects to study treatment (31 in US, 1 in Denmark and 1 in Norway). Enrollment was from 24-OCT-2014 to 16-OCT-2015.

All data provided in CSR are based on a 22-APR-2016 cutoff date, ≥6 months after the last subject was enrolled and initially treated with pembrolizumab.

Conduct of the study

Protocol amendments

The original protocol was dated 25-Jul-2014. Three amendments were released.

Protocol deviations

There were 104 major protocol deviations. Most of them were related to informed consent form (61 pts, 59%), safety assessment (23 pts, 22%) and entry criteria (16 pts, 15%).

Baseline data

Table 57: subject characteristics (ASaT population) (selected data)

	MK-3475 n (%)
Subjects in population	171
Age (Years)	
<65	107 (62.6)
>=65	64 (37.4)
Mean	61.2
SD	9.9
Median	61.0
Range	33 to 90
ECOG	
[0] Normal Activity	48 (28.1)
[1] Symptoms, but ambulatory	120 (70.2)
[2] Ambulatory but unable to work	3 (1.8)
Prior Adjuvant/Neoadjuvant therapy	
0	129 (75.4)
1	39 (22.8)
2	3 (1.8)
Number of Lines of Therapy for recurrent/Metastatic Disease	
0	3 (1.8)
1	39 (22.8)
2	68 (39.8)
3	35 (20.5)
4	17 (9.9)
5 or more	9 (5.3)
Prior Taxanes Flag	
Yes	114 (66.7)
No	57 (33.3)
Prior 5FU/Xeloda Therapy	
Yes	69 (40.4)
No	102 (59.6)
Prior Methotrexate Therapy	
Yes	15 (8.8)
No	156 (91.2)
Sum of target lesions measureable at baseline (mm)	
Subjects with data	171
Mean	104.1
SD	85.3
Median	82.7
Range	11.4 to 621.8
Status of Cigarette Use	
CURRENT USER	13 (7.6)
EX USER	99 (57.9)
NON USER	59 (34.5)
Prior Radiation Therapy?	
Y	152 (88.9)
N	19 (11.1)
Prior Surgery?	
Y	98 (57.3)
N	73 (42.7)
Primary Tumor Location	
HYPOPHARYNX	7 (4.1)
LARYNX	30 (17.5)
NASAL CAVITY	1 (0.6)
ORAL CAVITY	28 (16.4)
OROPHARYNX	100 (58.5)
PHARYX	1 (0.6)
OTHER	4 (2.3)

Abbreviations: ASaT = All Subjects as Treated, ECOG = Eastern Cooperative Oncology Group, SD = standard deviation
(Database Cutoff Date: 22APR2016).

According to PD-L1 status, patients were classified in:

- TPS=0%: 45 (26.3%); TPS≥1% and<50%: 77 (45%); TPS≥50%: 44 (25.7%); unknown 5 (2.9%)

- CPS<1: 26 (15.2%); CPS≥1: 140 (81.9%); unknown 5 (2.9%).

HPV positive patients were 71 (41.5%), HPV negative 97 (56.7%), unknown 3 (1.7%).

Numbers analysed

The primary population for efficacy analysis was the All Subjects as Treated (ASaT) population, defined as all randomized subjects who received at least 1 dose of study medication. ASaT population included 171 subjects.

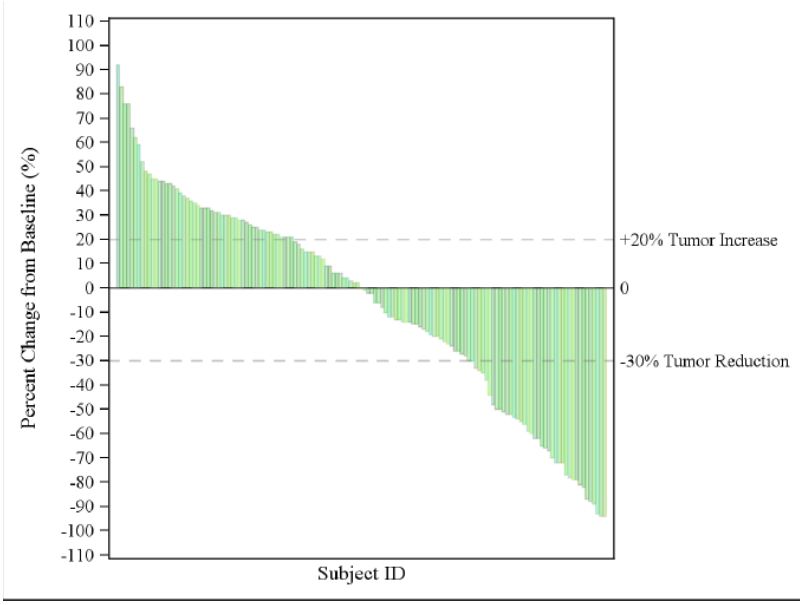
Outcomes and estimation

ORR (primary endpoint)

Table 58: Summary of Best Overall Response Based on RECIST 1.1 per Central Radiology Assessment (ASaT Population)

Response Evaluation	MK-3475 (N=171)			
	n	%	95% CI[†]	p-Value[‡]
Complete Response (CR)	1	0.6	(0.0, 3.2)	
Partial Response (PR)	27	15.8	(10.7, 22.1)	
Overall Response Rate (CR+PR)	**28**	**16.4**	**(11.2, 22.8)**	**< 0.001**
Stable Disease (SD)	33	19.3	(13.7, 26.0)	
Clinical Benefit Rate (SD ≥ 6 mos +CR+PR)	**35**	**20.5**	**(14.7, 27.3)**	
Progressive Disease (PD)	87	50.9	(43.1, 58.6)	
Non-evaluable (NE)	4	2.3	(0.6, 5.9)	
No Assessment	19	11.1	(6.8, 16.8)	

Only confirmed responses are included.
[†] Based on binomial exact confidence interval method.
[‡] One-sided p-value based on exact binomial distribution for testing. H_0: $p \leq 0.05$ versus H_1: $p > 0.05$
Abbreviations: ASaT = All Subjects as Treated, CI = confidence interval, RECIST = Response Evaluation Criteria in Solid Tumors
(Database Cutoff Date: 22APR2016)



Percentage changes >100% were truncated at 100%.
(Database Cutoff Date: 22APR2016)

Figure 21: Waterfall plot of best tumour change from baseline based on central radiology assessment (ASaT Population)

ORR according to PD-L1 status and by subgroups

TPS ≥50% [44 subjects (25.7%)]: 1 CR and 11 PRs with an ORR of 27.3% (95% CI: 15.0%, 42.8%). CBR was 31.8% (95% CI: 18.6%, 47.6%). Ten subjects (22.7%) had no scans available for assessment.

TPS ≥1% [121 subjects (70.7%)]: 1 CR and 21 PRs with an ORR of 18.2% (95% CI: 11.8%, 26.2%). CBR was 21.5% (95% CI: 14.5%, 29.9%). One subject (0.8%) had scans in which the lesion(s) could not be evaluated and 17 subjects (14.0%) had no scans available for assessment.

CPS ≥1% [140 subjects (81.8%)]: 1 CR and 24 PRs with an ORR of 17.9% (95% CI: 11.9%, 25.2%). CBR was 21.4% (95% CI: 14.9%, 29.2%). Two subjects (1.4%) had scans in which the lesion(s)could not be evaluated and 17 subjects (12.1%) had no scans available for assessment.

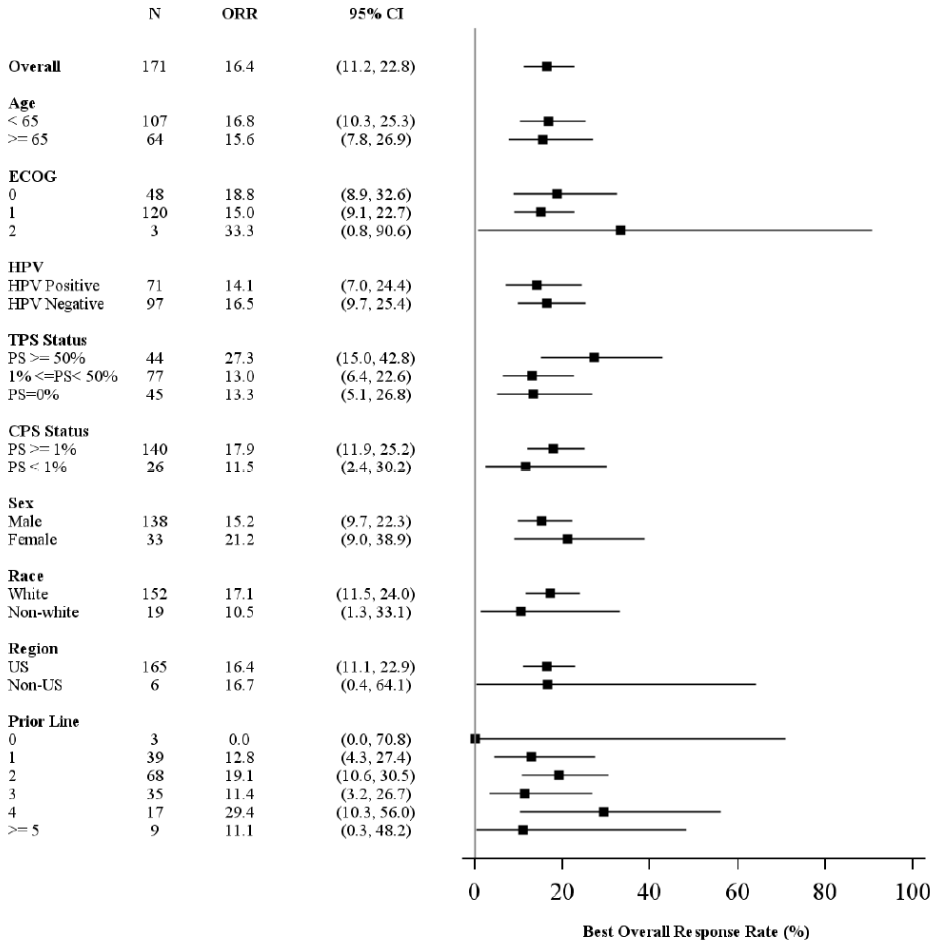


Figure 22: Forrest-plot of overall response rate based on RECIST 1.1 per central radiology assessment (ASaT Population)

DOR, TTR, PFS, OS (secondary endpoints)

Table 59: Summary of Time to Response and Response Duration Based on RECIST 1.1 per Central Radiology Assessment in Subjects with Confirmed Response (ASaT Population)

	MK-3475 (N=171)
Number of Subjects with Response[T]	28
Time to Response[†] (months)	
Mean (SD)	2.6 (0.9)
Median (Range)	2.1 (1.9-4.7)
Response Duration[‡] (months)	
Median (Range)	8.3 (1.6+ - 11.6+)
Number of Subjects with Response ≥ 6 Months (%)[‡]	8 (72)

Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.

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

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

Abbreviations: ASaT = All Subjects as Treated, RECIST = Response Evaluation Criteria in Solid Tumors, SD = standard deviation

Database Cutoff Date: 22APR2016

Median PFS was 2.1 months (95% CI: 2.1, 2.1) with 143 PFS events (83.6%) in all subjects. PFS rates were 22.9% at 6 months and 7.3 % at 12 months

With regard to OS, for subjects in the ASaT population, 87 subjects (50.9%) were reported to have died at the time of the analysis. The median OS was 8.4 months (95% CI: 6.2, 11.1). The OS rate was 59.1% at 6 months and 33.8% at 12 months.

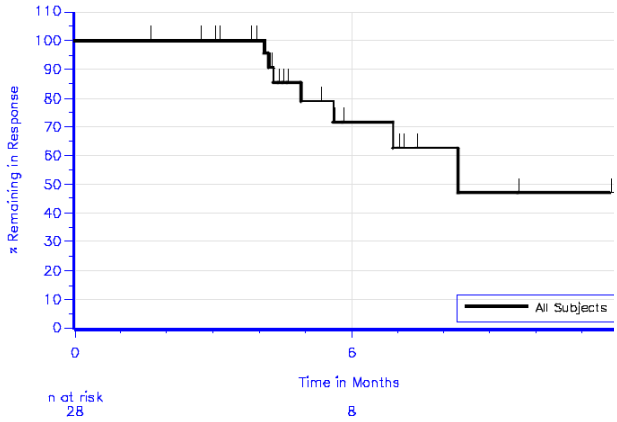


Figure 23: Kaplan-Meier estimates of objective response duration based on RECIST 1.1 per central radiology assessment in subjects with confirmed response (ASaT population)

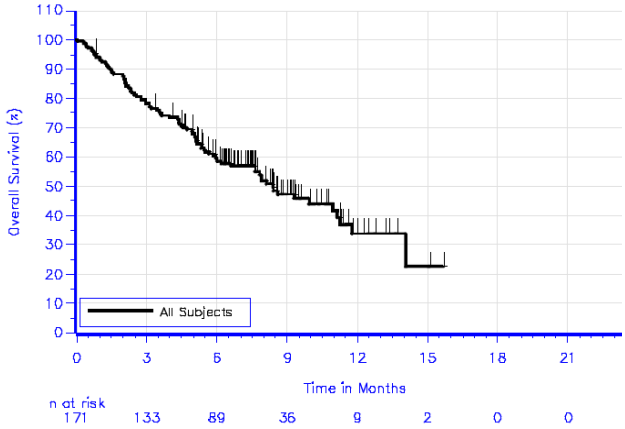


Figure 24: Kaplan-Meier estimates of overall survival (ASaT population)

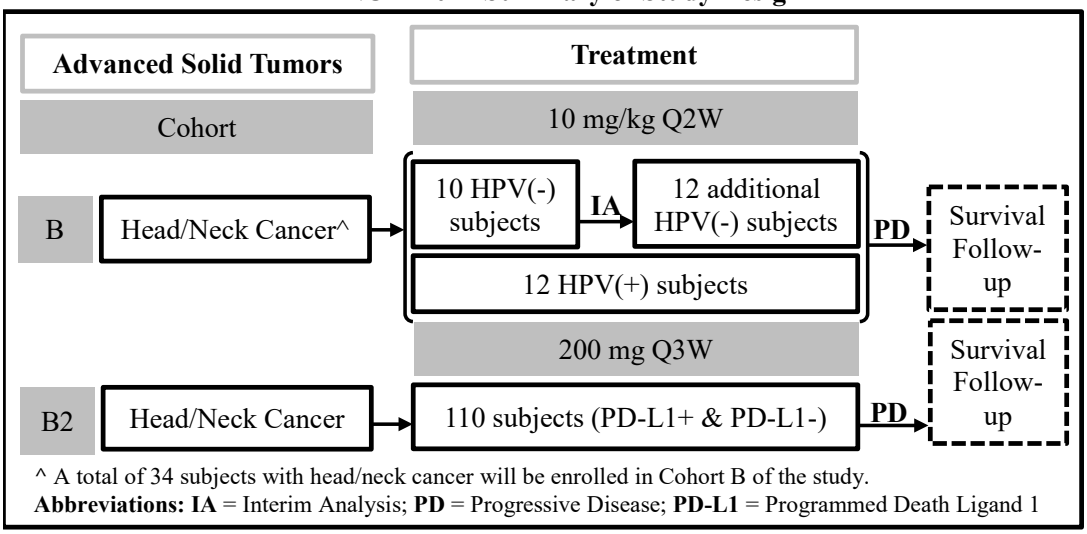
KEYNOTE-012

Title: A Phase Ib Multi-Cohort Study of Pembrolizumab in Subjects with Advanced Solid Tumors

KN012 is an open-label, multicohort, multicenter, nonrandomized Phase 1b clinical trial evaluating the safety, tolerability, and antitumor activity of pembrolizumab in subjects with advanced solid tumors, including R/M HNSCC. Enrollment is complete. Trial is ongoing.

Patients with HNSCC were enrolled in Cohort B (61 PD-L1 positive subjects) and Cohort B2 (132 subjects regardless PD-L1 expression), receiving pembrolizumab at 10 mg/kg Q2W and 200 mg Q3W, respectively. **Data for Cohorts B and B2 have been pooled (193 subjects)** and presented as supportive in this submission.

KEYNOTE-012 Summary of Study Design



^ A total of 34 subjects with head/neck cancer will be enrolled in Cohort B of the study.
Abbreviations: IA = Interim Analysis; **PD** = Progressive Disease; **PD-L1** = Programmed Death Ligand 1

Table 60: KN012 Head and Neck Squamous Cell Carcinoma Cohorts

Cohorts	Number of subjects	PD-L1 status	Dosage Regimen
Cohort B	61	Enrolled only if tumors were positive for PD-L1 expression based on a prototype IHC assay (≥1% PD-L1 membrane staining of tumor cells or the presence of a stromal banding pattern)	10 mg/kg Q2W
Cohort B2	132	Enrolled regardless of PD-L1 tumor expression status	200 mg Q3W

Abbreviations: IHC=immunohistochemistry; PD-L1=Programmed cell death-1 ligand 1; Q2W=Every 2 weeks; Q3W=Every 3 weeks.

Methods

Study participant

The trial enrolled male/female subjects of at least 18 years of age, ECOG 0-1 and adequate organ functions. For Cohort B and B2, subject must have had a histologically or cytologically-confirmed diagnosis of cancer that was recurrent, metastatic, or persistent squamous cell carcinoma of the head or neck, both HPV-positive and HPV-negative. Disease was measurable according to RECIST 1.1. There was no limit to the number of prior treatment regimens. In Cohort B, tumours were to be PD-L1 positive as determined by IHC at a central laboratory from either an archived FFPE tumor sample or a newly obtained biopsy, while in Cohort B2 patients were enrolled regardless PD-L1 status. Previously treated CNS metastases were allowed provided they were stable.

Patients with immunosuppression, receiving immunosuppressive therapy within 7 days prior to the first dose, active autoimmune disease or a documented history of clinically severe autoimmune disease, HIV, HBV, HCV were excluded.

Treatments

All patients received pembrolizumab, which was administered at 10 mg/kg Q2W in Cohort B, and at 200 mg Q3W in Cohort B2.

Imaging was performed every 8 weeks to assess response to treatment according to RECIST 1.1 based on independent central radiology review. If imaging showed PD, tumor assessment was repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment for clinically stable subjects. For the purpose of analysis, a PD that was not confirmed due to a missing confirmation assessment was considered a PD.

Objectives

Primary objectives Cohort B: To determine the safety, tolerability and antitumor activity based on RECIST 1.1 assessed by independent central radiology review of the 10 mg/kg Q2W dose of pembrolizumab in subjects with PD-L1 positive advanced solid tumors enrolled in Cohort B.

Primary objectives Cohort B2: To determine the safety, tolerability and antitumor activity based on RECIST 1.1 assessed by independent central radiology review of the 200 mg Q3W dose of pembrolizumab in subjects with advanced HNSCC enrolled into Cohort B2.

Outcomes/endpoints

Endpoints		**Analysis Populations**	**Definitions**
Primary	ORR	ASaT	Rate of confirmed CR or confirmed PR per RECIST 1.1 assessed by central radiology assessment.
Key Secondary	DOR	ASaT	Time from the earliest confirmed response to clinical progression or death due to any cause, whichever occurred first
	PFS	ASaT	Time from allocation to the first documented confirmed PD per RECIST 1.1 or death due to any cause, whichever occurred first
	OS	ASaT	Time from randomization to death due to any cause

Abbreviations: ASaT=All Subjects as Treated; CR=Complete response; DOR=Duration of response; ORR=Objective response rate; OS=Overall survival; PD=Progressive disease; PFS=Progression free survival; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

Sample size

Cohort B: HPV negative HNC subjects were evaluated separately from HPV positive subjects. With a maximum of 22 evaluable PD-L1 positive subjects with HPV negative head and neck cancer, the study has approximately 80% power to detect a 25% difference in ORR under the null hypothesis of ORR=10% with a type I error rate of 2.5% if the true ORR is 35%. Success for this hypothesis required at least 6/22 responses. The actual number of subjects enrolled might be larger than 22 to ensure that at least 22 subjects are evaluable for analysis. With a maximum of 12 evaluable PD-L1 positive subjects with HPV positive head and neck cancer, the study had approximately 73% power to detect a 35% difference in ORR under the null ORR=20% with a type I error rate of 5% if the true ORR is 55%. Success for this hypothesis required at least 6 responses. The actual number of subjects enrolled might be larger than 12 to ensure that at least 12 subjects are evaluable for analysis.

Statistical methods

For the RECIST 1.1 response rate (per independent central radiology review) in each cohort, an exact Clopper-Pearson 95% CI and p value were provided for testing the null hypothesis, using exact binomial distribution. Subjects who met the criteria for the primary analysis population but without response data were counted as non-responders.

For DOR, Kaplan-Meier curves and median estimates from the KM curves were provided. Subjects who did not achieve a response were excluded from the DOR analyses.

For PFS and OS, Kaplan-Meier curves and median estimates from the KM curves were provided. Subjects without efficacy evaluation data or without survival data were censored at Day 1 in the PFS analyses.

Results

Patient disposition

Table 61: Disposition of Subjects By Cohort (Cohorts B and B2 Combined) (ASaT Population)

	Head and Neck Cancer (MK3475 10mg/kg Q2W)		Head and Neck Cancer Expansion (MK3475 200mg Q3W)		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	60		132		192	
Subject Study Medication Disposition						
Discontinued	54	(90.0)	114	(86.4)	168	(87.5)
Adverse Event	8	(13.3)	15	(11.4)	23	(12.0)
Complete Response	1	(1.7)	1	(0.8)	2	(1.0)
Death	2	(3.3)	3	(2.3)	5	(2.6)
Excluded Medication	0	(0.0)	1	(0.8)	1	(0.5)
Physician Decision	0	(0.0)	1	(0.8)	1	(0.5)
Progressive Disease	41	(68.3)	83	(62.9)	124	(64.6)
Protocol Violation	0	(0.0)	1	(0.8)	1	(0.5)
Withdrawal By Subject	2	(3.3)	9	(6.8)	11	(5.7)
Treatment Ongoing	0	(0.0)	18	(13.6)	18	(9.4)
Two-year Treatment Completed	6	(10.0)	0	(0.0)	6	(3.1)

Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record. Cohort B: Head and Neck Cancer; Cohort B2: Head and Neck Cancer Expansion
(Database Cutoff Date: 26APR2016).

Recruitment

This trial was conducted at 16 centers (8 in US). Data cutoff date for the HNSCC Cohorts B and B2 presented here is 26-Apr-2016.

Baseline data

Male patients were approximately 80% in both cohorts. Most patients were White; there were 20% of Asiatic subjects in Cohort B2 vs only 2% in Cohort B. ECOG was 0 in 30% and 1 in 70% of patients in both cohorts. Patients were mainly metastatic (M1); none had brain metastases. All but three patients received prior treatment, median number of systemic therapy was 2 (range 0-7). 47% received prior adjuvant/neoadjuvant therapy. Further baseline data are presented in the table below:

Table 62: Subject Characteristics By Cohort (Cohorts B and B2 Combined) (ASaT Population) (selected)

	Cohort B Head and Neck Cancer (MK3475 10mg/kg Q2W)		Cohort B2 Head and Neck Cancer Expansion (MK3475 200mg Q3W)		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	60		132		192	
Age (Years)						
<65	34	(56.7)	91	(68.9)	125	(65.1)
>=65	26	(43.3)	41	(31.1)	67	(34.9)
Mean (SD)	61.2 (11.3)		58.9 (9.7)		59.6 (10.3)	
Median	63.0		60.0		60.0	
Range	20 to 83		25 to 84		20 to 84	
Metastatic Staging						
MX	0	(0.0)	1	(0.8)	1	(0.5)
M0	7	(11.7)	19	(14.4)	26	(13.5)
M1	53	(88.3)	112	(84.8)	165	(85.9)
Treatment Naïve						
Yes	2	(3.3)	1	(0.8)	3	(1.6)
No	58	(96.7)	131	(99.2)	189	(98.4)
Number of Lines of Therapy for recurrent/Metastatic Disease						
0	10	(16.7)	24	(18.2)	34	(17.7)
1	8	(13.3)	33	(25.0)	41	(21.4)

2	18	(30.0)	27	(20.5)	45	(23.4)
3	15	(25.0)	20	(15.2)	35	(18.2)
4	6	(10.0)	15	(11.4)	21	(10.9)
5 or more	3	(5.0)	13	(9.8)	16	(8.3)
Prior Platinum Therapy						
Yes	53	(88.3)	121	(91.7)	174	(90.6)
No	7	(11.7)	11	(8.3)	18	(9.4)
Prior Cetuximab and Platinum Therapy						
Yes	38	(63.3)	72	(54.5)	110	(57.3)
No	22	(36.7)	60	(45.5)	82	(42.7)
Prior Platinum without Cetuximab Therapy						
Yes	15	(25.0)	49	(37.1)	64	(33.3)
No	45	(75.0)	83	(62.9)	128	(66.7)
Prior Taxanes Therapy						
Yes	43	(71.7)	90	(68.2)	133	(69.3)
No	17	(28.3)	42	(31.8)	59	(30.7)
Prior 5FU/Xeloda Therapy						
Yes	30	(50.0)	67	(50.8)	97	(50.5)
No	30	(50.0)	65	(49.2)	95	(49.5)
Prior Methotrexate Therapy						
Yes	5	(8.3)	13	(9.8)	18	(9.4)
No	55	(91.7)	119	(90.2)	174	(90.6)
Sum of target lesions measureable at baseline (mm)(Central Radiology)						
Subjects with data	47		123		170	
Mean	106.7		119.9		116.3	
SD	84.7		100.5		96.3	
Median	80.6		99.5		97.6	
Range	10.0 to 336.3		16.0 to 664.1		10.0 to 664.1	

Cohort B: Head and Neck Cancer; Cohort B2: Head and Neck Cancer Expansion
(Database Cutoff Date: 26APR2016).

Among platinum-progressed subjects, 139 had tumors with PD-L1 CPS≥1 per CPS scoring method (80%). Fifty (29%) had tumors with strongly positive PD-L1 expression per the TPS scoring method (i.e. TPS≥50%). Baseline characteristics of patients CPS≥1 were comparable to the overall platinum-progressed population. In the TPS ≥50% population, some differences compared to the overall population are noted: i.e. lower median age (56.5 years), less patients with ECOG 0 (22%), no therapies for metastatic disease (26%), less patients received prior cetuximab (48%), lower median sum of target lesions (77).

Numbers analysed

The primary efficacy population consisted of the All Subjects as Treated population (ASaT, N = 192) in the combined Cohorts B (n = 60) and B2 (n = 132), and included all enrolled subjects who received at least one dose of study medication. A subset of the primary efficacy population consisted of subjects who had progressed on or after platinum-containing chemotherapy (n = 174, including 53 subjects in Cohort B and 121 subjects in Cohort B2).

Outcomes and estimation

Results reported below are related to subjects in Cohorts B (n=53) and B2 (n=121) combined who progressed following platinum-based chemotherapy, regardless of prior cetuximab exposure (n = 174).

ORR (Primary endpoint)

Table 63: Summary of Best Overall Response Based on RECIST 1.1 per Central Radiology Assessment (Head/Neck Cancer Initial + Expansion Cohort (B+B2), Subjects Who Progressed Following Platinum Treatment) (MK3475 10mg/kg Q2W / MK3475 200mg Q3W)* (ASaT Population)

Response Evaluation	Head/Neck Cancer Initial + Expansion Cohort (N=174)		
	n	%	95% CI[†]
Complete Response (CR)	8	4.6	(2.0, 8.9)
Partial Response (PR)	21	12.1	(7.6, 17.9)
Overall Response Rate (CR+PR)	**29**	**16.7**	**(11.5, 23.1)**
Stable Disease (SD)	31	17.8	(12.4, 24.3)
Clinical Benefit Rate (SD ≥ 6 mos +CR+PR)	**34**	**19.5**	**(13.9, 26.2)**
NonCR/NonPD (NN)	6	3.4	(1.3, 7.4)
Progressive Disease (PD)	86	49.4	(41.8, 57.1)
Non-evaluable (NE)	3	1.7	(0.4, 5.0)
No Assessment	19	10.9	(6.7, 16.5)

Confirmed responses are included.

[†] Based on binomial exact confidence interval method.

* The dose for Head and Neck Cancer Initial Cohort is 10mg/kg Q2W and Head/Neck Cancer Expansion Cohort is 200mg Q3W. (Database Cutoff Date: 26APR2016)

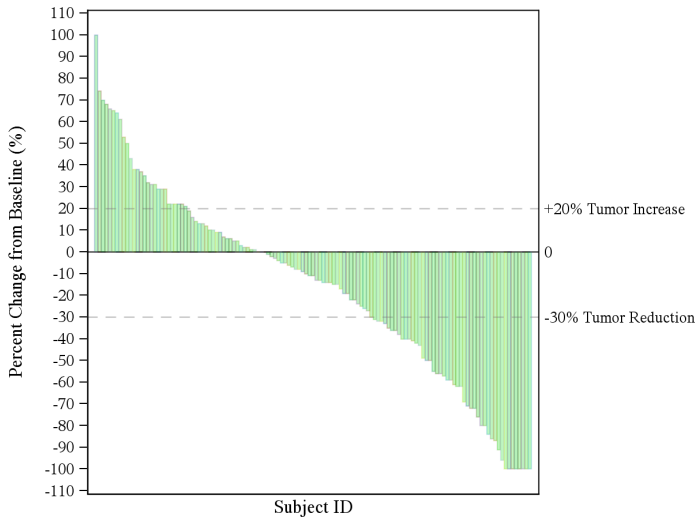


Figure 25: Waterfall Plot of Best Tumor Change from Baseline Based on Central Radiology Data (Head/Neck Cancer Initial + Expansion Cohort (B+B2), Subjects Who Progressed Following Platinum Treatment) (MK3475 10mg/kg Q2W / MK3475 200mg Q3W)* (ASaT Population)

Response rates ranged from 16.7% for the confirmed responses by independent central radiology review to 22.4% for the confirmed and unconfirmed responses by investigator assessment.

DOR (secondary endpoint)

Table 64: Summary of Time to Response and Response Duration Based on RECIST 1.1 per Central Radiology Assessment in Subjects with Confirmed Response (Head/Neck Cancer Initial + Expansion Cohort (B+B2), Subjects Who Progressed Following Platinum Treatment) (MK3475 10mg/kg Q2W / MK3475 200mg Q3W)* (ASaT Population)

	Head/Neck Cancer Initial + Expansion Cohort (N=174)
Number of Subjects with Response†	29
Time to Response† (months)	
Mean (SD)	3.8 (3.2)
Median (Range)	3.4 (1.6-16.7)
Response Duration‡ (months)	
Median (Range)	Not reached (2.4+ - 29.5+)
Number of Subjects with Response ≥ 6 Months (%)‡	23 (82)
Number of Subjects with Response ≥ 12 Months (%)‡	17 (71)

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.

‡ Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.

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

* The dose for Head and Neck Cancer Initial Cohort is 10mg/kg Q2W and Head/Neck Cancer Expansion Cohort is 200mg Q3W. (Database Cutoff Date: 26APR2016)

The median duration of follow-up for the 29 responders was 20.1 months (range: 8.4 to 32.2 months).

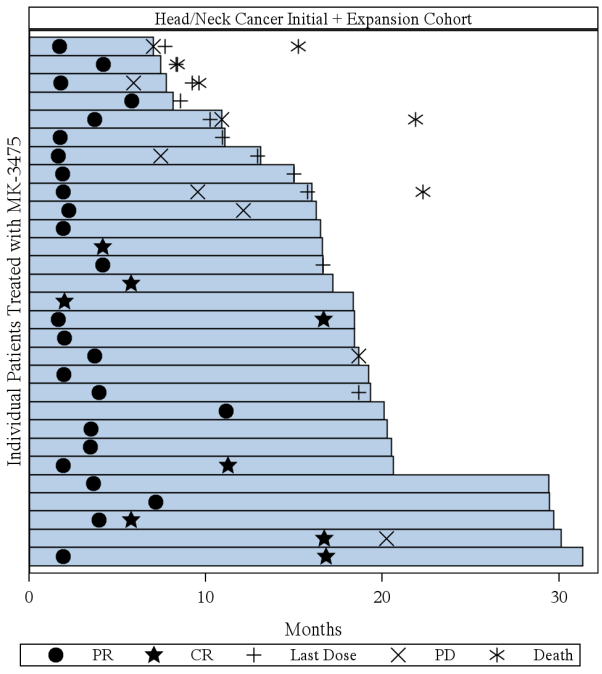


Figure 26: Plot of Time to Response and Time to Progression

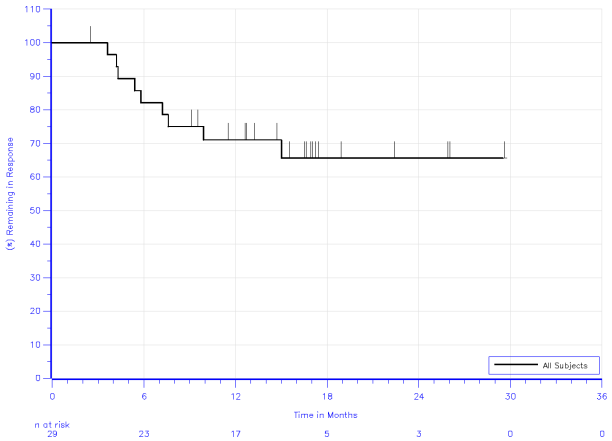


Figure 27: KM Estimates of Objective Response Duration

Of the 8 subjects who experienced CR, 4 had previously a response of PR.

PFS and OS (secondary endpoints)

PFS based on RECIST 1.1 per central radiology assessment results in platinum-progressed subjects in Cohorts B and B2, as assessed by independent central radiology review, showed median PFS of 2.0

months (95% CI: 1.9, 2.1), with 150 (86.2%) PFS events. The PFS rate was 24.3% at 6 months and 16.0% at 12 months.

Of the 174 platinum-progressed subjects in Cohorts B and B2, 125 (71.8%) subjects were reported to have died by the time of the analysis. The median OS was 8.4 months (95% CI: 6.1, 10.0). The OS rate was 58.0% at 6 months and 37.5% at 12 months.

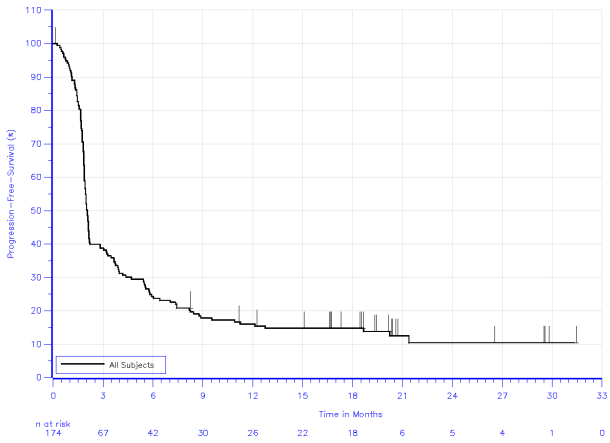


Figure 28: KM estimates of PFS

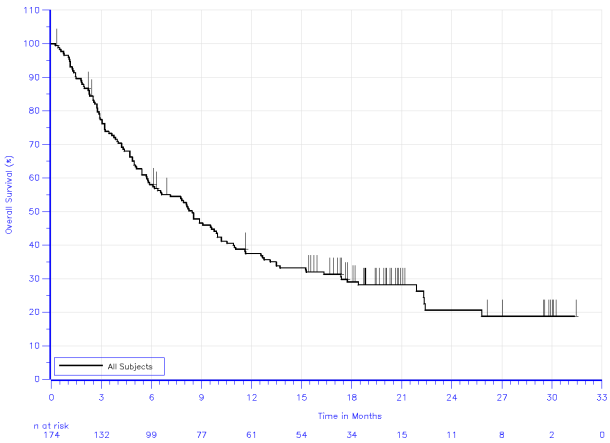


Figure 29: KM estimates of OS

Efficacy results in PD-L1 positive platinum-progressed patients in KN012

Among platinum-progressed subjects in the combined cohorts, subjects with PD-L1 CPS≥1 tumours were 139; subjects with strongly positive PD-L1 TPS≥50% were 50.

An overview of the main results for the pivotal study KN040 and the supportive studies KN012 and KN055 is presented in tables below:

Table 65: Key Overall Survival Findings of KN040, KN012 (Cohorts B and B2) and KN055

		Pembrolizumab/Standard Treatment				
	Population	**No. of Subjects**	**No. of Events**	**Median OS (months)**	**HR* (95% CI)**	**One-sided p-value***
KN040V01 All Subjects	ITT	247/248	181/207	8.4/6.9	0.80 (0.65, 0.98)	0.01605
	CPS ≥1	196/191	138/162	8.7/7.1	0.74 (0.58, 0.93)	0.00493
	TPS ≥50%	64/65	41/56	11.6/6.6	0.53 (0.35, 0.81)	0.00136
KN040V01 EU	ITT	147/158	107/141	8.3/6.4	0.65 (0.50, 0.84)	0.00038
	CPS ≥1	118/125	84/114	8.7/6.4	0.61 (0.46, 0.81)	0.00025
	TPS ≥50%	39/43	27/40	11.4/5.7	0.43 (0.26, 0.70)	0.00032
KN040V01 NA	ITT	73/60	52/38	8.7/11.8	1.29 (0.85, 1.96)	0.88410
	CPS ≥1	58/44	38/28	9.1/11.8	1.05 (0.65, 1.72)	0.58204
	TPS ≥50%	18/17	9/11	20.1/12.0	0.61 (0.25, 1.48)	0.13359
KN040V01 ROW	ITT	27/30	22/28	6.1/5.3	0.66 (0.36, 1.18)	0.07880
	CPS ≥1	20/22	16/20	7.3/5.0	0.70 (0.36, 1.39)	0.15561
	TPS ≥50%	7/5	5/5	8.7/8.0	0.56 (0.16, 1.95)	0.17685
KN012V03 Platinum-progressed subjects	ASaT	174	125	8.4	-	-
	CPS ≥1	139	96	9.5	-	-
	TPS ≥50%	50	35	8.4	-	-
KN055V02 All Subjects	ASaT	171	87	8.4	-	-
	CPS ≥1	140	70	8.4	-	-
	TPS ≥50%	44	25	7.6	-	-

* Cox regression model & one-sided log-rank test with treatment as a covariate. EU=European Union; NA=North America; OS=Overall Survival; ROW=Rest of World. Note: KN040 data in this table are based on the 13-OCT-2017 critical change to the database

Table 66: Key Progression Free Survival of KN040, KN012 (Cohorts B and B2) and KN055

		Pembrolizumab/Standard Treatment				
	Population	**No. of Subjects**	**No. of Events**	**Median PFS (months)**	**HR* (95% CI)**	**One-sided p-value***
KN040V01 All Subjects	ITT	247/248	218/224	2.1/2.3	0.96 (0.79, 1.16)	0.32504
	CPS ≥1	196/191	170/170	2.2/2.3	0.86 (0.69, 1.06)	0.07736
	TPS ≥50%	64/65	52/58	3.5/2.1	0.58 (0.39, 0.86)	0.00277
KN040V01 EU	ITT	147/158	127/150	2.1/2.3	0.86 (0.68, 1.10),	0.10588
	CPS ≥1	118/125	101/118	2.1/2.2	0.81 (0.62, 1.05)	0.05225
	TPS ≥50%	39/43	32/41	3.0/2.1	0.54 (0.34, 0.87)	0.00473
KN040V01 NA	ITT	73/60	64/46	2.1/2.2	1.11 (0.76, 1.63)	0.70863
	CPS ≥1	58/44	49/32	2.3/2.4	1.05 (0.67, 1.65)	0.57698
	TPS ≥50%	18/17	13/12	4.6/2.1	0.52 (0.23, 1.18)	0.05919
KN040V01 ROW	ITT	27/30	27/28	3.3/2.4	0.88 (0.52, 1.51)	0.33005
KN012V03 Platinum-progressed subjects	ASaT	174	150	2.0	-	-
	CPS ≥1	139	117	2.0	-	-
	TPS ≥50%	50	43	1.9	-	-
KN055V02 All Subjects	ASaT	171	143	2.1	-	-
	CPS ≥1	140	115	2.1	-	-
	TPS ≥50%	44	33	2.1	-	-

* Cox regression model & one-sided log-rank test with treatment as a covariate. EU=European Union; NA=North America; PFS=Progression-Free Survival; ROW=Rest of World.

Table 67: Key Objective Response Rate Findings of KN040, KN012 (Cohorts B and B2) and KN055

	Pembrolizumab/Standard Treatment			
	Population	**No. of Subjects**	**ORR (%)**	**One-sided p-value***
KN040V01 All Subjects	ITT	247/248	36 (14.6)/25 (10.1)	0.0610
	CPS ≥1	196/191	34 (17.3)/19 (9.9)	0.0171
	TPS ≥50%	64/65	17 (26.6)/6 (9.2)	0.0009
KN040V01 EU	ITT	147/158	23(15.6)/18 (11.4)	0.1386
	CPS ≥1	118/125	22 (18.6)/13 (10.4)	0.0340
	TPS ≥50%	39/43	10 (25.6)/4 (9.3)	0.0255
KN040V01 NA	ITT	73/60	10 (13.7)/5 (8.3)	0.1661
	CPS ≥1	58/44	10 (17.2)/4 (9.1)	0.1192
	TPS ≥50%	18/17	6 (33.3)/2 (11.8)	0.0672
KN040V01 ROW	ITT	27/30	3 (11.1)/2 (6.7)	0.2786
	CPS ≥1	20/22	2 (10.0)/2 (9.1)	0.4606
	TPS ≥50%	7/5	1 (14.3)/0 (0.0)	0.1990
KN012V03 Platinum-progressed subjects Best Overall Response	ASaT	174	29 (16.7)	-
	CPS ≥1	139	27 (19.4)	-
	TPS ≥50%	50	10 (20.0)	-
KN055V02 All Subjects Best Overall Response	ASaT	171	28 (16.4)	-
	CPS ≥1	140	25 (17.9)	-
	TPS ≥50%	44	12 (27.3)	-

* Cox regression model & one-sided log-rank test with treatment as a covariate. EU=European Union; NA=North America; ORR=Objective response rate; ROW=Rest of World.

Table 68: Key Duration of Response Findings of KN040, KN012 (Cohorts B and B2) and KN055

		Pembrolizumab/Standard Treatment		
	Population	**No. of Subjects**	**No. of Subjects with Response**	**Median DOR(range) (months)**
KN040V01 All Subjects	ITT	247/248	26/18	18.4 (2.7 - 18.4)/5.0 (1.4+ - 18.8)
	CPS ≥1	196/191	26/15	18.4 (2.7 - 18.4)/9.6 (1.4+ - 18.8)
	TPS ≥50%	64/65	15/4	Not reached (2.7 - 13.8+)/6.9 (4.2 - 18.8)
KN040V01 EU	ITT	147/158	17/13	Not reached (2.7 - 12.4+)/4.8 (1.4+ - 14.1+)
	CPS ≥1	118/125	17/10	Not reached (2.7 - 12.4+)/6.9 (1.4+ - 14.1+)
	TPS ≥50%	39/43	10/2	Not reached (2.7 - 11.8+)/6.9 (4.2 - 9.6)
KN040V01 NA	ITT	73/60	7/4	Not reached (3.0 - 17.4+)/5.0 (4.3 - 18.8)
	CPS≥1	58/44	7/4	Not reached (3.0 - 17.4+)/5.0 (4.3 - 18.8)
	TPS ≥50%	18/17	4/2	Not reached (5.2+ - 13.8+/11.6 (4.3 - 18.8)
KN040V01 ROW	ITT	27/30	2/1	11.2 (3.9 - 18.4)/Not reached (10.4+ - 10.4)
KN012V03 Platinum-progressed subjects	ASaT	174	29	Not reached (2.4+ - 29.5+)
	CPS ≥1	139	27	Not reached (2.4+ - 29.5+)
	TPS ≥50%	50	10	Not reached (4.3 - 25.8+)
KN055V02 All Subjects	ASaT	171	28	8.3 (1.6+ - 11.6+)
	CPS ≥1	140	25	Not reached (2.7+ - 11.6+)
	TPS ≥50%	44	12	Not reached (3.8+ - 11.6+)

* Cox regression model & one-sided log-rank test with treatment as a covariate. EU=European Union; NA=North America; DOR=Duration of Response; ROW=Rest of World.

2.4.3. Discussion on clinical efficacy

The MAH is requesting an extension of indication for Keytruda (pembrolizumab) as monotherapy for the treatment of adult patients with recurrent or metastatic (R/M) HNSCC with disease progression on or after platinum-containing chemotherapy, based on the data from the pivotal study KEYNOTE-040 and the two supportive studies KEYNOTE-055 and KEYNOTE-012.

Design and conduct of clinical studies

KEYNOTE-040 (pivotal study)

KN040 is an ongoing, Phase 3, randomized, multicenter, active-controlled, open-label clinical trial to examine the efficacy and safety of pembrolizumab versus the choice of 3 different standard treatment options in subjects with R/M HNSCC whose disease has progressed on or after platinum-containing chemotherapy. Subjects were randomized to receive treatment with either pembrolizumab 200 mg Q3W, or investigator's choice of methotrexate, docetaxel, or cetuximab. Subjects were stratified by ECOG PS (0 versus 1), HPV status (positive versus negative) for oropharynx cancer only, and PD-L1 status (strongly positive versus not strongly positive, where strongly positive is defined as tumour proportion score [TPS] ≥50%).

Eligible patients were histologically or cytologically-confirmed recurrent (not amenable to curative treatment with local and/or systemic therapies) or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx. All subjects had disease progression to prior platinum treatment. At the time of SA, it was evaluated that 1st line patients may be considered similar to second-line patients, the homogeneity of the trial population being thus preserved.

The proposed control arm is considered adequate. Although cetuximab is approved as monotherapy in second line in R/M HNSCC by FDA but not in EU, its inclusion among the options in the control arm is considered appropriate from a clinical perspective.

The primary efficacy endpoint was OS in the ITT population. Key secondary efficacy endpoints included OS in subjects with PD-L1 by CPS ≥1, PFS, ORR and DOR (both based on central radiology review). PFS, ORR and DOR were evaluated both in the ITT and CPS ≥1 populations.

PD-L1 scoring method was changed from TPS (tumor proportion score, i.e. PD-L1 expression on tumour cells only), which was used as stratification factor, to CPS (combined positive score, i.e. PD-L1 expression on tumour cells and immune cells infiltrating the tumour stroma), used for the analyses. CPS is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The choice of the CPS score with the cut-off 1 was based on a retrospective evaluation of ORR in 190 HNSCC patients from KN012, showing that CPS with cut-off 1 was able to better discriminate patients with worse and better outcome following pembrolizumab treatment compared to TPS, although the number of subjects whose tumor had CPS score < 1 was quite limited (35/190). Based on these results, the KN040 clinical protocol was amended, prior to data analysis, to include CPS ≥ 1 as the primary PD-L1 scoring method and cut-off. CPS score is also applied to the ongoing HNSCC first-line study KN048.

The final OS analysis in all subjects was planned to be conducted after ~340 deaths overall. Under the proportional hazard assumption with 340 events at the final analysis, the study provided 90% power to demonstrate superiority in OS of pembrolizumab relative to standard treatment at the alpha = 2.5% (one-sided) level with a true HR of 0.7 and median of 6.2 months in the standard treatment group. Approximately 466 subjects were therefore to be randomized in a 1:1 ratio into the pembrolizumab group or the standard treatment group. Several changes of the sample size assumptions have been adopted. The initial projected number of death events at the final analysis (351 OS events and 466 patients) was revised in Amendment 11 onward to account for the delayed separation in the overall survival curves that have been observed with immunotherapies and additional follow-up time was incorporated into the trial to ensure that the final analysis was conducted at an appropriate time to characterize the potential benefit of immunotherapy, as stated by the MAH. Therefore, in the last protocol version, the study was based on 340 OS events (466 patients). The rationale is acknowledged. However, it is not clear why the final analysis was conducted after 388 OS events occurred (495 patients enrolled). It should be noted that an increase of the number of events affects the minimal detectable HR that it is slightly shifted toward the null hypothesis. In addition, amendment 11 (2.11.2016) has been released after the two planned interim analyses were performed (IA1 OS all subjects, 144 OS events, cut-off date 15.4.2016, IA2 216 OS events, cut-off date 1.8.2016). Therefore, there is a concern that modifications were not entirely driven by data external to the current study.

Overall, the statistical analyses proposed in the protocol are considered adequate. However, the protocol was amended several times and the changes have heavily modified the statistical component of the study design (definition of primary endpoint, stratification factors, follow-up duration, unplanned crossover) and sample size, and therefore have influenced the conduction of the study, having implications for the clinical interpretation of the results.

KEYNOTE-055 and KEYNOTE-012 (supportive studies)

KEYNOTE-055 is an ongoing Phase 2, multicenter, nonrandomized, single-cohort trial of pembrolizumab in subjects with R/M HNSCC (regardless PD-L1 and HPV status) who had progressed on platinum and cetuximab therapy, which have been presented as supportive study.

KEYNOTE-012 is an open-label, multicohort, multicenter, nonrandomized Phase 1b clinical trial evaluating the safety, tolerability, and antitumor activity of pembrolizumab in subjects with advanced solid tumors, including R/M HNSCC. Subjects with PD-L1-positive (based on a prototype IHC assay ≥1% PD-L1 membrane staining of tumor cells or the presence of a stromal banding pattern) HNSCC were enrolled in Cohort B and treated with pembrolizumab 10 mg/kg Q2W. Following a protocol amendment, subjects with HNSCC regardless of PD-L1 status were enrolled in Cohort B2 and treated with pembrolizumab 200 mg Q3W.

In both KN012 and KN055, the primary efficacy endpoint was ORR using RECIST 1.1 criteria by central radiology assessment; DOR, PFS and OS were among secondary endpoints. The primary population for efficacy analysis was the All Patients as Treated (ASaT) in both studies. Data cut-off date is 22-APR-2016 (≥6 months after enrollment of the last subject) for KN055, and 26-APR-2016 for KN012.

Efficacy data and additional analyses

KEYNOTE-040 (pivotal study)

There were 699 patients screened and 495 randomized (247 in the pembrolizumab and 248 in the standard treatment arm). It is noted that a higher number of patients in the standard therapy arm did not receive treatment (1 vs 14). There were more subjects who stopped treatment due to patients' consent withdrawal or physician decision in the standard arm compared to the control arm (10.3% vs 4.1%), which is not unexpected. Since this imbalance might have exerted a negative impact on the performance of the SOC arm in the ITT analysis, two sensitivity analyses for OS with different handling of these patients to provide further insight in the best versus worst scenario have been requested (analysis 1: censoring time at the date of the database lock; analysis 2: put an event instead of a censoring at the observed censoring time). Both sensitivity analyses were consistent with the primary OS ITT analysis. There was approximately the same rate of radiological (60.6% vs 59%) and clinical progression (14.6% vs 14.1%) in both arms. Slightly more patients discontinued treatment in the chemotherapy arm due to side effect (11% vs 15.8%).

The majority of subjects were male, White, former smokers, about 70% with ECOG-PS of 1, median age 60 years. Most subjects had a negative HPV status (~75%). Tumour PDL-1 score was CPS ≥1 in 79.4% vs 77% of patients. Baseline characteristics appeared overall balanced, with few minimal differences noted between treatment arms. Information regarding baseline disease burden were requested; indeed, this might be relevant also with regard to the issue of the excess of early deaths observed with pembrolizumab as compared to the control arm (in Checkmate141 study, high tumour burden was associated with early deaths in Opdivo treated R/M HNSCC patients compared to docetaxel). Higher median tumour size as well as higher variability in baseline tumour size in the control arm compared to the pembrolizumab arm is noted. However, further analyses showed that the incorporation of tumour size into the model does not substantially change the magnitude of the OS effect.

The major protocol deviations appeared balanced between arms, therefore it is not considered to have had impact on the final study results.

The primary OS analysis was based on a data cutoff date of 15-MAY-2017 (388 OS events occurred) and a database lock date of 04-JUN-2017 (information on 377 OS events were available), which is the only p-value provided for statistical inference and adjusted for multiplicity. OS HR was 0.82 (95%CI 0.67-1.01, p=0.0316). From a statistical point of view, the result was not statistically significant as it missed the pre-specified primary statistical hypothesis of a p-value OS boundary of 0.0175 for 377 deaths.

A sensitivity analysis was performed at 340 OS events, corresponding to the planned final number of OS events, showing an even lower benefit of pembrolizumab over standard treatment (HR 0.86, 95%CI 0.69-1.06, p=0.081).

All the efficacy data presented by the MAH are based on a database lock date of 13-OCT-2017 (not adjusted for multiplicity), at which time data on all the 388 subjects who had died as of the data cutoff date of 15-MAY-2017 were included in the database (388 events). The HR for OS in the overall population was 0.80 (95%CI 0.65, 0.98), with a one-sided p-value of 0.01605 in favour of pembrolizumab, corresponding to a gain in median OS of 1.5 months (8.4 vs 6.9 months in pembrolizumab vs standard

arm respectively). OS events were 73.3% vs 83.5% in pembrolizumab vs standard treatment arm respectively.

The first portion of the pembrolizumab KM OS curve lies slightly below/overlaps the standard treatment arm up to approximately month 4-5. However, a clear separation in favour of pembrolizumab is seen afterwards, and curves appeared to further divide over time, as shown by an increasing difference in OS rate between arms (from 2.8% difference in OS rate at 6 months to 10.5% difference at 12 months). The same trend was observed in CheckMate-141 study testing nivolumab vs standard treatment (same comparator's drugs as in KN040) in the same R/M HNSCC setting. The MAH has been requested to provide analyses to identify patient/disease characteristics that may have contributed to the early crossing of the OS curves, and provide further data regarding patients who died within 4-5 months and discuss potential factors to be considered in the selection of patients and to evaluate whether appropriate information should be included in the SmPC to guide physicians in the choice of treatment. In the pembrolizumab arm, there are slightly more patients compared to the control arm with more advanced disease (e.g. Stage IVC, M1, liver disease), although baseline median tumor size was slightly higher in the standard treatment group. Also, more patients who progressed <3 months from prior platinum treatment or systemic therapy are noted in the pembrolizumab arm compared to the control arm, as well as more lines of prior therapies. The MAH didn't discuss association of tumour PD-L1 expression status with a higher risk of early death; however, this obviously also plays a role. If excluding subjects with CPS<1, differences appear less pronounced. The overlapping of the 95% CIs for both treatment groups in the OS Kaplan-Meier curves in the initial time period before the crossover of the curves are acknowledged. However, a trend toward an increased risk of death with pembrolizumab compared to standard treatment is noted in the first two months, based both on the number of deaths in the two arms and on the instantaneous hazard rate. Baseline characteristics of patients who died within 2 months from randomization, as well as univariate analyses (data not shown), showed that the most relevant difference appears to be related to the PD-L1 expression status, with lower number of TPS≥50% patients who died early with pembrolizumab compared to subjects receiving standard treatment. This observation is compatible with the OS KM curves of the TPS≥50% population which are not crossing. The possibility to draw solid conclusion on other single factors is hampered by the limited number of subjects analysed.

According to subgroup analysis, no benefit is seen in OS for pembrolizumab compared to docetaxel.

Female patients did not appear to gain advantage from pembrolizumab treatment with regard to OS, acknowledging the limited number of female patients enrolled in KN040 (expected due to the epidemiology of the disease). Some imbalances in baseline characteristics in female patients have been noted, some of them possibly favouring control arm.

Crossover was not pre-specified in the protocol, although unplanned crossover occurred. In the ITT population, 42 subjects received an immunotherapy after trial treatment, 31 in the control arm (12.5%), and 11 patients in the pembrolizumab arm. The rate of crossover does not appear high and the sensitivity analyses performed to analyze the unplanned crossover are not improving OS results to a large extent. It should also be noted that such analyses can break the randomization balance.

Overall, about 62% of subjects were enrolled in EU, where pembrolizumab showed higher OS advantage for pembrolizumab over standard treatment compared to the ITT population (OS HR=0.65). On the contrary, standard treatment shower higher OS advantage compared to pembrolizumab in North America (HR=1.29). This difference seems to be related to a highly better OS performance of the standard treatment in NA compared to EU (median OS 11.8 vs 6.4 months in NA vs EU, respectively), while the pembrolizumab arm has similar OS outcome in both regions. However a negative OS HR would not be expected even with a 100% rate of crossover. The MAH further discussed the unfavourable treatment effect of pembrolizumab in the NA subpopulation. Baseline characteristics were largely comparable between ITT and NA apart from differences in the HPV status (overall more HPV positive subjects in NA

compared to ITT population), although this imbalance is considered not to explain the better efficacy results in the control arm of the NA subpopulation. The post-progression therapies are considered not to fully explain the magnitude of regional differences in efficacy results. Patients were not stratified by region, therefore the statistical analyses are not based on randomized comparison. Baseline characteristics of the EU population did not show any meaningful differences compared to the ITT population. The OS results in the NA population appeared therefore to remain lastly unexplained.

No benefit in PFS was evident for pembrolizumab compared to the standard treatment (HR=0.96, 95%CI 0.79, 1.16, p=0.325). Median PFS was similar in both arms (2.1 vs 2.3 months), although curves seems to slightly diverge since month 5, with a 4% absolute difference in PFS rate at month 9 and 12 in favor of pembrolizumab. A supportive analysis using RMST restricted mean survival time showed that the PFS benefit of pembrolizumab over standard treatment seems to increase over time.

ORR by BICR was slightly better with pembrolizumab (14.6%, 95% CI: 10.4, 19.6) compared to standard therapy (10.1%, 95% CI: 6.6, 14.5), although a higher rate of progressive disease occurred in the pembrolizumab arm (43.7% vs 39.1%). Patients who achieved CR were 4 (1.6%) with pembrolizumab vs 1 (0.4%) with chemotherapy (docetaxel). Docetaxel lead to higher ORR among standard treatment drugs (11.8%). Median DOR was notably longer with pembrolizumab (18.4 vs 5 months) as well as more patients had extended (i.e. ≥6 months) response duration (71.5% vs 47.1%). Median time to response was almost doubled for pembrolizumab compared to standard treatment (4.5 vs 2.2 months), both in the overall population and in all subgroups according to PD-L1 expression, although it is acknowledged that this is based on a limited number of patients.

In relation to the exploratory endpoint Health-related Quality of Life, changes from baseline in the EORTC QLQ-C30 and EORTC QLQ-H&N35 were primarily evaluated at Week 9 and at Week 15, showing over 15 weeks of follow-up that subjects receiving pembrolizumab had stable global health status/QOL, while those treated with standard treatment had a decline of global health status/QOL. The lowest compliance to ePRO questionnaires is reported at Week 15, when it was approximately 75% in both arms. HRQoL were exploratory endpoints with no pre-specified hypothesis. The open-label design further hampers the interpretation of data.

With regard to PD-L1 expression, efficacy results by PD-L1-expression status demonstrated a consistent association between PD-L1 expression and treatment effect of pembrolizumab. PD-L1 positive (CPS≥1) patients appeared to benefit more from pembrolizumab treatment compared with the ITT population, with the highest advantage for TPS ≥50% tumors (strongly positive). On the other hand, PD-L1 expression status does not appear to influence the activity of the standard treatments in R/M HNSCC in KN040 study.

In the CPS<1 population, no advantage of pembrolizumab monotherapy over standard treatment is seen in all efficacy endpoints, in addition to a detrimental effect in ORR [OS CPS<1: HR=1.28 (95%CI 0.80, 2.07), p=0.848; OS in EU CPS<1: HR=0.82 (95%CI 0.46, 1.45); PFS CPS<1: HR=1.33 (95%CI 0.86, 2.07), p=0.9; ORR CPS<1: 4.0% (0.5,13.7) vs 11.1% (4.2,22.6)]. A possible advantage for pembrolizumab in duration of response cannot be defined in CPS<1 population, as no confirmed responses were reported in this subgroup. Acknowledging the intrinsic limitation of subgroup analyses, based on the available data from KN040, there is no evidence of benefit to support an indication of pembrolizumab in R/M HNSCC in subjects whose tumor has PD-L1 CPS score <1.

A relevant advantage of pembrolizumab compared to standard treatment is seen in strongly positive PD-L1 expressing tumours (i.e. TPS≥50%) comprising about 25% of the overall population (and approximately 33% of CPS≥1 subjects). In the TPS≥50% population, the benefit of pembrolizumab vs standard treatment is clear and observed in all efficacy endpoints. OS curves do not overlap, clearly separating from the beginning, with OS HR=0.53 (95%CI 0.35-0.81).

To provide a more complete picture on the impact of different PD-L1 expression levels on the treatment effect of pembrolizumab, the MAH was requested to provide efficacy analysis on main endpoints (OS, PFS and ORR) for subjects with CPS≥1 and TPS<50% and for subjects with TPS <1 (representing 40% of study population) (it is acknowledged that these cut-offs have not been validated). For the post-hoc exploratory CPS ≥1 and TPS <50% population, an OS HR of 0.85 (95% CI: 0.64, 1.12) was shown, with comparable PFS and ORR results between the two treatment arms. The benefit in the group with CPS≥1 and TPS<50% has not been convincingly demonstrated

Evaluation of PD-L1 expression in tumour- and immune cells (CPS) has not been implemented as stratification factor at randomization (but TPS <50% vs. ≥50%), since the clinical relevance of CPS has been only learned during the conduct of the study based on phase II data.

Based on KN012, the CPS cut-off of 10 showed lower sensitivity (75%) but higher specificity (45.4%) compared to cut-off 1 (sensitivity 95.8%, specificity 22.2%), although this cut-off has not been further explored. In order to evaluate whether a different PD-L1 cut-off could better discriminate patients who gain benefit from pembrolizumab and can be more useful in clinical practice, the MAH presented and discussed baseline characteristics and all efficacy results (e.g. OS, PFS, ORR, DoR etc) of KN040 according to CPS cut-off of 10 (both in CPS ≥ 10 and CPS < 10 populations), as well as in the KN012 population which have been used to define the ROC curve and the new PD-L1 CPS score. In KN040, in both CPS<10 and CPS≥10 subgroups, no meaningful imbalances in baseline characteristics between treatment arms are observed. In addition, overall baseline characteristics appear comparable with the ones of the ITT population. Comparable efficacy results are shown in CPS≥1 and CPS≥10 populations. Based on the provided data, it could be speculated that in the population with a CPS score between 1 and 10 (CPS≥1 and <10) there is a trend toward a non detrimental effect compared to the standard treatment (OS HR<1).

Greater OS advantage of pembrolizumab over standard treatment was seen in the HPV negative compared to HPV positive subjects (data not shown).

KEYNOTE-055 and KEYNOTE-012 (supportive studies)

Patients in the supportive studies KN012 and KN055 were more heavily pretreated compared to the pivotal trial: indeed, patients who had 2 or more prior lines therapy for metastatic disease were and 71.1% in Cohort B and 63.2% in Cohort B2 of KN012, and 75.5% in KN055, compared to 28.1% in KN040. Composition according to age and ECOG were similar in all three studies. As in KN040, about 80% of patients in both KN055 and KN012 had PD-L1 CPS ≥1 score.

In KN055 study, 171 patients were included in the ASaT population. ORR based on RECIST 1.1 per central radiology assessment (confirmed responses only) was 16.4% (95%CI 11.2, 22.8), with only 1 CR, with a trend toward higher response rate with higher PD-L1 expression. Median duration of response was 8.3 months (range 1.6+ - 11.6+), with 72% of subjects with Response ≥ 6 months similar to KN040. PFS and OS results are overall comparable to the pembrolizumab arm of KN040.

In the KN012 study, a subset of the primary efficacy population consisted of subjects who had progressed on or after platinum-containing chemotherapy (n = 174, including 53 subjects in Cohort B and 121 subjects in Cohort B2) of which results have been presented. Overall, ORR was 16.7% (95%CI 11.5, 23.1). Median time to response was Not Reached (range 2.4+ - 29.5+), with number of subjects with response ≥ 6 Months 85% and ≥ 12 Months 71%.

It is considered that the supportive studies KN055 and KN012 are providing further evidence to support the durability of response of pembrolizumab in R/M HNSCC after prior treatment, although the rate of subjects who achieve response is not outstanding. In addition, a trend toward higher ORR in positive PD-L1 subjects is also confirmed.

2.4.4. Conclusions on the clinical efficacy

The protocol was amended several times and the changes have heavily modified the statistical component of the study design (definition of primary endpoint, stratification factors, follow-up duration, unplanned crossover) and sample size, and therefore have influenced the conduction of the study, having implications for the clinical interpretation of the results. In view of these methodologically issues (especially considering the formal lack of statistical significance in a single pivotal trial) it could be a possible option to reject the trial based on regulatory and statistical principles. However, in a more general view - taking the overall data and knowledge into account- this would be not considered the most appropriate way to address the provided evidence regarding the treatment effect of pembrolizumab in 2L HNSCC and there is a biological plausibility of the observed relation between PD-L1 expression and efficacy, therefore to look into subgroups based on PD-L1 expression.

The use of the CPS≥1 PD-L1 cut-off does not convincingly identify a population that will benefit from pembrolizumab. In the TPS≥50% population, the benefit of pembrolizumab vs standard treatment is demonstrated and observed in all efficacy endpoints.

2.5. Clinical safety

The overall safety profile of pembrolizumab, evaluated across clinical studies in patients with different solid tumours, is mainly associated with immune-related adverse reactions, and characterised by general (fatigue, decreased appetite), gastrointestinal (nausea, diarrhoea, constipation), respiratory (cough, dyspnoea), and skin (pruritus and rash) disorders.

The present submission focuses on the use of pembrolizumab for R/M HNSCC in patients with disease progression on or after platinum-containing chemotherapy by evaluating the KN040 trial results and by comparing KN040 pembrolizumab-treated subjects with a Reference Safety Dataset. Safety analyses included two integrated datasets either in all subjects with R/M HNSCC (Pooled HNSCC Dataset) and in all pembrolizumab trials (Cumulative Running Safety Dataset), in order to show consistency of safety data within R/M HNSCC and across multiple indications, respectively.

Analyses in all four datasets were conducted on the Subject as Treated (AsaT) population, including all randomized patients who received at least one dose of treatment.

Introduction

For the purpose of safety evaluation of pembrolizumab in subjects with disease progression on or after platinum-containing chemotherapy for R/M HNSCC, the pembrolizumab-treated group receiving 200 mg administered as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W) within the active controlled Phase 3 KN040 trial (N=246) was compared to:

1. The group treated with standard treatment for R/M HNSCC according to investigator's decision in the KN040 trial (pooled or single type of treatment with cetuximab [n=71], methotrexate [n=64], docetaxel [n=99]) (N=234);
2. 3 other pembrolizumab-treated patient populations:
    a. **Pooled HNSCC Dataset**: all subjects with pretreated R/M HNSCC from KN040, KN012 (Cohorts B and B2) and KN055 (N=609) allowing for evaluation of pembrolizumab safety in R/M HNSCC indication.

Trial	Per Protocol Cohort/Group (Dose/Regimen)	Eligibility	Nomenclature	Enrollment period / cut-off date
R/M HNSCC				
KN040	Pembrolizumab group (200 mg Q3W) Standard treatment group (methotrexate, docetaxel, or cetuximab)	Disease progression following platinum-containing chemotherapy[a] and regardless of PD-L1	KN040 pembrolizumab group (N=246) KN040 standard treatment group (N=234)	From 03-DEC-2014 to 13-MAY-2016 / 15-May-2017
KN012	Cohort B (10 mg/kg Q2W) Cohort B2 (200 mg Q3W)	Disease progression with or without prior therapy and regardless of PD-L1; Cohort B positive PD-L1 status only	KN012 subjects (Cohort B N=60) Cohort B2 (N=132)	From 07-JUN-2013 to 08-OCT-2014 / 26-APR-2016
KN055	N/A (200 mg Q3W)	Disease progression following platinum containing chemotherapy[a] in combination with, or followed by, cetuximab therapy and regardless of PD-L1	KN055 subjects (N=172)	From 24-OCT-2014 to 16-OCT-2015 / 22-APR-2016

Abbreviations: HNSCC=Head and neck squamous cell carcinoma; KN=KEYNOTE; N/A=Not applicable; PD-L1=Programmed cell death ligand 1; Q2W=Every 2 weeks; Q3W=Every 3 weeks; R/M=Recurrent or metastatic.
[a] Platinum-containing chemotherapy: carboplatin or cisplatin.

b. **Reference Safety Dataset**: 1567 subjects with advanced melanoma from trials KN001, KN002, and KN006, and 1232 subjects with NSCLC from trials KN001 and KN010 (N=2799), allowing for comparison of the KN040 safety profile with pembrolizumab used for other indications. The Reference Safety Dataset has been defined by the MAH as to represent the established safety profile for pembrolizumab in a broad population, across various treatment settings, and therefore used for comparison.

c. **Cumulative Running Safety Dataset**: pooled safety data from trials including participants of all pembrolizumab trials that have been submitted to the regulatory authority up to 4 weeks prior to the data cutoff for KN040 (15-MAY-2017): KN001 (NSCLC and melanoma), KN002 (melanoma), KN006 (melanoma), KN010 (NSCLC), KN012 (HNSCC: Cohorts B and B2, urothelial tract cancer: Cohort C, and gastric cancer: Cohort D), KN013 (Hodgkin's lymphoma [HL]: Cohort 3), KN024 (NSCLC), KN040 (HNSCC), KN045 (urothelial carcinoma), KN052 (urothelial carcinoma), KN055 (HNSCC), KN059 (gastric cancer: Cohort 1), KN087 (classical HL), KN164 (colorectal carcinoma: Cohort A) (N=4831). This dataset has been provided to support the consistency in the safety data of pembrolizumab across multiple indications.

Patient exposure

Overall Patient Exposure

In KN040 trial the data cutoff was 15-MAY-2017 (database lock of 13-OCT-2017 applied). Patient exposure in KN040 trial is presented in the table below:

Table 69: Summary of Drug Exposure in the KN040 trial

	MK-3475 200 mg Q3W (N=246)	Methotrexate (N=64)	Cetuximab (N=71)	Docetaxel (N=99)
Treatment Duration (days)				
Mean	142.6	56.8	120.3	79.9
Median	85	43	71	53
SD	156.67	54.47	121.97	67.87
Range	1 to 731	1 to 280	1 to 547	1 to 402
Number of Administrations				
Mean	7.4	8.0	17.3	4.6
Median	5	7	11	3
SD	7.03	6.93	16.63	3.10
Range	1 to 35	1 to 38	1 to 75	1 to 20

Drug exposure was lower in participants of the KN040 trial and in the Pooled HNSCC Dataset in respect to the other Datasets:

Table 70: Clinical Trial Exposure to Drug by Duration (Subjects in ASaT Population Treated with MK-3475¶)

	KN040 data for MK-3475* (N=246)			KN040, 012 and 055 data for MK-3475‖ (N=609)			Reference Safety Dataset for MK-3475†† (N=2799)			Cumulative Running Safety Dataset for MK-3475¶ (N=4831)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Study Days On- Therapy												
>0 m	246	(100.0)	(96.0)	609	(100.0)	(249.8)	2,799	(100.0)	(1,517.7)	4,831	(100.0)	(2,353.9)
>=1 m	185	(75.2)	(94.0)	478	(78.5)	(245.7)	2,394	(85.5)	(1,503.6)	4,035	(83.5)	(2,326.9)
>=3 m	111	(45.1)	(81.8)	294	(48.3)	(215.9)	1,656	(59.2)	(1,379.5)	2,729	(56.5)	(2,108.2)
>=6m	68	(27.6)	(66.3)	176	(28.9)	(173.4)	1,153	(41.2)	(1,197.8)	1,780	(36.8)	(1,760.3)
>=12m	28	(11.4)	(37.9)	66	(10.8)	(98.1)	600	(21.4)	(800.3)	778	(16.1)	(1,048.1)

Each subject is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

* Includes all subjects who received at least one dose of MK-3475 in KN040.

‖ Includes all subjects who received at least one dose of MK-3475 in KN040, Cohorts B and B2 from KN012, and KN055.

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

¶ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial-Tract-Cancer), and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN040, KN045, KN052, KN055, KN059 Cohort 1, KN087, and KN164 Cohort A (Colorectal Carcinoma).)

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015)

MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 09MAY2016)

MK-3475 Database Cutoff Date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

MK-3475 Database Cutoff Date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 16JAN2017)

MK-3475 Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 03JUN2016, KN087: 27JUN2016)

MK-3475 Database Cutoff Date for Bladder (KN012-Urothelial-Tract-Cancer: 01SEP2015, KN045: 07SEP2016, KN052: 01SEP2016)

MK-3475 Database Cutoff Date for Colorectal (KN164-Cohort A: 03JUN2016)

Subject characteristics

In KN040, approximately 83% were male gender, 33% aged =>65 years, and 71% with ECOG performance status of 1 (only ECOG 0-1 were allowed in the trial). Baseline demographic and disease characteristics and tumor assessments were generally well balanced between pembrolizumab and standard treatment groups. There was a higher proportion of patients with metastases in the pembrolizumab group (74.4%) than in the standard treatment group (66.2%).

Compared to the Reference Safety and Cumulative Running Safety Datasets, participants in the KN040 trial as well as in the Pooled HNSCC Dataset were more often male gender, aged <65 years, and with an ECOG =>1. Further, KN040 participants for two-thirds (78%) were enrolled outside the US, while the other Datasets included more often patients from the US (Pooled HNSCC Dataset) or with equal distribution among geographical areas (Reference Safety and Cumulative Running Safety Datasets).

Adverse events

All AEs that occurred from Day 1 of treatment through 30 days after the last dose and SAEs that occurred from Day 1 of treatment through 90 days after the last dose were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	X	X	X
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade 3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

SOC = System Organ Class.

All Adverse Events (AEs)

A summary of all AEs reported in KN040 trial and exposure-adjusted incidence rates are presented by treatment group in the tables below:

Table 71: Adverse Events – Summary KN040 (ASaT Population)

	MK-3475 200 mg Q3W		Standard Treatment		Difference in % vs Standard Treatment Estimate (95% CI)[†]
	n	(%)	n	(%)	
Subjects in population	246		234		
with one or more adverse events	238	(96.7)	227	(97.0)	-0.3 (-3.7, 3.2)
with no adverse event	8	(3.3)	7	(3.0)	0.3 (-3.2, 3.7)
with drug-related[‡] adverse events	155	(63.0)	196	(83.8)	-20.8 (-28.3, -13.0)
with toxicity grade 3-5 adverse events	143	(58.1)	138	(59.0)	-0.8 (-9.6, 8.0)
with toxicity grade 3-5 drug-related adverse events	33	(13.4)	85	(36.3)	-22.9 (-30.4, -15.4)
with serious adverse events	110	(44.7)	92	(39.3)	5.4 (-3.4, 14.1)
with serious drug-related adverse events	22	(8.9)	36	(15.4)	-6.4 (-12.5, -0.6)
with dose modification[§] due to an adverse event	84	(34.1)	106	(45.3)	-11.2 (-19.8, -2.4)
who died	20	(8.1)	25	(10.7)	-2.6 (-8.0, 2.7)
who died due to a drug-related adverse event	4	(1.6)	2	(0.9)	0.8 (-1.6, 3.4)
discontinued drug due to an adverse event	28	(11.4)	37	(15.8)	-4.4 (-10.7, 1.7)
discontinued drug due to a drug-related adverse event	15	(6.1)	12	(5.1)	1.0 (-3.4, 5.3)
discontinued drug due to a serious adverse event	24	(9.8)	27	(11.5)	-1.8 (-7.5, 3.8)
discontinued drug due to a serious drug-related adverse event	11	(4.5)	5	(2.1)	2.3 (-1.0, 6.0)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Estimated differences are provided in accordance with the statistical analysis plan.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15MAY2017

Source: [P040V01MK3475: adam-adsl; adae]
Source: [P040V01MK3475: adam-adsl; adrte]

Table 72: Exposure-Adjusted Adverse Events Overall (Including Multiple Occurrences of Events)

	Event Count and Rate (Events/100 person-years)[†]	
	MK-3475 200 mg Q3W	Standard Treatment
Number of subjects exposed	246	234
Total exposure[‡] person-years	115.39	74.07
Total events (rate)	725 (628.28)	850 (1147.61)
AE Category		
Blood and lymphatic system disorders	**94 (81.5)**	**81 (109.4)**
Anaemia	94 (81.5)	81 (109.4)
Endocrine disorders	**42 (36.4)**	**11 (14.9)**
Hypothyroidism	42 (36.4)	11 (14.9)
Gastrointestinal disorders	**172 (149.1)**	**196 (264.6)**
Constipation	52 (45.1)	46 (62.1)
Diarrhoea	63 (54.6)	53 (71.6)
Nausea	47 (40.7)	60 (81.0)
Stomatitis	10 (8.7)	37 (50.0)
General disorders and administration site conditions	**178 (154.3)**	**233 (314.6)**
Asthenia	52 (45.1)	56 (75.6)
Fatigue	59 (51.1)	85 (114.8)
Mucosal inflammation	22 (19.1)	52 (70.2)
Pyrexia	45 (39.0)	40 (54.0)
Infections and infestations	**32 (27.7)**	**27 (36.5)**
Pneumonia	32 (27.7)	27 (36.5)
Investigations	**34 (29.5)**	**61 (82.4)**
Neutrophil count decreased	11 (9.5)	35 (47.3)
Weight decreased	23 (19.9)	26 (35.1)
Metabolism and nutrition disorders	**48 (41.6)**	**52 (70.2)**
Decreased appetite	48 (41.6)	52 (70.2)
Respiratory, thoracic and mediastinal disorders	**91 (78.9)**	**78 (105.3)**
Cough	52 (45.1)	44 (59.4)
Dyspnoea	39 (33.8)	34 (45.9)
Skin and subcutaneous tissue disorders	**34 (29.5)**	**111 (149.9)**
Alopecia	1 (0.9)	30 (40.5)
Rash	33 (28.6)	81 (109.4)

[†] Event rate per 100 person-years of exposure=event count *100/person-years of exposure.

[‡] Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

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

Database Cutoff Date: 15MAY2017

Source: [P040V01MK3475: adam-adsl; adae]

Table 73: Exposure-Adjusted Adverse Events by Observation Period (Including Multiple occurrences of Events) (Incidence > 10% in One or More Treatment Groups) (ASaT Population)

Observation period of drug exposure	Event Count and Rate (Events/100 person-years)[†]							
	MK-3475 200 mg Q3W				Standard Treatment			
	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of Subjects exposed[‡]	246	149	74	33	234	107	37	6
Total exposure[§] person-years	51.01	26.65	25.67	12.07	47.95	16.67	7.43	2.01
Total events (rate)	451 (884.16)	113 (423.97)	77 (299.99)	29 (240.35)	636 (1326.29)	134 (803.80)	43 (578.69)	4 (198.78)
AE Category								
Blood and lymphatic system disorders	54 (105.9)	14 (52.5)	11 (42.9)	3 (24.9)	45 (93.8)	17 (102.0)	8 (107.7)	2 (99.4)
Anaemia	54 (105.9)	14 (52.5)	11 (42.9)	3 (24.9)	45 (93.8)	17 (102.0)	8 (107.7)	2 (99.4)
Endocrine disorders	25 (49.0)	13 (48.8)	1 (3.9)	2 (16.6)	5 (10.4)	4 (24.0)	0 (0.00)	0 (0.00)
Hypothyroidism	25 (49.0)	13 (48.8)	1 (3.9)	2 (16.6)	5 (10.4)	4 (24.0)	0 (0.00)	0 (0.00)
Gastrointestinal disorders	106 (207.8)	26 (97.6)	27 (105.2)	6 (49.7)	157 (327.4)	26 (156.0)	6 (80.8)	0 (0.00)
Constipation	32 (62.7)	9 (33.8)	7 (27.3)	2 (16.6)	40 (83.4)	4 (24.0)	2 (26.9)	0 (0.00)
Diarrhoea	35 (68.6)	8 (30.0)	15 (58.4)	4 (33.2)	43 (89.7)	7 (42.0)	2 (26.9)	0 (0.00)
Nausea	32 (62.7)	7 (26.3)	4 (15.6)	0 (0.00)	44 (91.8)	8 (48.0)	2 (26.9)	0 (0.00)
Stomatitis	7 (13.7)	2 (7.5)	1 (3.9)	0 (0.00)	30 (62.6)	7 (42.0)	0 (0.00)	0 (0.00)
General disorders and administration site conditions	116 (227.4)	26 (97.6)	12 (46.8)	7 (58.0)	185 (385.8)	30 (180.0)	9 (121.1)	2 (99.4)
Asthenia	33 (64.7)	9 (33.8)	4 (15.6)	3 (24.9)	42 (87.6)	6 (36.0)	6 (80.8)	0 (0.00)
Fatigue	42 (82.3)	7 (26.3)	3 (11.7)	0 (0.00)	67 (139.7)	13 (78.0)	2 (26.9)	0 (0.00)
Mucosal inflammation	14 (27.5)	4 (15.0)	2 (7.8)	1 (8.3)	42 (87.6)	9 (54.0)	1 (13.5)	0 (0.00)
Pyrexia	27 (52.9)	6 (22.5)	3 (11.7)	3 (24.9)	34 (70.9)	2 (12.0)	0 (0.00)	2 (99.4)
Infections and infestations	22 (43.1)	2 (7.5)	4 (15.6)	0 (0.00)	17 (35.5)	5 (30.0)	4 (53.8)	0 (0.00)
Pneumonia	22 (43.1)	2 (7.5)	4 (15.6)	0 (0.00)	17 (35.5)	5 (30.0)	4 (53.8)	0 (0.00)
Investigations	18 (35.3)	5 (18.8)	4 (15.6)	7 (58.0)	53 (110.5)	7 (42.0)	1 (13.5)	0 (0.00)
Neutrophil count decreased	3 (5.9)	2 (7.5)	2 (7.8)	4 (33.2)	32 (66.7)	3 (18.0)	0 (0.00)	0 (0.00)
Weight decreased	15 (29.4)	3 (11.3)	2 (7.8)	3 (24.9)	21 (43.8)	4 (24.0)	1 (13.5)	0 (0.00)
Metabolism and nutrition disorders	31 (60.8)	6 (22.5)	6 (23.4)	0 (0.00)	40 (83.4)	5 (30.0)	4 (53.8)	0 (0.00)
Decreased appetite	31 (60.8)	6 (22.5)	6 (23.4)	0 (0.00)	40 (83.4)	5 (30.0)	4 (53.8)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	58 (113.7)	14 (52.5)	9 (35.1)	2 (16.6)	54 (112.6)	17 (102.0)	3 (40.4)	0 (0.00)
Cough	33 (64.7)	7 (26.3)	5 (19.5)	2 (16.6)	31 (64.7)	7 (42.0)	3 (40.4)	0 (0.00)
Dyspnoea	25 (49.0)	7 (26.3)	4 (15.6)	0 (0.00)	23 (48.0)	10 (60.0)	0 (0.00)	0 (0.00)
Skin and subcutaneous tissue disorders	21 (41.2)	7 (26.3)	3 (11.7)	2 (16.6)	80 (166.8)	23 (138.0)	8 (107.7)	0 (0.00)
Alopecia	0 (0.00)	1 (3.8)	0 (0.00)	0 (0.00)	25 (52.1)	2 (12.0)	3 (40.4)	0 (0.00)
Rash	21 (41.2)	6 (22.5)	3 (11.7)	2 (16.6)	55 (114.7)	21 (126.0)	5 (67.3)	0 (0.00)

[†]Event rate per 100 person-years of exposure=event count *100/person-years of exposure.
[‡]Number of subjects exposed to drug at the start of indicated time interval.
[§]Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15MAY2017

Source: [P040V01MK3475: adam-adsl; adae]

Table 74: Adverse Events by SOC (Incidence >0% in One or More Treatment Groups)

	MK-3475, n (%)	Standard treatment, n (%)
Subjects in population	**246**	**234**
with one or more adverse events	**238 (96.7)**	**227 (97.0)**
with no adverse events	**8 (3.3)**	**7 (3.0)**
Blood and lymphatic system disorders	73 (29.7)	74 (31.6)
Cardiac disorders	13 (5.3)	10 (4.3)
Ear and labyrinth disorders	10 (4.1)	12 (5.1)
Endocrine disorders	43 (17.5)	12 (5.1)
Eye disorders	23 (9.3)	19 (8.1)
Gastrointestinal disorders	136 (55.3)	138 (59.0)
General disorders and administration site conditions	130 (52.8)	153 (65.4)
Hepatobiliary disorders	9 (3.7)	6 (2.6)
Immune system disorders	5 (2.0)	5 (2.1)
Infections and infestations	101 (41.1)	104 (44.4)
Injury, poisoning and procedural complications	35 (14.2)	29 (12.4)
Investigations	66 (26.8)	92 (39.3)
Metabolism and nutrition disorders	104 (42.3)	102 (43.6)
Musculoskeletal and connective tissue disorders	82 (33.3)	64 (27.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	43 (17.5)	26 (11.1)
Nervous system disorders	64 (26.0)	74 (31.6)
Product issues	1 (0.4)	3 (1.3)
Psychiatric disorders	39 (15.9)	29 (12.4)
Renal and urinary disorders	15 (6.1)	15 (6.4)
Reproductive system and breast disorders	1 (0.4)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	116 (47.2)	90 (38.5)
Skin and subcutaneous tissue disorders	74 (30.1)	117 (50.0)
Vascular disorders	32 (13.0)	26 (11.1)

Table 75: Adverse Events By Decreasing Frequency of Preferred Term (Incidence ≥0% in the Pembrolizumab Treatment Group)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	238	(96.7)	227	(97.0)
with no adverse events	8	(3.3)	7	(3.0)
Anaemia	66	(26.8)	53	(22.6)
Fatigue	48	(19.5)	63	(26.9)
Constipation	43	(17.5)	37	(15.8)
Cough	42	(17.1)	36	(15.4)
Diarrhoea	39	(15.9)	42	(17.9)
Asthenia	37	(15.0)	41	(17.5)
Hypothyroidism	37	(15.0)	9	(3.8)
Decreased appetite	35	(14.2)	43	(18.4)
Dyspnoea	34	(13.8)	27	(11.5)
Nausea	34	(13.8)	44	(18.8)
Pneumonia	27	(11.0)	22	(9.4)
Pyrexia	25	(10.2)	27	(11.5)
Rash	25	(10.2)	38	(16.2)
Weight decreased	22	(8.9)	26	(11.1)
Mucosal inflammation	17	(6.9)	36	(15.4)
Stomatitis	8	(3.3)	29	(12.4)
Neutrophil count decreased	4	(1.6)	26	(11.1)
Alopecia	1	(0.4)	27	(11.5)

The rainfall plot below shows the risk difference with 95%CI for observed AEs in KN040 study:

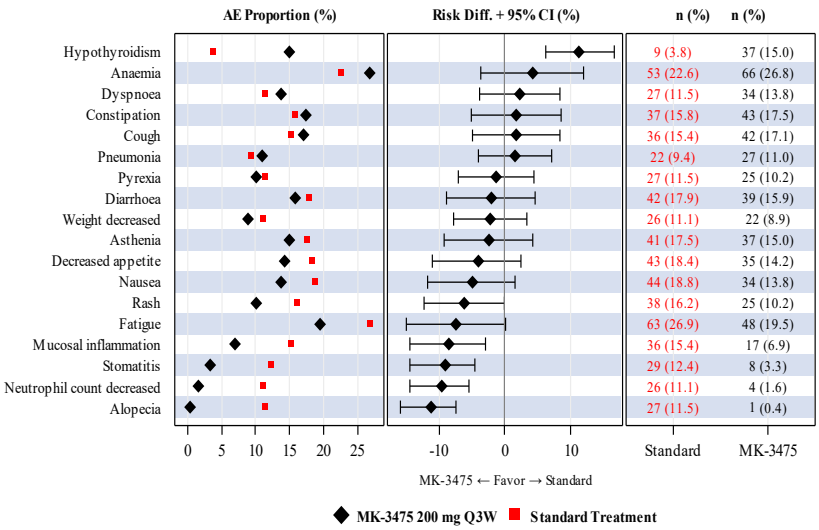


Figure 30: AEs (>=10% Incidence) with significant risk difference in favour of MK-3475 or the standard treatment shown by treatment comparison MK-3475 200 mg Q3W (N=246) *vs* Standard Treatment (N=234)

Table 76: Subjects With Adverse Events by Decreasing Incidence by Treatment (Incidence ≥ 10% in One or More Treatment Groups) (ASaT Population)

	MK-3475 200 mg Q3W		Methotrexate		Cetuximab		Docetaxel	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		64		71		99	
with one or more adverse events	238	(96.7)	63	(98.4)	69	(97.2)	95	(96.0)
with no adverse events	8	(3.3)	1	(1.6)	2	(2.8)	4	(4.0)
Anaemia	66	(26.8)	20	(31.3)	8	(11.3)	25	(25.3)
Fatigue	48	(19.5)	12	(18.8)	17	(23.9)	34	(34.3)
Constipation	43	(17.5)	12	(18.8)	11	(15.5)	14	(14.1)
Cough	42	(17.1)	12	(18.8)	13	(18.3)	11	(11.1)
Diarrhoea	39	(15.9)	14	(21.9)	12	(16.9)	16	(16.2)
Asthenia	37	(15.0)	14	(21.9)	6	(8.5)	21	(21.2)
Hypothyroidism	37	(15.0)	4	(6.3)	2	(2.8)	3	(3.0)
Decreased appetite	35	(14.2)	15	(23.4)	9	(12.7)	19	(19.2)
Dyspnoea	34	(13.8)	10	(15.6)	7	(9.9)	10	(10.1)
Nausea	34	(13.8)	15	(23.4)	11	(15.5)	18	(18.2)
Pneumonia	27	(11.0)	4	(6.3)	5	(7.0)	13	(13.1)
Pyrexia	25	(10.2)	9	(14.1)	7	(9.9)	11	(11.1)
Rash	25	(10.2)	2	(3.1)	28	(39.4)	8	(8.1)
Hypokalaemia	23	(9.3)	11	(17.2)	3	(4.2)	5	(5.1)
Vomiting	23	(9.3)	7	(10.9)	7	(9.9)	9	(9.1)
Weight decreased	22	(8.9)	9	(14.1)	7	(9.9)	10	(10.1)
Headache	21	(8.5)	5	(7.8)	11	(15.5)	6	(6.1)
Pruritus	18	(7.3)	2	(3.1)	12	(16.9)	4	(4.0)
Mucosal inflammation	17	(6.9)	12	(18.8)	6	(8.5)	18	(18.2)
Hyponatraemia	15	(6.1)	4	(6.3)	1	(1.4)	11	(11.1)
Alanine aminotransferase increased	10	(4.1)	7	(10.9)	2	(2.8)	2	(2.0)
Aspartate aminotransferase increased	10	(4.1)	8	(12.5)	3	(4.2)	2	(2.0)
Hypomagnesaemia	10	(4.1)	5	(7.8)	13	(18.3)	2	(2.0)
Stomatitis	8	(3.3)	11	(17.2)	5	(7.0)	13	(13.1)
Platelet count decreased	7	(2.8)	10	(15.6)	0	(0.0)	3	(3.0)
Dry skin	4	(1.6)	3	(4.7)	13	(18.3)	1	(1.0)
Neutrophil count decreased	4	(1.6)	10	(15.6)	0	(0.0)	16	(16.2)
Alopecia	1	(0.4)	1	(1.6)	1	(1.4)	25	(25.3)
Dermatitis acneiform	0	(0.0)	0	(0.0)	17	(23.9)	1	(1.0)
Febrile neutropenia	0	(0.0)	1	(1.6)	1	(1.4)	11	(11.1)
Skin fissures	0	(0.0)	0	(0.0)	9	(12.7)	1	(1.0)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15MAY2017

Source: [P040V01MK3475: adam-adsl; adae]
Source: [P040V01MK3475: adam-adsl; adtte]

The maximum toxicity grade by treatment arm is overall comparable and shown in the table below.

Table 77: Subjects with adverse events by decreasing incidence by maximum toxicity grade (incidence ≥10% in one or more treatment groups) (ASaT population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	238	(96.7)	227	(97.0)
Grade 1	19	(7.7)	24	(10.3)
Grade 2	76	(30.9)	65	(27.8)
Grade 3	102	(41.5)	82	(35.0)
Grade 4	21	(8.5)	31	(13.2)
Grade 5	20	(8.1)	25	(10.7)
with no adverse events	8	(3.3)	7	(3.0)

Proportions of AEs for the KN040 trial and the other datasets is depicted in the next table.

Table 78: Subjects With Adverse Events (Subjects in ASaT Population)

	KN040 data for MK-3475*		KN040, 012 and 055 data for MK-3475‖		Reference Safety Dataset for MK-3475††		Cumulative Running Safety Dataset for MK-3475¶	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		609		2,799		4,831	
with one or more adverse events	238	(96.7)	592	(97.2)	2,727	(97.4)	4,680	(96.9)
with no adverse events	8	(3.3)	17	(2.8)	72	(2.6)	151	(3.1)
Anaemia	66	(26.8)	142	(23.3)	347	(12.4)	718	(14.9)
Fatigue	48	(19.5)	198	(32.5)	1,044	(37.3)	1,628	(33.7)
Constipation	43	(17.5)	118	(19.4)	498	(17.8)	881	(18.2)
Cough	42	(17.1)	105	(17.2)	615	(22.0)	950	(19.7)
Diarrhoea	39	(15.9)	87	(14.3)	625	(22.3)	964	(20.0)
Asthenia	37	(15.0)	47	(7.7)	362	(12.9)	549	(11.4)
Hypothyroidism	37	(15.0)	92	(15.1)	236	(8.4)	446	(9.2)
Decreased appetite	35	(14.2)	105	(17.2)	630	(22.5)	1,018	(21.1)
Dyspnoea	34	(13.8)	98	(16.1)	534	(19.1)	819	(17.0)
Nausea	34	(13.8)	102	(16.7)	685	(24.5)	1,071	(22.2)
Pneumonia	27	(11.0)	56	(9.2)	140	(5.0)	246	(5.1)
Pyrexia	25	(10.2)	70	(11.5)	357	(12.8)	637	(13.2)
Rash	25	(10.2)	69	(11.3)	500	(17.9)	729	(15.1)

Grade 3-5 AEs

Exposure-adjusted incidence rates of toxicity Grade 3-5 AEs were lower in pembrolizumab-treated subjects than in the standard treatment group (316.31 *vs* 502.25 x 100 person-years of exposure).

Table 79: Grade 3-5 Adverse Events by Decreasing Incidence in KN040 (Incidence >1% in the Pembrolizumab Treatment Group)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	143	(58.1)	138	(59.0)
with no adverse events	103	(41.9)	96	(41.0)
Pneumonia	23	(9.3)	14	(6.0)
Anaemia	15	(6.1)	14	(6.0)
Hypercalcaemia	9	(3.7)	1	(0.4)
Dysphagia	8	(3.3)	5	(2.1)
Tumour haemorrhage	8	(3.3)	2	(0.9)
Hyponatraemia	7	(2.8)	10	(4.3)
Pneumonia aspiration	7	(2.8)	4	(1.7)
Diarrhoea	6	(2.4)	3	(1.3)
Death	5	(2.0)	4	(1.7)
Decreased appetite	5	(2.0)	0	(0.0)
Dyspnoea	5	(2.0)	4	(1.7)
Fatigue	5	(2.0)	5	(2.1)
Hypokalaemia	5	(2.0)	4	(1.7)
Hypophosphataemia	5	(2.0)	3	(1.3)
Lymphocyte count decreased	5	(2.0)	4	(1.7)
Sepsis	5	(2.0)	3	(1.3)
Tumour pain	5	(2.0)	3	(1.3)
Arthralgia	3	(1.2)	1	(0.4)
Blood bilirubin increased	3	(1.2)	1	(0.4)
Cellulitis	3	(1.2)	0	(0.0)
Dehydration	3	(1.2)	2	(0.9)
Hypercalcaemia of malignancy	3	(1.2)	1	(0.4)
Hypoxia	3	(1.2)	0	(0.0)
Infected neoplasm	3	(1.2)	0	(0.0)
Mouth haemorrhage	3	(1.2)	3	(1.3)
Pneumonitis	3	(1.2)	3	(1.3)
Respiratory failure	3	(1.2)	0	(0.0)

Higher incidences (difference in incidence at least 2.0%) were observed in the

- pembrolizumab arm for *Pneumonia*, *Hypercalcaemia*, *Tumour haemorrhage* and *Decreased appetite*,
- standard treatment arm *Neutrophil count decreased*, *Febrile neutropenia*, *WBC decreased*, *Stomatitis*, *Asthenia*, *Platelet count decreased* and *ALT increased* (see Figure below)

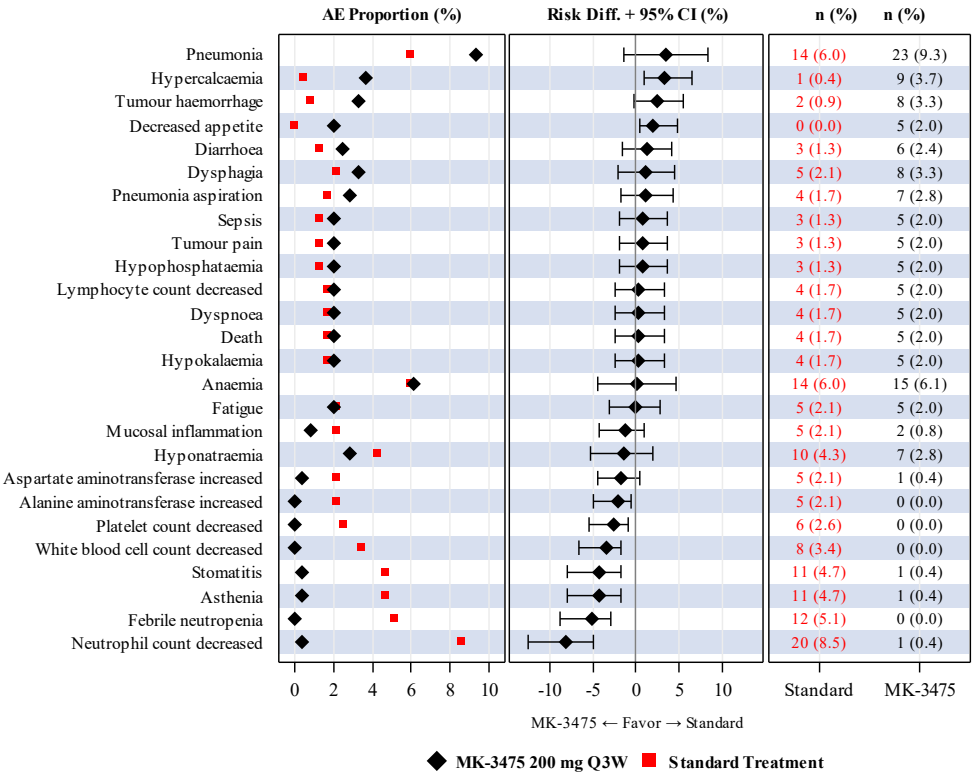


Figure 31: Grade 3-5 AEs with significant risk difference in favor of MK-3475 or the Standard treatment shown by treatment comparison MK-3475 200 mg Q3W (N=246) *vs*. Standard Treatment (N=234)

Proportion of subjects with Grade 3-5 AEs by type of treatment in the KN040 trial are summarized in the next Table. Frequencies of grade 3-5 adverse events varied between pembrolizumab (58.1%) and the 3 standard treatment arms, cetuximab 45.1%, docetaxel 66.7% and methotrexate 66.7%.

Table 80: Subjects with grade 3-5 adverse events by decreasing incidence by treatment (incidence> 0% in one or more treatment groups) (ASaT population)

	MK-3475 200 mg Q3W		Methotrexate		Cetuximab		Docetaxel	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		64		71		99	
with one or more adverse events	143	(58.1)	40	(62.5)	32	(45.1)	66	(66.7)
with no adverse events	103	(41.9)	24	(37.5)	39	(54.9)	33	(33.3)

Table 81: Subjects With Grade 3-5 Adverse Events (Incidence ≥ 2% in Pembrolizumab KN040 Treatment Group) By Decreasing Frequency of Preferred Term - Subjects in ASaT Population Treated with MK-3475¶

	KN040 data for MK-3475*		KN040, 012 and 055 data for MK-3475‖		Reference Safety Dataset for MK-3475††		Cumulative Running Safety Dataset for MK-3475¶	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		609		2,799		4,831	
with one or more adverse events	143	(58.1)	348	(57.1)	1,273	(45.5)	2,330	(48.2)
with no adverse events	103	(41.9)	261	(42.9)	1,526	(54.5)	2,501	(51.8)
Pneumonia	23	(9.3)	43	(7.1)	75	(2.7)	149	(3.1)
Anaemia	15	(6.1)	44	(7.2)	90	(3.2)	232	(4.8)
Hypercalcaemia	9	(3.7)	21	(3.4)	15	(0.5)	41	(0.8)
Dysphagia	8	(3.3)	16	(2.6)	7	(0.3)	31	(0.6)
Tumour haemorrhage	8	(3.3)	11	(1.8)	1	(0.0)	13	(0.3)
Hyponatraemia	7	(2.8)	26	(4.3)	62	(2.2)	130	(2.7)
Pneumonia aspiration	7	(2.8)	21	(3.4)	4	(0.1)	29	(0.6)
Diarrhoea	6	(2.4)	10	(1.6)	36	(1.3)	66	(1.4)
Death	5	(2.0)	11	(1.8)	17	(0.6)	31	(0.6)
Decreased appetite	5	(2.0)	12	(2.0)	26	(0.9)	59	(1.2)
Dyspnoea	5	(2.0)	15	(2.5)	78	(2.8)	119	(2.5)
Fatigue	5	(2.0)	15	(2.5)	69	(2.5)	132	(2.7)
Hypokalaemia	5	(2.0)	16	(2.6)	25	(0.9)	53	(1.1)
Hypophosphataemia	5	(2.0)	15	(2.5)	14	(0.5)	38	(0.8)
Lymphocyte count decreased	5	(2.0)	11	(1.8)	12	(0.4)	30	(0.6)
Sepsis	5	(2.0)	10	(1.6)	13	(0.5)	37	(0.8)
Tumour pain	5	(2.0)	8	(1.3)	17	(0.6)	34	(0.7)

Drug-related AEs

AEs that were classified as "possibly, probably, or definitely" associated with pembrolizumab by the investigator are considered together as drug-related AEs.

Overall drug-related AEs

Summary of drug-related AEs in KN040 trial is presented in the table below:

Table 82: Drug-Related Adverse Events in KN040 (ASaT population) - Incidence ≥5% in One or More Treatment Groups) by Decreasing Incidence in the MK-3475 group

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	155	(63.0)	196	(83.8)
with no adverse events	91	(37.0)	38	(16.2)
Hypothyroidism	33	(13.4)	2	(0.9)
Fatigue	31	(12.6)	43	(18.4)
Diarrhoea	20	(8.1)	24	(10.3)
Rash	19	(7.7)	34	(14.5)
Asthenia	18	(7.3)	28	(12.0)
Anaemia	17	(6.9)	33	(14.1)
Decreased appetite	14	(5.7)	22	(9.4)
Nausea	12	(4.9)	29	(12.4)
Pruritus	12	(4.9)	16	(6.8)
Mucosal inflammation	9	(3.7)	30	(12.8)
Stomatitis	6	(2.4)	28	(12.0)
Vomiting	4	(1.6)	16	(6.8)
Hypomagnesaemia	3	(1.2)	13	(5.6)
Neutrophil count decreased	3	(1.2)	25	(10.7)
Dry skin	2	(0.8)	13	(5.6)
Alopecia	1	(0.4)	25	(10.7)
Dermatitis acneiform	0	(0.0)	17	(7.3)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 15MAY2017

Except for hypothyroidism, incidences of all other drug-related AEs (≥5%) were higher in the standard treatment group. Drug-related AEs, occurred in a similar percentage with all the three drugs of the KN040 standard treatment arm: cetuximab 88.7%, methotrexate 78.1%, docetaxel 83.3%.

Grade 1-2 drug-related AEs were found in 74% of subjects treated with pembrolizumab and in 80% of those receiving standard treatment.

Drug-related AEs in KN040 and in the other Safety Datasets analysed are summarised in the table below:

Table 83: Drug-Related Adverse Events By Decreasing Frequency of Preferred Term (Incidence ≥ 5% in One or More Treatment Groups)

	KN040 data for MK-3475*		KN040, 012 and 055 data for MK-3475†		Reference Safety Dataset for MK-3475††		Cumulative Running Safety Dataset for MK-3475‡	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		609		2,799		4,831	
with one or more adverse events	155	(63.0)	387	(63.5)	2,062	(73.7)	3,346	(69.3)
with no adverse events	91	(37.0)	222	(36.5)	737	(26.3)	1,485	(30.7)
Hypothyroidism	33	(13.4)	68	(11.2)	213	(7.6)	381	(7.9)
Fatigue	31	(12.6)	103	(16.9)	678	(24.2)	981	(20.3)
Diarrhoea	20	(8.1)	35	(5.7)	343	(12.3)	494	(10.2)
Rash	19	(7.7)	46	(7.6)	386	(13.8)	542	(11.2)
Asthenia	18	(7.3)	19	(3.1)	218	(7.8)	290	(6.0)
Anaemia	17	(6.9)	31	(5.1)	94	(3.4)	174	(3.6)
Decreased appetite	14	(5.7)	39	(6.4)	255	(9.1)	393	(8.1)

The incidence of pembrolizumab-related *Pneumonia* was 0.4% in KN040, 0.2% in the Pooled HNSCC Database, 0.6% in the Reference Safety Dataset, and 0.5% in the Cumulative Running Safety Dataset.

Approximately half of subjects had a drug-related AE that was of maximum toxicity Grade 1 or 2 (49.6% in KN040 compared to 59.9% in the Reference Safety Dataset, respectively).

Grade 3-5 drug-related AEs

Table 84: Drug-Related Grade 3-5 Adverse Events by Decreasing Incidence in KN040 (ASaT Population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	33	(13.4)	85	(36.3)
with no adverse events	213	(86.6)	149	(63.7)
Diarrhoea	4	(1.6)	1	(0.4)
Fatigue	4	(1.6)	2	(0.9)
Dyspnoea	2	(0.8)	0	(0.0)
Pneumonitis	2	(0.8)	0	(0.0)

Grade 3-5 drug related AEs occurred in a similar percentage of patients treated with methotrexate (42.2%) and docetaxel (46.5%), while the proportion was lower in subjects receiving cetuximab (16.9%).

In KN040, 64% of Grade 3-5 AEs were observed in one single patient. Events registered in 2 or more participants treated with pembrolizumab were: *Diarrhoea, Fatigue, Dyspnoea, Pneumonitis*. In the standard treatment arm *Neutrophil count decreased* (8.5%), *Stomatitis* (4.7%), and *Febrile neutropenia* (4.3%) were the most common Grade 3-5 AEs.

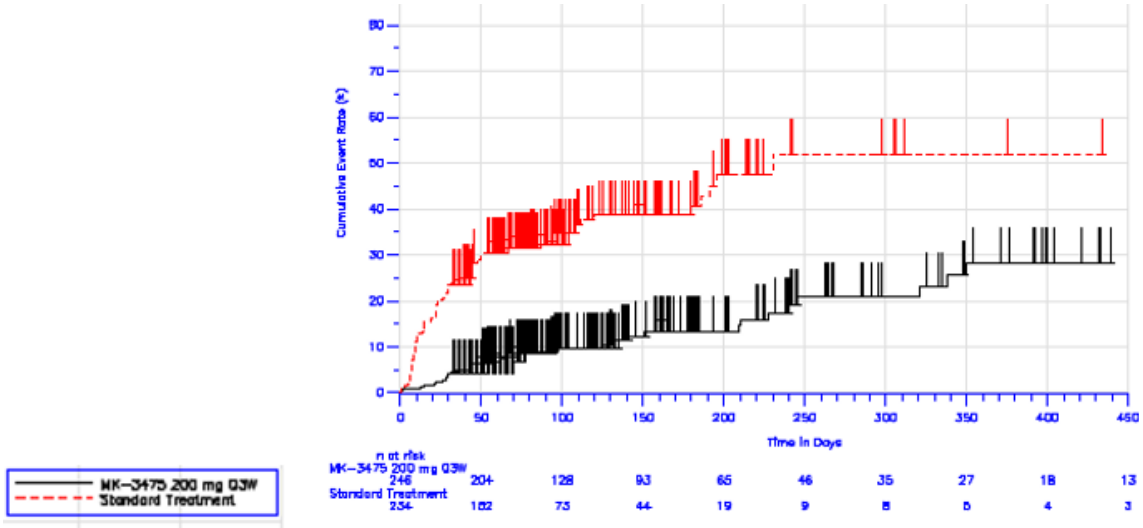


Figure 32: Kaplan-Meier of Time to First Drug-Related Grade 3-5 Adverse Event (ASaT Population)

Proportion of subjects with pembrolizumab-related Grade 3-5 AEs in the KN040 population was consistent across all Datasets and among Grade 3-5 drug-related AEs, specific PTs were reported in ≤1.6% of all populations (see table below).

Drug-Related Grade 3-5 Adverse Events By Decreasing Frequency of Preferred Term
(Incidence >0.6% in Pembrolizumab Treatment Group)

	KN040 data for MK-3475*		**KN040, 012 and 055 data for MK-3475‖**		**Reference Safety Dataset for MK-3475††**		**Cumulative Running Safety Dataset for MK-3475¶**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects in population	**246**		**609**		**2,799**		**4,831**	
with one or more adverse events	**33**	**(13.4)**	**83**	**(13.6)**	**386**	**(13.8)**	**696**	**(14.4)**
with no adverse events	**213**	**(86.6)**	**526**	**(86.4)**	**2,413**	**(86.2)**	**4,135**	**(85.6)**
Diarrhoea	4	(1.6)	5	(0.8)	25	(0.9)	46	(1.0)
Fatigue	4	(1.6)	7	(1.1)	30	(1.1)	60	(1.2)

Dyspnoea	2	(0.8)	2	(0.3)	12	(0.4)	19	(0.4)
Pneumonitis	2	(0.8)	6	(1.0)	32	(1.1)	51	(1.1)

Frequency of Grade 3-5 pembrolizumab-related *Pneumonia* was similar among all 4 datasets (0.4%, 0.2%, 0.3% and 0.2% in KN040, Pooled HNSCC Dataset, Reference Safety Dataset, Cumulative Running Safety Dataset, respectively).

Other Significant Events (Adverse Events of Special interest, AEOSIs)

Immune-mediated events and infusion-related reactions associated with pembrolizumab were considered AEOSIs. A pre-specified and continually up-dated list of PTs was used for data collection and analyses (see table below):

Table 85 Immune mediated events and infusion-related reactions associated with Pembrolizumab

AEOSI	Preferred Terms	Important Identified Risk	Important Potential Risk	Immune-mediated (Yes/No)
Pneumonitis	Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome	Yes	No	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive	Yes	No	Yes
Hepatitis	Hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes	No	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome	Yes	No	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency	Yes	No	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes	No	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis	Yes	No	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism	Yes	No	Yes

Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute	Yes	No	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus	Yes	No	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): Any grade from Severe cutaneous reactions SMQ narrow **Severe Skin (continued): If grade 3 or higher:**	Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Oculomucocutaneous syndrome, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis and Toxic skin eruption; Any event from the Epidermal and dermal conditions HLGT of the Skin and subcutaneous tissue disorders SOC. See Appendix I for complete list of PTs from this HLGT	Yes	No	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis,	Yes	No	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising	Yes	No	Yes

Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy	Yes	No	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome	Yes	No	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis	Yes	No	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis	Yes	No	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, ocular sarcoidosis, Pulmonary sarcoidosis	Yes	No	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction,	Yes	No	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	No	Yes	Yes

Among AEOSIs, frequencies of all-causality AEs (21.6 *vs* 12.0%), drug-related AEs (21.5 *vs* 5.1%) and SAEs (3.7 *vs* 0.4%) were noticeably higher in subjects treated with pembrolizumab than in those receiving standard treatment. Also, treatment discontinuation due to AEOSI was more frequently registered in the pembrolizumab arm. AEOSI Grade 3-5 AEs rates were similar among the two treatment arms (See the next table).

AEs were reported for the following AEOSI categories in the pembrolizumab group:

- Hypothyroidism (15.0%), pneumonitis (4.1%), skin including Stevens-Johnson syndrome (2.8) , hyperthyroidism (2.0%), colitis (0.8%), hepatitis (0.8%), Guillain-Barre syndrome (0.8%), and infusion reactions (3.3%),

AEs were reported for the following AEOSI categories in the standard treatment group:

- Hypothyroidism (3.8%), skin (3.8%), pneumonitis (1.3%), colitis (0.4%), hyperthyroidism (0.4%), and infusion reactions (3.0%).

Table 86: AEOSIs in KN040 (ASaT population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	63	(25.6)	28	(12.0)
with no adverse event	183	(74.4)	206	(88.0)
with drug-related[†] adverse events	53	(21.5)	12	(5.1)
with toxicity grade 3-5 adverse events	11	(4.5)	11	(4.7)
with toxicity grade 3-5 drug-related adverse events	7	(2.8)	7	(3.0)
with serious adverse events	13	(5.3)	5	(2.1)
with serious drug-related adverse events	9	(3.7)	1	(0.4)
with dose modification[‡] due to an adverse event	16	(6.5)	13	(5.6)
who died	1	(0.4)	0	(0.0)
who died due to a drug-related adverse event	1	(0.4)	0	(0.0)
discontinued drug due to an adverse event	6	(2.4)	2	(0.9)
discontinued drug due to a drug-related adverse event	6	(2.4)	1	(0.4)
discontinued drug due to a serious adverse event	4	(1.6)	1	(0.4)
discontinued drug due to a serious drug-related adverse event	4	(1.6)	1	(0.4)

[†] Determined by the investigator to be related to the drug.
[‡] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

The most frequently reported (≥2% of subjects) AEOSI for the pembrolizumab arm of the KN040 Population were *Hypothyroidism*, *Pneumonitis*, *Infusion Reactions, Severe Skin Reactions*, and *Hyperthyroidism*. Most AEOSIs were mild to moderate in severity (Grade 1 or 2). One subject (0.4%) experienced a Grade 4 AEOSI of *Hepatitis* (autoimmune hepatitis) which resolved. Only one AEOSI fatal event was registered (Grade 5 Stevens-Johnson syndrome) and recorded as being related to pembrolizumab. No new AEOSIs were recorded in the KN040 study population.

Table 87: Subjects With Adverse Events by Maximum Toxicity Grade – AEOSI Overall (ASaT Population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	63	(25.6)	28	(12.0)
Grade 1	17	(6.9)	6	(2.6)
Grade 2	35	(14.2)	11	(4.7)
Grade 3	9	(3.7)	11	(4.7)
Grade 4	1	(0.4)	0	(0.0)
Grade 5	1	(0.4)	0	(0.0)
with no adverse events	183	(74.4)	206	(88.0)

Concerning outcome, among the 63 subjects in the KN040 Population who experienced 1 or more AEOSIs, these were recorded as fatal in 1 subject (1.6%), resolved in 20 subjects (31.7%), resolved with sequelae in 1 subject (1.6%), resolving in 5 subjects (7.9%), not resolved in 34 subjects (54.0%), and of unknown outcome in 2 subjects (3.2%). A higher proportion of AEOSIs of the pembrolizumab group remained unresolved at the time of data cut-off when compared to the standard treatment arm (54% *vs* 39.3%, respectively). With regard to specific AEOSIs, the proportion of not resolved events was 67.6% of *Hypothyroidism* (N=25/37), 40% of *Pneumonitis* (N=4/10), 42.9% of *Severe skin reaction* (N=3/7), 50% of *Guillain-Barre syndrome* (N=1/2), and 20% of *Hyperthyroidism* (N=1/5).

Hypothyroidism and radiation status

Hypothyroidism is one of the long-term toxicities of radiation therapy in HNSCC.

The great majority of subjects had received prior radiation in both treatment arms in the KN040 ASaT population. In the KN040 trial, *Hypothyroidism* was more frequently recorded in pembrolizumab-treated subjects (N=37/246; 15%) than in the group receiving standard treatment (N=9/234; 3.8%). Toxicity severity of hypothyroidism was classified as Grade 1 or 2 in all KN040 pembrolizumab-treated cases, except for one. A previous radiation therapy had been administered to almost all pembrolizumab-treated subjects developing the event (94.9%).

Table 88: Radiation Status Among Subjects with and without hypothyroidism

	MK-3475 200 mg Q3W		Standard Treatment	
	With Hypothyroidism N=79 n (%)	Without Hypothyroidism N=167 n (%)	With Hypothyroidism N=54 n (%)	Without Hypothyroidism N=180 n (%)
Prior Radiation Reported	75 (94.9%)	142 (85.0%)	52 (96.3%)	148 (82.2%)
Prior Radiation Not Reported	4 (5.1%)	25 (15.0%)	2 (3.7%)	32 (17.8%)

Only 1/37 (2.7%) subjects with hypothyroidism received systemic corticosteroids started at low dose. In 67.6% of hypothyroidism cases, the event remained unresolved at the cut-off date, needing chronic hormone replacement treatment.

A similar frequency of hypothyroidism was reported in both KN040 (15.0%) and in the Pooled HNSCC Dataset (15.1%). However, *Hypothyroidism* rate was higher with pembrolizumab in HNSCC patients compared to that in subjects of the other datasets, where it was 8.5% and 9.3% in the Reference Safety Dataset and in the Cumulative Running Safety Dataset, respectively. Hypothyroidism tended to occur earlier in HNSCC treated patients: indeed, median time to onset of first hypothyroidism event was 64 days in both KN040 and HNSCC Pooled Safety Dataset, versus 106 and 103 days in the Reference Safety Dataset and in the Cumulative Running Safety Dataset, respectively.

Oedema

Table 89: Oedema

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	29	(11.8)	18	(7.7)
with no adverse event	217	(88.2)	216	(92.3)
with drug-related† adverse events	12	(4.9)	5	(2.1)
with toxicity grade 3-5 adverse events	3	(1.2)	5	(2.1)
with toxicity grade 3-5 drug-related adverse events	1	(0.4)	2	(0.9)
with serious adverse events	1	(0.4)	1	(0.4)
with serious drug-related adverse events	0	(0.0)	0	(0.0)
with dose modification‡ due to an adverse event	0	(0.0)	3	(1.3)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

Table 90: Five most common adverse events of oedema regardless of causality (ASaT population)

	KN040 data for MK-3475	KN040 data for Standard treatment	KN040, 012 and 055 data for MK-3475	Reference Safety Dataset for MK-3475
	N (%)	N (%)	N (%)	N (%)
Subjects in population	246	234	609	2,799
Face oedema	11 (4.5)	3 (1.3)	27 (4.4)	11 (0.4)
Localized oedema	6.(2.4)	3 (1.3)	13 (2.1)	10 (0.4)
Localized swelling	5 (2.0)	4 (1.7)	10 (1.6)	7 (0.3)
Swollen tongue	3 (1.2)	1 (0.4)	7 (1.1)	1 (0.0)
Tongue oedema	2 (0.8)	2 (0.9)	5 (0.8)	0 (0)

Table 91: Five most common drug-related adverse events of oedema (ASaT population)

	KN040 data for MK-3475	KN040 data for Standard treatment	KN040, 012 and 055 data for MK-3475	Reference Safety Dataset for MK-3475
	N (%)	N (%)	N (%)	N (%)
Subjects in population	246	234	609	2,799
Face oedema	3 (1.2)	1 (0.4)	9 (1.5)	6 (0.2)
Localized oedema	2 (0.8)	0 (0.0)	3 (0.5)	3 (0.1)
Localized swelling	2 (0.8)	2 (0.8)	5 (0.8)	0 (0.0)
Swollen tongue	1 (0.4)	1 (0.4)	3 (0.5)	0 (0.0)
Tongue oedema	2 (0.8)	0 (0.0)	2 (0.3)	0 (0.0)

Other events: Haemorrage adverse events

Table 92: Subjects With Haemorrhage Adverse Events (Incidence > 0% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

	KN040 MK-3475		KN040 Standard		KN012, KN040 and KN055 for MK-3475	
	n	(%)	n	(%)	N	(%)
Subjects in population	246		234		609	
with one or more adverse events	50	(20.3)	41	(17.5)	106	(17.4)
with no adverse events	196	(79.7)	193	(82.5)	503	(82.6)
Haemoptysis	15	(6.1)	6	(2.6)	29	(4.8)
Tumour haemorrhage	15	(6.1)	5	(2.1)	24	(3.9)
Mouth haemorrhage	5	(2.0)	4	(1.7)	15	(2.5)
Post procedural haemorrhage	5	(2.0)	0	(0.0)	10	(1.6)
Epistaxis	4	(1.6)	8	(3.4)	7	(1.1)
Haemorrhage	2	(0.8)	0	(0.0)	3	(0.5)
Bone contusion	1	(0.4)	0	(0.0)	1	(0.2)
Gastrointestinal haemorrhage	1	(0.4)	2	(0.9)	1	(0.2)
Haematochezia	1	(0.4)	0	(0.0)	1	(0.2)
Haematoma	1	(0.4)	1	(0.4)	2	(0.3)
Haematuria	1	(0.4)	4	(1.7)	5	(0.8)
Pharyngeal haemorrhage	1	(0.4)	0	(0.0)	1	(0.2)
Rectal haemorrhage	1	(0.4)	0	(0.0)	1	(0.2)
Skin haemorrhage	1	(0.4)	1	(0.4)	4	(0.7)
Skin neoplasm bleeding	1	(0.4)	0	(0.0)	1	(0.2)
Soft tissue haemorrhage	1	(0.4)	0	(0.0)	1	(0.2)
Tracheal haemorrhage	1	(0.4)	1	(0.4)	2	(0.3)
Upper gastrointestinal haemorrhage	1	(0.4)	1	(0.4)	3	(0.5)

Blood urine present	0	(0.0)	2	(0.9)	0	(0.0)
Bloody discharge	0	(0.0)	1	(0.4)	0	(0.0)
Cerebral haemorrhage	0	(0.0)	0	(0.0)	1	(0.2)
Contusion	0	(0.0)	0	(0.0)	2	(0.3)
Ecchymosis	0	(0.0)	1	(0.4)	0	(0.0)
Gastric haemorrhage	0	(0.0)	0	(0.0)	1	(0.2)
Gingival bleeding	0	(0.0)	2	(0.9)	1	(0.2)
Haematemesis	0	(0.0)	0	(0.0)	1	(0.2)
Haemorrhagic anaemia	0	(0.0)	0	(0.0)	1	(0.2)
Immune thrombocytopenic purpura	0	(0.0)	0	(0.0)	1	(0.2)
Laryngeal haemorrhage	0	(0.0)	1	(0.4)	3	(0.5)
Lymph node haemorrhage	0	(0.0)	1	(0.4)	0	(0.0)
Peritoneal haemorrhage	0	(0.0)	0	(0.0)	2	(0.3)
Pulmonary alveolar haemorrhage	0	(0.0)	1	(0.4)	0	(0.0)
Respiratory tract haemorrhage	0	(0.0)	1	(0.4)	0	(0.0)
Stoma site haemorrhage	0	(0.0)	1	(0.4)	1	(0.2)
Subarachnoid haemorrhage	0	(0.0)	1	(0.4)	1	(0.2)
Subcutaneous haematoma	0	(0.0)	1	(0.4)	0	(0.0)
Subdural haematoma	0	(0.0)	0	(0.0)	1	(0.2)
Wound haemorrhage	0	(0.0)	1	(0.4)	0	(0.0)

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

In the KN040 trial, the proportion of subjects with one or more SAEs in the pembrolizumab and the standard treatment group were 44.7% and 39.3%, respectively. SAEs for Pembrolizumab *vs* Standard Treatment in the KN040 trial are presented in the table below:

Table 93: Serious Adverse Events Up to 90 Days After Last Dose by Decreasing Incidence in the MK-3475 group (Incidence >1% in the MK-3475 Treatment Group)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Subjects in population	246		234	
with one or more adverse events	110	(44.7)	92	(39.3)
with no adverse events	136	(55.3)	142	(60.7)
Pneumonia	20	(8.1)	16	(6.8)
Tumour haemorrhage	9	(3.7)	2	(0.9)
Hypercalcaemia	7	(2.8)	0	(0.0)
Diarrhoea	6	(2.4)	2	(0.9)
Pneumonia aspiration	6	(2.4)	3	(1.3)
Pneumonitis	6	(2.4)	3	(1.3)
Anaemia	5	(2.0)	2	(0.9)
Death	5	(2.0)	4	(1.7)
Decreased appetite	4	(1.6)	0	(0.0)
Dysphagia	4	(1.6)	3	(1.3)
Dyspnoea	4	(1.6)	1	(0.4)
Sepsis	4	(1.6)	3	(1.3)
Cellulitis	3	(1.2)	0	(0.0)
Hypercalcaemia of malignancy	3	(1.2)	2	(0.9)
Hyponatraemia	3	(1.2)	0	(0.0)
Mouth haemorrhage	3	(1.2)	3	(1.3)

The most frequently reported SAEs (>2.0 %) were

- pneumonia, tumor haemorrhage, hypercalcaemia, diarrhoea, pneumonia aspiration, and pneumonitis in subjects treated with pembrolizumab,

- pneumonia and febrile neutropenia (3.8%) in subjects treated with standard treatment.

Cumulative frequency of *Pneumonia*, *Pneumonia aspiration*, and *Pneumonitis* accounted for 12.9% in the pembrolizumab arm and 9.4% in the standard treatment group.

In comparison with the other datasets, frequency of SAEs in the KN040 pembrolizumab-treated group (44.7%) was to some extent higher than in that found in the Reference Safety Dataset (37.2%) and the Cumulate Running Safety Dataset (38.4%), but consistent with that of the Pooled HNSCC Dataset (46.1%).

Table 94: Subjects With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 2% in Pembrolizumab KN040 Treatment Group) By Decreasing Frequency of Preferred Term (Subjects in ASaT Population Treated with MK-3475)

	KN040 data for MK-3475*		KN040, 012 and 055 data for MK-3475‖		Reference Safety Dataset for MK-3475††		Cumulative Running Safety Dataset for MK-3475¶	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		609		2,799		4,831	
with one or more adverse events	110	(44.7)	281	(46.1)	1,041	(37.2)	1,857	(38.4)
with no adverse events	136	(55.3)	328	(53.9)	1,758	(62.8)	2,974	(61.6)
Pneumonia	20	(8.1)	38	(6.2)	85	(3.0)	156	(3.2)
Tumour haemorrhage	9	(3.7)	12	(2.0)	3	(0.1)	16	(0.3)
Hypercalcaemia	7	(2.8)	14	(2.3)	12	(0.4)	31	(0.6)
Diarrhoea	6	(2.4)	9	(1.5)	26	(0.9)	49	(1.0)
Pneumonia aspiration	6	(2.4)	15	(2.5)	4	(0.1)	22	(0.5)
Pneumonitis	6	(2.4)	11	(1.8)	46	(1.6)	80	(1.7)

Drug-related serious adverse events (SAEs)

In the KN040 trial, drug-related SAEs were less often registered in the pembrolizumab group than in the overall standard treatment arm (8.9% *vs* 15.4%, respectively). More in detail, drug-related SAEs in pembrolizumab-treated patients were more frequent compared to patients receiving cetuximab (5.6%), and less common than in subjects receiving both methotrexate (17.2%) or docetaxel (21.2%).

Pembrolizumab-related SAEs occurring in two or more subjects were: *Pneumonitis* (1.6%), *Diarrhoea* (1.6%), and *Colitis* (0.8%); all other events were reported in a single subject.

The most frequently reported drug-related SAEs among subjects treated with standard treatment were *Febrile neutropenia* (3.4%), *Pneumonia*, *Neutrophil count decreased*, and *Stomatitis* (each 1.3%), *Diarrhoea*, *Sepsis*, and *Dehydration* (each 0.9%); all other events occurred in a single subject.

Frequency of drug-related SAEs was consistent between KN040 (8.9%) and the other Datasets (Pooled HNSCC Dataset 9.9%; Running Safety Dataset 10.0%; Cumulative Running Dataset 10.1%).
Drug-related SAEs of *Pneumonitis* and *Pneumonia* occurred at the same frequency in KN040 and in all the other Datasets (cumulative proportions were: 2.0% in KN040, 1.7% in the Pooled HNSCC Dataset, 1.9% in the Reference Safety Dataset, and 1.7% in the Cumulative Running Dataset).

Deaths

Analysis of deaths from AEs did not include events attributed to progression of malignant neoplasm or of disease that were not considered related to trial treatment.

Deaths for Pembrolizumab *vs* Standard Treatment in the KEYNOTE-040 (KN040) trial

Table 95: Summary of death reasons

	MK-3475 200 mg Q3W (N=247) n(%)	Standard Treatment (N=248) n(%)	Total (N=495) n(%)
Subjects who died	181 (73.3)	207 (83.5)	388 (78.4)
Progressive Disease	**143 (57.9)**	**164 (66.1)**	**307 (62.0)**
Adverse Event	**24 (9.7)**	**26 (10.5)**	**50 (10.1)**
Not Related	17 (6.9)	19 (7.7)	36 (7.3)
Related	7 (2.8)	7 (2.8)	14 (2.8)
Unknown	**14 (5.7)**	**17 (6.9)**	**31 (6.3)**
Withdrawal By Subject	3 (1.2)	4 (1.6)	7 (1.4)
Other	11 (4.5)	13 (5.2)	24 (4.8)
Database cutoff date: 15MAY2017			

Four subjects (1.6%) of the pembrolizumab arm were considered by the Investigator to have developed a drug-related fatal AE: *Stevens-Johnson syndrome, Death due to unknown cause, Malignant neoplasm progression, Large intestine perforation*.

In the standard treatment group, the following fatal events were registered: *Pneumonia* in 5 subjects (2.1%), *Death due to not specified cause* in 4 subjects (1.7%), *Tumor hemorrhage* and *Lung infection* each recorded in 2 subjects (0.9%). Other events leading to death in single subjects were: *Myocardial infarction, Mouth hemorrhage, Alcoholic cirrhosis, Respiratory tract infection, Septic shock, Euthanasia, Malignant neoplasm progression, Asphyxia, Pneumonia aspiration, Dyspnea, Pulmonary embolism, Respiratory tract hemorrhage.*

Two of these deaths were considered related to standard treatment by the Investigator (0.8%): *Pneumonia* and *Malignant neoplasm progression*.

Two deaths due to tumour haemorrhage both reported in the pembrolizumab KN040 treatment arm.

Deaths from the comparison of KN040 with the Pooled HNSCC Dataset, the Reference Safety Dataset, and the Cumulative Running Safety Dataset

The rate of AEs leading to death in the pembrolizumab-treated group of KN040 (8.1%) was higher than in the Reference Safety Dataset (3.9%) and the Cumulative Running Dataset (4.8%), but comparable to that of the Pooled HNSCC Dataset (8.9%) and similar to the KN040 standard treatment arm (10.7%).

Also, proportions of death due to pneumonia, death (cause not specified), tumour haemorrhage and respiratory failure were higher in subjects in the HNSCC population, both in study KN040 and pooled across studies in HNSCC, in comparison to the Reference Safety Dataset. The rate of *Pneumonia*, the most frequently reported AEs leading to death in KN040 pembrolizumab treatment group (2.4%), was higher compared to all the other datasets (1.3% in the Pooled Safety HNSCC Dataset, 0.4% in the Reference Safety Database).

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 in the pembrolizumab and standard treatment groups.

- In the pembrolizumab group, the only Grade 3-4 hematologic abnormalities reported in ≥5% of treated subjects with both baseline and post-baseline measurements were decreased haemoglobin (10.5 % Grade 3 only) and decreased lymphocytes (15.3 % Grade 3; 2.3 % Grade 4).
- In the standard treatment, the only Grade 3-4 hematologic abnormalities reported in ≥5% of subjects were decreased haemoglobin (10.3% Grade 3 only), decreased leukocytes (6.7% Grade 3; 5.3% Grade 4), decreased lymphocytes (26.1% Grade 3; 6.6% Grade 4), and decreased neutrophil count (6.6% Grade 3; 10.8% Grade 4).

The most frequent (>5%) ≥2-grade shifts from baseline to a Grade 3 or 4 hematologic abnormality included

- lymphopenia and anemia among pembrolizumab-treated subjects, and
- Lymphopenia, neutropenia, leukopenia, and anemia in the standard treatment group.

Electrolytes

Abnormalities in electrolyte tests performed during treatment or within 30 days of last dose of study drug were mainly Grade 1-2 in the pembrolizumab and standard treatment group.

- In the pembrolizumab group, the only Grade 3-4 electrolyte abnormalities reported in ≥5% of treated subjects with both baseline and post-baseline measurements were hypercalcaemia (3.2% Grade 3; 4.1% Grade 4), hyponatremia (8.1% Grade 3; 3.2% Grade 4) and hypophosphatemia (9.9% Grade 3 only)
- In the standard treatment group the only Grade 3-4 electrolyte abnormalities reported in ≥5% of treated subjects with both baseline and post-baseline measurements were hyponatremia (11.5% Grade 3; 1.9% Grade 4) and hypophosphatemia (8.2% Grade 3 only)

The most frequent (>5%) ≥2-grade shifts from baseline to a Grade 3 or 4 electrolyte abnormality included

- hyponatremia and hypophosphatemia among pembrolizumab-treated subjects, and
- hyponatremia and hypophosphatemia in the standard treatment group.

Hypercalcaemia

Proportions of subjects with laboratory abnormalities of increased calcium (hypercalcaemia) were similar in the KN040 population (24.2%) and in the total HNSCC population (21.1 %), but lower in the Reference Safety Dataset (8.0%).

For comparison, distribution by maximum toxicity Grade is shown for the AEs of hypercalcaemia and hypercalcaemia of malignancy.

Proportions of the AE hypercalcaemia were higher in the in the KN040 population (7.7%) and in the total HNSCC population (9.0%), but lower in the Reference Safety Dataset (2.0%). Numbers and proportions of the drug-related AE hypercalcaemia were low in the KN040 population (n=1 [0.4%]) and in the total HNSCC population (n=3 [0.5]™) and in the Reference Safety Dataset (n=6 [0.2%]).

Table 96: Summary of Subjects with Increases in Highest Laboratory Test Toxicity Grade from Baseline – Calcium increased (Overall Incidence > 0% in One or More Treatment Groups) (Subjects with both Baseline and Post-baseline Measurements) (ASaT population)

Laboratory Test	MK-3475 200 mg Q3W (N=246) n	(%)	Standard Treatment (N=234) n	(%)
Calcium Increased (Hypercalcemia)				
Subjects with Baseline and Post-baseline Measurements	219		206	
Grade 1	27	(12.3)	20	(9.7)
Grade 2	10	(4.6)	7	(3.4)
Grade 3	7	(3.2)	2	(1.0)
Grade 4	9	(4.1)	8	(3.9)
Grade 3-4	16	(7.3)	10	(4.9)
All Grades	53	(24.2)	37	(18.0)

Table 97: Subjects with Adverse Events Hypercalcaemia and Hypercalcaemia of malignancy by Maximum Toxicity Grade in One or More Treatment Groups) (ASaT Population)

	MK-3475 200 mg Q3W		Standard Treatment	
	n	(%)	n	(%)
Hypercalcaemia	19	(7.7)	13	(5.6)
Grade 1	2	(0.8)	8	(3.4)
Grade 2	8	(3.3)	4	(1.7)
Grade 3	7	(2.8)	1	(0.4)
Grade 4	2	(0.8)	0	(0.0)
Hypercalcaemia of malignancy	3	(1.2)	2	(0.9)
Grade 1	0	(0.0)	1	(0.4)
Grade 3	2	(0.8)	1	(0.4)
Grade 4	1	(0.4)	0	(0.0)

Liver function tests

In both treatment groups, liver function test (LFT) abnormalities during treatment or within 30 days of last dose of study drug were primarily Grade 1 to 2 in severity.

- Grade 3-4 liver function test abnormalities were recorded in less than 5% of treated subjects with both baseline and post-baseline measurements;
- ≥2-grade shifts from baseline to a Grade 3 or 4 liver function test abnormality were recorded in less than 5 % in both treatment groups.

Data were additionally analysed according to predetermined criteria for detection of drug-induced liver injury.

The most frequent liver function finding observed in both treatment groups was ALT and AST elevations; a higher proportion of liver laboratory abnormalities was reported in the standard treatment group.

Table 98: Subjects With Liver Function Laboratory Findings That Met Predetermined Criteria (ASaT Population)

Criteria	MK-3475 200 mg Q3W		Standard Treatment	
	n/m	(%)	n/m	(%)
Alanine Aminotransferase				
≥3 x ULN	6/246	(2.4)	18/234	(7.7)
≥5 x ULN	2/246	(0.8)	9/234	(3.8)
≥10 x ULN	1/246	(0.4)	5/234	(2.1)
≥20 x ULN	1/246	(0.4)	2/234	(0.9)
Aspartate Aminotransferase				
≥3 x ULN	8/246	(3.3)	19/234	(8.1)
≥5 x ULN	4/246	(1.6)	10/234	(4.3)
≥10 x ULN	2/246	(0.8)	4/234	(1.7)
≥20 x ULN	1/246	(0.4)	1/234	(0.4)
Aminotransferase (ALT or AST)				
≥3 x ULN	11/246	(4.5)	24/234	(10.3)
≥5 x ULN	4/246	(1.6)	13/234	(5.6)
≥10 x ULN	2/246	(0.8)	5/234	(2.1)
≥20 x ULN	1/246	(0.4)	3/234	(1.3)
Bilirubin				
≥2 x ULN	6/246	(2.4)	6/234	(2.6)
Alkaline Phosphatase				
≥1.5 x ULN	37/246	(15.0)	26/233	(11.2)
Aminotransferase (ALT or AST) and Bilirubin				
AT ≥3 x ULN and BILI ≥1.5 x ULN	4/246	(1.6)	3/234	(1.3)
AT ≥3 x ULN and BILI ≥2 x ULN	3/246	(1.2)	2/234	(0.9)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	1/246	(0.4)	0/234	(0.0)

n = Number of Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
Database Cutoff Date: 15MAY2017

Source: [P040V01MK3475: adam-adsl; addili]

Renal function tests

Abnormalities in creatinine measurements performed during treatment or within 30 days of last dose of study drug were mostly Grade 1-2 in the pembrolizumab and standard treatment group

- Grade 3-4 renal function test abnormalities were recorded in less than 5% of treated subjects with both baseline and post-baseline measurements;
- ≥2-grade shifts from baseline to a Grade 3 or 4 renal function test abnormality were recorded in less than 5 % in both treatment groups.

Thyroid function tests

Thyroid function tests (thyroid stimulating hormone [TSH], total T3 [T3], and free thyroxine [FT4]) were done at baseline and throughout the trial in all subjects.

There are no data analysing the thyroid function test results with respect to prior radiation status.

Table 99: Summary of Subjects with Normal Baseline TSH and FT4 and Abnormal Post-baseline TSH and/or FT4 Value at the Same Visit (ASaT Population)

Category	MK-3475 200 mg Q3W		Standard Treatment		Total	
	n	%	n	%	n	%
Number of Subjects	246		234		480	
Normal baseline TSH and FT4	143		124		267	
Normal baseline TSH and FT4 and at least one post baseline abnormality in either TSH or FT4:	67	46.9	32	25.8	99	37.1
High TSH and Normal FT4 (Subclinical-Hypothyroidism)	41	28.7	23	18.5	64	24.0
High TSH and Low FT4 (Primary Hypothyroidism)	15	10.5	2	1.6	17	6.4
Normal or Low TSH and Low FT4 (Secondary Hypothyroidism)	18	12.6	5	4.0	23	8.6
Low TSH and Normal FT4 (Subclinical Hyperthyroidism)	15	10.5	4	3.2	19	7.1
Low TSH and High FT4 (Primary Hyperthyroidism)	8	5.6			8	3.0
Every subject is counted a single time for each applicable row and column. Database Cutoff Date: 15MAY2017						

Source: [P040V01MK3475: adam-adsl; adlb]

Safety in special populations

Safety was evaluated in subgroups defined by intrinsic and extrinsic factors (age, gender, ECOG performance status, and region). Some differences were found with regards to gender and performance status.

Safety profile by Age

The proportion of drug-related AEs was higher in the cohort ≥65 years (77.8%) in the pembrolizumab arm as compared to the cohort <65 years (55.8%), but similar to the respective cohort in the standard treatment arm (77.0%).

Only few patients ≥75 years were treated in the study, 19 in the pembrolizumab group and 10 in the standard treatment group. Of these, 1 subject in the pembrolizumab arm was ≥85 years, and none in the standard treatment arm.

Proportion of subjects ≥65 years was lower in the KN040 population (32.9%) than in Reference Safety Dataset (43.3%). No data on the safety profile was provided for the subgroups of subjects ≥75 to < 85 years and ≥85 years.

Table 100: Adverse Event Summary by Age in the KN040 trial (ASaT population)

	Age (Years)													
	MK-3475 200 mg Q3W								Standard Treatment					
	< 65		>= 65 to < 75		>= 75 to < 85		>= 85		< 65		>= 65 to < 75		>= 75 to < 85		>= 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	165		62		18		1		160		64		10		0	
with one or more adverse events	158	(95.8)	61	(98.4)	18	(100)	1	(100)	155	(96.9)	62	(96.9)	10	(100)	0	(0.0)
Who died	15	(9.1)	2	(3.2)	3	(16.7)	0	(0.0)	18	(11.3)	6	(9.4)	1	(10.0)	0	(0.0)
with serious adverse events	74	(44.8)	26	(41.9)	10	(55.6)	0	(0.0)	63	(39.4)	23	(35.9)	6	(60.0)	0	(0.0)
discontinued due to an adverse event	22	(13.3)	3	(4.8)	3	(16.7)	0	(0.0)	21	(13.1)	12	(18.8)	4	(40.0)	0	(0.0)
CNS (confusion/extrapyramidal)	11	(6.7)	4	(6.5)	0	(0.0)	0	(0.0)	12	(7.5)	2	(3.1)	0	(0.0)	0	(0.0)
AE related to falling	9	(5.5)	4	(6.5)	3	(16.7)	0	(0.0)	8	(5.0)	5	(7.8)	0	(0.0)	0	(0.0)
CV events	28	(17.0)	12	(19.4)	1	(5.6)	0	(0.0)	27	(16.9)	6	(9.4)	0	(0.0)	0	(0.0)
Cerebrovascular events	2	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	2	(3.1)	0	(0.0)	0	(0.0)
Infections	65	(39.4)	24	(38.7)	12	(66.7)	0	(0.0)	75	(46.9)	24	(37.5)	5	(50.0)	0	(0.0)
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment. Database Cutoff Date: 15MAY2017.														

Safety profile by Gender

In the KN040 trial, women accounted for only 16.3% (40 subjects) of the total population.

Table 101: Adverse Event Summary by Gender in the KN040 trial

	MK-3475 200 mg Q3W				Standard Treatment			
	M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	206		40		194		40	
with one or more adverse events	199	(96.6)	39	(97.5)	188	(96.9)	39	(97.5)
with no adverse event	7	(3.4)	1	(2.5)	6	(3.1)	1	(2.5)
with drug-related† adverse events	133	(64.6)	22	(55.0)	162	(83.5)	34	(85.0)
with toxicity grade 3-5 adverse events	119	(57.8)	24	(60.0)	116	(59.8)	22	(55.0)
with toxicity grade 3-5 drug-related adverse events	26	(12.6)	7	(17.5)	70	(36.1)	15	(37.5)
with serious adverse events	90	(43.7)	20	(50.0)	78	(40.2)	14	(35.0)
with serious drug-related adverse events	17	(8.3)	5	(12.5)	31	(16.0)	5	(12.5)
with dose modification‡ due to an adverse event	68	(33.0)	16	(40.0)	91	(46.9)	15	(37.5)
who died	13	(6.3)	7	(17.5)	21	(10.8)	4	(10.0)
who died due to a drug-related adverse event	1	(0.5)	3	(7.5)	1	(0.5)	1	(2.5)
discontinued drug due to an adverse event	20	(9.7)	8	(20.0)	34	(17.5)	3	(7.5)
discontinued drug due to a drug-related adverse event	9	(4.4)	6	(15.0)	10	(5.2)	2	(5.0)
discontinued drug due to a serious adverse event	18	(8.7)	6	(15.0)	26	(13.4)	1	(2.5)
discontinued drug due to a serious drug-related adverse event	7	(3.4)	4	(10.0)	5	(2.6)	0	(0.0)

† 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 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 15MAY2017

Safety profile by Performance Status

As expected, in the KN040 trial patients with performance status of 1 had worse safety profile than those with ECOG of 0 in both treatment groups (ECOG >1 was a trial exclusion criterion). Details are presented in the table below:

Table 102: Adverse Event Summary by Performance Status in the KN040 trial

	MK-3475 200 mg Q3W				Standard Treatment			
	0		1		0		1	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	71		175		64		170	
with one or more adverse events	68	(95.8)	170	(97.1)	61	(95.3)	166	(97.6)
with no adverse event	3	(4.2)	5	(2.9)	3	(4.7)	4	(2.4)
with drug-related† adverse events	42	(59.2)	113	(64.6)	58	(90.6)	138	(81.2)
with toxicity grade 3-5 adverse events	32	(45.1)	111	(63.4)	32	(50.0)	106	(62.4)
with toxicity grade 3-5 drug-related adverse events	6	(8.5)	27	(15.4)	25	(39.1)	60	(35.3)
with serious adverse events	20	(28.2)	90	(51.4)	16	(25.0)	76	(44.7)
with serious drug-related adverse events	2	(2.8)	20	(11.4)	9	(14.1)	27	(15.9)
with dose modification‡ due to an adverse event	20	(28.2)	64	(36.6)	21	(32.8)	85	(50.0)
who died	1	(1.4)	19	(10.9)	3	(4.7)	22	(12.9)
who died due to a drug-related adverse event	0	(0.0)	4	(2.3)	2	(3.1)	0	(0.0)
discontinued drug due to an adverse event	4	(5.6)	24	(13.7)	5	(7.8)	32	(18.8)
discontinued drug due to a drug-related adverse event	3	(4.2)	12	(6.9)	3	(4.7)	9	(5.3)
discontinued drug due to a serious adverse event	2	(2.8)	22	(12.6)	2	(3.1)	25	(14.7)

Table 103: Adverse event summary by ECOG status category (0, 1) (Subjects in ASaT population treated with MK-3475)

	KN040 data for MK-3475*				KN040, 012 and 055 data for MK-3475‖				Reference Safety Dataset for MK-3475††				Cumulative Running Safety Dataset for MK-3475¶			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	71		175		176		430		1,446		1,347		2,149		2,509	
with one or more adverse events	68	(95.8)	170	(97.1)	172	(97.7)	417	(97.0)	1,417	(98.0)	1,305	(96.9)	2,094	(97.4)	2,424	(96.6)
with no adverse event	3	(4.2)	5	(2.9)	4	(2.3)	13	(3.0)	29	(2.0)	42	(3.1)	55	(2.6)	85	(3.4)
with drug-related# adverse events	42	(59.2)	113	(64.6)	118	(67.0)	268	(62.3)	1,149	(79.5)	911	(67.6)	1,608	(74.8)	1,648	(65.7)
with toxicity grade 3-5 adverse events	32	(45.1)	111	(63.4)	69	(39.2)	276	(64.2)	588	(40.7)	682	(50.6)	872	(40.6)	1,366	(54.4)
with toxicity grade 3-5 drug-related adverse events	6	(8.5)	27	(15.4)	14	(8.0)	68	(15.8)	201	(13.9)	184	(13.7)	283	(13.2)	388	(15.5)
with non-serious adverse events	66	(93.0)	162	(92.6)	169	(96.0)	399	(92.8)	1,404	(97.1)	1,263	(93.8)	2,071	(96.4)	2,351	(93.7)
with serious adverse events	20	(28.2)	90	(51.4)	46	(26.1)	232	(54.0)	466	(32.2)	572	(42.5)	671	(31.2)	1,112	(44.3)
with serious drug-related adverse events	2	(2.8)	20	(11.4)	8	(4.5)	51	(11.9)	148	(10.2)	133	(9.9)	198	(9.2)	274	(10.9)
with dose modification‡ due to an adverse event	20	(28.2)	64	(36.6)	45	(25.6)	171	(39.8)	423	(29.3)	459	(34.1)	596	(27.7)	872	(34.8)
who died	1	(1.4)	19	(10.9)	5	(2.8)	48	(11.2)	38	(2.6)	71	(5.3)	60	(2.8)	159	(6.3)
who died due to a drug-related adverse event	0	(0.0)	4	(2.3)	1	(0.6)	4	(0.9)	4	(0.3)	6	(0.4)	7	(0.3)	16	(0.6)
discontinued drug due to an adverse event	4	(5.6)	24	(13.7)	10	(5.7)	73	(17.0)	148	(10.2)	185	(13.7)	185	(8.6)	320	(12.8)
discontinued drug due to a drug-related adverse event	3	(4.2)	12	(6.9)	6	(3.4)	29	(6.7)	82	(5.7)	64	(4.8)	104	(4.8)	128	(5.1)
discontinued drug due to a serious adverse event	2	(2.8)	22	(12.6)	6	(3.4)	60	(14.0)	104	(7.2)	148	(11.0)	131	(6.1)	258	(10.3)

Safety profile by Region

The overall incidence of AEs reported in the US was similar to ex-US in both treatment groups. No notable differences were found in the pembrolizumab-treated arm due to region. In the standard treatment group, a higher proportion of subjects in the ex-US region experienced Grade 3 to 5 AEs (including drug-related), SAEs, dose modifications, and deaths (≥5% difference).

Safety related to drug-drug interactions and other interactions

This issue is not applicable because no specific studies have been performed on food or drug-drug interactions with pembrolizumab. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a PK DDI with pembrolizumab as a victim was assessed as part of the population PK analysis. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure.

Discontinuation due to adverse events

AEs leading to treatment discontinuation

Table 104: Subjects with adverse events resulting in treatment discontinuation by decreasing incidence by treatment (incidence > 0% in one or more treatment groups) (ASaT population)

	MK-3475 200 mg Q3W		Methotrexate		Cetuximab		Docetaxel	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	246		64		71		99	
with one or more adverse events	28	(11.4)	15	(23.4)	7	(9.9)	15	(15.2)
with no adverse events	218	(88.6)	49	(76.6)	64	(90.1)	84	(84.8)
Pneumonia	6	(2.4)	2	(3.1)	0	(0.0)	1	(1.0)
Death	2	(0.8)	0	(0.0)	0	(0.0)	2	(2.0)
Respiratory failure	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
Stevens-Johnson syndrome	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)

The proportion of drug-related AEs leading to treatment discontinuation in the KN040 trial was comparable among the two treatment arms (6.1% *vs* 5.1%, in the pembrolizumab and the standard

treatment arm, respectively). *Stevens-Johnson syndrome* was the only drug-related AE leading to treatment discontinuation in >1 subject (2 subjects [0.8%]) in the pembrolizumab arm.

The proportion of subjects with AEs (regardless causality) leading to treatment discontinuation in KN040 and the other Datasets was comparable and ranged from 10.9% to 13.8%.

Rate of drug-related AEs leading to treatment discontinuation in the KN040 trial (6.1%) was similar to that observed in the Reference Safety Dataset (5.2%). In both, the Pooled HNSCC Dataset and the Reference Safety Dataset, the most common drug-related AE leading to treatment discontinuation was *Pneumonitis* (5 subjects [0.8%] and 34 subjects [1.2%], respectively, *vs* 1 subject [0.4%] in KN040).

AEs leading to treatment Interruption

AEs leading to treatment discontinuation for Pembrolizumab *Versus* Standard Treatment in KEYNOTE-040 (KN040)

In the KN040 trial, the rate of dose interruption was similar between the two arms (26.4% *vs* 29.9% in pembrolizumab and standard treatment group, respectively). The most frequently recorded AEs (regardless causality) resulting in treatment interruption in ≥ 2% of subjects were *Anaemia* and *Pneumonia* in both treatment arms. In addition, *Stomatitis* and *Neutrophils count decreased* also resulted in treatment interruption of the standard treatment in ≥2% of patients. Drug-related AEs leading to treatment interruption were instead less common with pembrolizumab (9.8% *vs* 20.1% in pembrolizumab arm *vs* standard treatment arm, respectively), most common being *Anaemia* and *Pneumonitis* with pembrolizumab, *vs Stomatitis* and haematological toxicity with standard treatment.

AEs leading to treatment interruption from the comparison of KN040 with the Pooled HNSCC Dataset, the Reference Safety Dataset, and the Cumulative Running Safety Dataset

When comparing the KN040 trial population to that of the other datasets, rate of AEs (regardless causality) leading to treatment interruption was comparable (26.4% and 22.2%, respectively in the KN040 trial and the Reference Safety Dataset).

Frequency of drug-related AEs leading to treatment interruption was similar among the pembrolizumab-treated KN040 population (9.8%) and the Reference Safety Dataset (12.5%). The majority of drug-related AEs leading to treatment interruption in the pembrolizumab-treated KN040 population were reported in a single subject. Of those events reported in >1 subject, *Anaemia*, *Pneumonitis*, *Rash*, and *Infusion-related reaction* were more frequent in the KN040 population than in the Reference Safety Dataset.

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-Mar-2017 through 03-Sep-2017 (EMEA/H/C/PSUSA/00010403/201709).

As a result of the review of the PSUR, the SmPC section 4.8 was updated to add pericarditis and pericardial effusion as new adverse drug reactions (ADR) with a frequency uncommon and to add a footnote to the existing ADR 'myasthenic syndrome' to indicate that the event 'myasthenia gravis' is included.

2.5.1. Discussion on clinical safety

The evaluation of pembrolizumab safety profile in subjects with disease progression on or after platinum-containing chemotherapy for R/M HNSCC is based on the pivotal KN040 trial, comparing pembrolizumab (N=246) to the investigator's choice of standard treatments (N=234). A Reference Safety

Dataset (including 2799 subjects with melanoma and NSCLC treated with pembrolizumab monotherapy from clinical trials KN001, KN002, KN006 and KN010) was provided to allow for comparison of the KN040 safety profile with pembrolizumab used for other indications. The Pooled HNSCC Dataset, comprising participants in three pembrolizumab R/M HNSCC trials (KN040, KN12 and KN055, N=609), and the Cumulative Running Dataset, including data from all pembrolizumab trials submitted to regulatory authority up to 4 weeks prior to the data cut-off for KN040 (15 MAY 2017) (N=4831), were also included for evaluation of an integrated safety analysis in the HNSCC setting and across multiple indications. For a more appropriate safety evaluation, the MAH has been asked to provide an Integrated Summary of Safety for all indications authorized in the EU (advanced melanoma, NSCLC, urothelial carcinoma and Hodgkin's lymphoma altogether comprising 3,830 subjects), along with further comparative tables. Review of the data provided did not reveal relevant changes to the reference safety dataset of 2,799 subjects submitted with the initial application. There were no new safety signals. The primary safety analysis population presented in this application is the ASaT population, which includes all enrolled subjects who were randomized and received at least 1 dose of pembrolizumab in KN040 (N=246). Data cut-off date was 15-MAY-2017.

In the KN040 trial, drug exposure was slightly longer for pembrolizumab-treated subjects (median study days 85) than for those receiving standard HNSCC treatment (cetuximab 71; methotrexate 43; docetaxel 53). Further, drug exposure was lower in HNSCC subjects of the KN040 and the Pooled HNSCC Dataset in respect to the Reference Safety and the Cumulative Running Safety Datasets. Main patient characteristics were similar in KN040 and in the Pooled HNSCC Dataset. Compared to the Reference Safety or the Cumulative Running Safety Datasets, KN040 participants were more often male gender, aged <65 years, enrolled outside the US, and with ECOG of 1. The HNSCC population appears to be sicker than the population in the Reference Safety Dataset considering the high proportion of subjects with a baseline ECOG status of 1 and the less favourable safety profile. Differences in drug exposure and patient characteristics among datasets were likely due to epidemiological and clinical features associated with R/M HNSCC.

Overall, the adverse event summary demonstrated a favourable safety profile for pembrolizumab compared to standard treatment options (cetuximab, docetaxel, or methotrexate) mainly due to lower frequencies of drug-related toxicity (drug-related AEs 63% *vs* 83.8%, drug-related Grade 3-5 AEs 13.4% *vs* 36.3%, drug-related SAEs 8.9% *vs* 15.4%, drug-related discontinuations 11.4% vs 15.8%) and deaths (8.1% *vs* 10.7%). Differently, SAEs (44.7% *vs* 39.3%), and discontinuation due to SAEs (4.5% *vs* 2.1%) or to drug-related AEs (6.1% *vs* 5.1%) were slightly more common with pembrolizumab than with standard treatment. In addition, it is noted that drug-related grade 3-5 AEs did not differ significantly in pembrolizumab- compared to cetuximab-treated patients (13.4% vs 16.9%).

Exposure-adjusted incidence rate of AEs and of Grade 3-5 AEs were lower for the pembrolizumab arm than for the standard treatment group (628.28 *vs* 1147.61 x 100 and 316.31 *vs* 502.25 x 100 person-years of exposure, respectively). Also, exposure-adjusted rates of individual AEs (incidence ≥10%) were lower in the pembrolizumab treatment group in comparison to the standard treatment group with the exception of hypothyroidism.

The adverse event profile of both study arms reflects the well-known differences and is related to the different mode of actions of pembrolizumab and chemotherapeutics. Adverse events regardless of causality were recorded in 96.7% and 97.0% in the pembrolizumab and standard treatment arms, respectively. AEs by SOCs occurring more often in the standard treatment than in the pembrolizumab arm belonged to the following: *General disorders and administration site conditions* (52.8% *vs* 65.4%), *Investigations* (26.8% *vs* 39.3%), *Skin and subcutaneous tissue disorders* (30.1% *vs* 50%). On the contrary, *Endocrine disorders* (17.5% *vs* 5.1%), and *Respiratory, thoracic and mediastinal disorders* (47.2% *vs* 38.5%) were more frequently recorded with pembrolizumab than with standard treatment.

Among PTs, *Anaemia* (26.8% *vs* 22.6% in pembrolizumab and standard treatment arm, respectively) and *Fatigue* (19.5% *vs* 26.9%) were the most often observed AEs in both treatment arms. *Hypothyroidism* was more commonly reported in the pembrolizumab arm compared to the standard treatment group (15% *vs* 3.8%), and risk difference was in favour of standard treatment; differently, *Mucosal inflammation*, *Stomatitis*, *Neutrophil count decreased* and *Alopecia* were more often registered in subjects receiving standard treatment, with risk difference favouring pembrolizumab.

At specific treatment comparisons, *Hypothyroidism* was steadily more frequently reported in pembrolizumab-treated subjects than in cetuximab-, methotrexate-, or docetaxel-treated participants. As expected, cetuximab showed a different safety profile compared to chemotherapy, with the highest difference in favour of pembrolizumab *vs* cetuximab reported for skin toxicities and hypomagnesaemia.

Among Grade 3-5 AEs (58.1% in pembrolizumab and 59.0% in the standard treatment), *Pneumonia* (9.3% *vs* 6.0%) and *Anaemia* (6.1% *vs* 6.0%) were the most common in pembrolizumab-treated subjects; differently, *Neutrophil count decreased* was the most frequent Grade 3-5 AE in the standard treatment arm (8.5% vs 0.4%).

Frequencies of SAEs were higher in pembrolizumab-treated subjects (44.7% vs 39.3%). SAEs most frequently reported (>2.0 %) were *Pneumonia* (8.1%), *Tumour haemorrhage* (3.7%), *Hypercalcaemia* (2.8%), *Diarrhea*, *Pneumonia aspiration*, and *Pneumonitis* (2.4% each) in subjects treated with pembrolizumab, and pneumonia (6.8%) and *Febrile neutropenia* (3.8%) in subjects treated with standard treatment. 2 SAEs, *Tumour haemorrhage* and *Hypercalcaemia*, accounted largely for the overall higher proportion of SAEs in the pembrolizumab treatment arm.

In terms of drug-related AEs, the most often observed drug-related AEs in the pembrolizumab arm (incidence >5%) were *Hypothyroidism* (13.4% *vs* 0.9%), *Fatigue* (12.6% *vs* 18.4%), *Diarrhoea* (8.1% *vs* 10.3%), *Rash* (7.7% *vs* 14.5%), *Asthenia* (7.3% *vs* 12%), *Anaemia* (6.9 *vs* 14.1), and *Decreased appetite* (5.7% *vs* 9.4%). All events, except hypothyroidism, had higher rates in the standard treatment compared to the pembrolizumab arm. Toxicity Grade 3-5 drug-related AEs more often seen in the pembrolizumab arm were *Diarrhea* (1.6% *vs* 0.4%) and *Fatigue* (1.6% *vs* 0.9%), while the most frequently observed in the standard treatment arm were *Neutrophil count decreased* (0.4% *vs* 8.5%), *Stomatitis* (0.4% *vs* 4.7%) and *Febrile neutropenia* (0% *vs* 4.3%). Notably, time to first drug-related Grade 3-5 AE was shorter in the group receiving standard treatment in respect to that treated with pembrolizumab.

Among drug-related SAEs, events occurring in two or more pembrolizumab-treated subjects were *Pneumonitis* (1.6%), *Diarrhoea* (1.6%), and *Colitis* (0.8%). The most frequently reported drug-related SAEs among subjects treated with standard treatment were *Febrile neutropenia* (3.4%), *Pneumonia*, *Neutrophil count decreased*, and *Stomatitis* (each 1.3%).

Frequency of AEs leading to death was quite similar across the KN040 study arms (20/246 [8.1%] *vs* 25/234 [10.7%]), and in both treatment arms the most common cause was *Pneumonia* (2.4% *vs* 2.1%).

The 20 deaths reported in the KN040 pembrolizumab-treated arm were due to: *Pneumonia* in 6 subjects (2.4%), *Death with unknown cause* in 5 subjects (2%), *Tumor hemorrhage*, and *Respiratory failure* in 2 subjects each (0.8%). Further, *Stevens-Johnson syndrome*, *Malignant neoplasm progression*, *Alcohol poisoning*, *Fall*, and *Large intestine perforation* were recorded in a single case each. None of the 5 subjects who died due to unknown cause, underwent autopsy. In one of these cases, the Investigator judged the event to be related to pembrolizumab. As the narratives provided only scarce in information, it is not possible to assess study drug causality.

Four subjects (1.6%) of the pembrolizumab arm were judged by the Investigator to have developed a drug-related, immune-related, fatal AE: *Stevens-Johnson syndrome, Death due to unknown cause,*

Malignant neoplasm progression, Large intestine perforation. Relation with the study drug was considered unlikely by the MAH, because of confounding variables (limited data available, concomitant antibiotics intake, progression of underlying neoplasm, concomitant disorder). Based on the existing information, causality of the fatal event with the study drug is however considered to be as follows:

- "Probably-related" in one case of fatal *Stevens-Johnson syndrome*: even though acknowledging confounding co-medications, temporal relationship between exposure and event occurrence are plausible. Diagnosis was biopsy-proven. Stevens-Johnson syndrome (including fatal events) is a known adverse drug reaction associated with pembrolizumab and addressed in the current SmPC for Keytruda.

- "Probably-related" in one subject with *Large intestine perforation*: immune-mediated AE with perforation of the intestine is listed in SmPC. Though biologic causality is plausible and time to onset is appropriate, association with mesenteric ischemia is likely. It is agreed that peripheral artery disease is a confounding factor;
- "Possibly-related" in one case with *Death due to unknown cause*: causality with the study drug cannot be excluded, given the temporal relationship. No active comorbid condition, relevant comedication, or life-style health risks were recorded;
- "Unlikely-related" in one case with *Malignant disease progression*: disease progression is a more plausible explanation for the fatal event.

Two deaths in the control arm were considered related to standard treatment (0.8%): *Pneumonia* and *Malignant neoplasm progression*.

The Applicant provided a tabular overview of all 388 deaths by category. Most subjects died due to progressive disease in both the pembrolizumab group and standard treatment group (57.9% and 66.1%, respectively). Two deaths due to tumour haemorrhage resulted from carotid artery bleeding (verbatims acute arterial bleed from tumour in one subject and tumour bleeding from carotid artery) in another subject , both in the pembrolizumab KN040 treatment arm. Another death due to bleeding from the carotid arteryin a subject) treated for HNSCC was reported from the uncontrolled phase Ib study 3475-012. Based on the medical review of the bleeding events, the MAH concluded that the higher incidence of haemoptysis and tumour haemorrhage in the pembrolizumab was not drug-related, but rather related to the underlying disease. Currently, it cannot be conclusively decided whether the higher incidences of these 2 bleeding events in the pembrolizumab arm might be possibly associated with pembrolizumab or were rather a chance finding. In the latter case AEs of tumor haemorrhage or haemoptysis would be expected to be more balanced between treatment arms in further randomized clinical trials of pembrolizumab in the indication HNSCC. It might be considered to describe the information regarding the imbalance in bleeding events between treatment arms in the SmPC. However, data are currently limited to one randomized study. The Applicant reviewed all SAEs of haemorrhage with respect to associated carotid artery bleeding both in the KN040 population and in HNSCC population as per CHMP request. No new safety signal was detected.

At comparison of KN040 pembrolizumab-treated subjects with the other submitted Datasets, the overall frequency of AEs (regardless causality) was similar in the KN040 and the Reference Safety Dataset (96.7% *vs* 97.4%, respectively). Considering the comparable pattern of fatal SAEs in both treatment arms in study KN040, the higher frequency of fatal SAEs as compared to the Reference Safety Dataset seems to generally reflect the course of the underlying disease.

Individual AEs registered with higher frequency in the KN040 population than in the Reference Safety Dataset were: *Anaemia* (26.8% *vs* 12.4%), *Hypothyroidism* (15% *vs* 8.4%), *Pneumonia* (11% *vs* 5%), and *Dysphagia* (9.8% *vs* 2.1%).

Drug-related AEs were quite comparable in KN040 pembrolizumab-treated subjects (63%) and the population of the Reference Safety Dataset (69.3%). Only *Hypothyroidism* (13.4% *vs* 7.6%) and *Anaemia* (6.9% *vs* 3.4%) had higher rates in the trial than in the Reference Safety Dataset. Nevertheless, frequency and profile were superimposable to that of the Pooled HNSCC Dataset (63.5%). Frequency of drug-related grade 3-5 AEs consistently ranged from 13.4% to 14.4% across all Datasets.

Proportion of SAEs was to some extent higher among HNSCC patients treated with pembrolizumab either in the KN040 trial (44.7%) or in the Pooled HNSCC Dataset (46.1%), when compared to subjects included in the Reference Safety (37.2%) or the Cumulative Running Safety (38.4%) Datasets. Frequency of drug-related SAEs was instead consistent among all datasets (range 8.9%-10%). When summarizing the individual SAEs of *Pneumonia*, *Pneumonia aspiration* and *Pneumonitis*, the rate appeared higher in HNSCC compared to the other safety datasets. When the SOC *Respiratory, thoracic and mediastinal disorders* is analysed, no substantial differences have been observed across datasets. In the KN040 trial (8.1%) and the Pooled HNSCC Dataset (8.1%) AEs leading to death rates were twice as high as that of the Reference Safety Dataset (3.9%). Unbalance is seen in the rate of *Pneumonia*, which was higher in KN040 (2.4%) and in Pooled HNSCC Dataset (1.3%) compared to the Reference Safety Dataset (0.6%).

The number of elderly subjects ≥75 years included in the ASaT population is low (18 subjects in the age group between ≥75 years and <85 years, and 1 subject ≥85years in the pembrolizumab arm), and no conclusions can be drawn regarding subjects ≥75 years due to limited dataset. Based on the provided data, no concerns are raised, when analyzing safety profile across different levels of age. As expected, ECOG performance status had a marked influence on the safety profile in both treatment groups, with higher frequencies of Grade 3 to 5 AEs, SAEs, deaths, dose modifications and discontinuations from treatment in subjects with ECOG status of 1 at baseline compared to ECOG status of 0. With regard to gender, though comparison of overall AEs was similar among males and females, women had a higher frequency of overall and drug-related SAEs, deaths, and treatment modifications, as well as discontinuations. This finding has not been confirmed in the Reference Safety Dataset, where no major difference has been observed among gender, and could be influenced by the underrepresentation of female participants included in HNSCC trials (predictable based on epidemiology of HNSCC). The MAH was asked to discuss this apparent difference in safety profile by gender. It is acknowledged that pembrolizumab-related AEs are higher in male compared to female (64.6% vs 55%). On the contrary, slightly higher frequencies of drug-related SAE, and drug-related AEs leading to death and discontinuation were observed in female compared to male. The limited number of women in the pembrolizumab arm could have influenced the reported differences, although the small subgroup is not allowing reaching solid conclusion.

The MAH has provided adverse events summary tables according to PD-L1 expression (CPS <1 vs CPS ≥1; and CPS <10 vs CPS ≥10), as requested, as well as exposure-adjusted AEs (data not shown). Overall, the safety profile of pembrolizumab does not appear to be impacted by PD-L1 status. With regards to AEOSIs (which include Immune-mediated events and Infusion-related reactions), no new immune-mediated events associated with pembrolizumab treatment for R/M HNSCC were identified. However, a higher rate of pembrolizumab-related hypothyroidism was seen in the KN040 pembrolizumab arm (13.4%) and consistently in the Pooled HNSCC Dataset (11.2%), compared to both the KN040 standard treatment group (0.9%) and to the Reference Safety Dataset (7.6%). Grade of hypothyroidism was generally 1-2, and no SAE or deaths have been related to this type of event. Almost all subjects (95%) with hypothyroidism had previously received radiotherapy. Only very few subjects were treated with systemic corticosteroids, that were started at low dose. At study cut-off date, 67% of the events remained unresolved with the need of long-term hormone replacement therapy. No difference was observed in severity nor in the management of hypothyroidism in subjects with HNSCC compared to subjects treated with pembrolizumab for other indications, with the exception of a shorter median time to onset of first hypothyroidism event (64 days in both KN040 and Pooled HNSCC Dataset *vs* 106 and 103

days in the Reference Safety and in the Cumulative Running Safety Datasets, respectively). The MAH included in Section 4.4 of the SmPC, a warning for the more frequent occurrence of hypothyroidism in HNSCC patients receiving pembrolizumab and previously treated with RT, as requested.

The MAH analyzed specifically the AEOSI Oedema, as previous pembrolizumab R/M HNSCC trials frequently reported the occurrence of localized oedema. In the KN040 trial, proportions of drug-related oedema were comparable between the two arms (2.9% *vs* 2.1% for pembrolizumab and standard treatment, respectively), and the majority of events were low grade and not impacting on treatment. Frequencies of the 5 most common oedema events were similar in the pembrolizumab treatment group and the total HNSCC population, but higher when compared to the Reference Safety Dataset. Therefore, based on the data provided, oedema does not raise major concerns. Oedema (comprising the following terms: oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localized oedema and periorbital oedema) is listed in section 4.8 of the current SmPC for Keytruda™ with the frequency "common".

A trend towards higher proportions of hypercalcaemia can be seen in the laboratory tests, and in the Grade 3-4 AEs in the pembrolizumab treatment group. Some of the AEs of hypercalcaemia are possibly AEs of hypercalcaemia of malignancy that have not been reported (and therefore, not coded) as such; however, hypercalcaemia is also listed as adverse drug reaction to pembrolizumab in section 4.8 of the current SmPC for Keytruda™ with the frequency "uncommon".

2.5.2. Conclusions on clinical safety

The submitted safety analyses support the conclusion that overall pembrolizumab compares favourably with standard treatment, particularly with regard to drug-related events and time to first Grade 3-5 AE in subjects with R/M HNSCC failing platinum-containing chemotherapy. No new safety issues have emerged. The safety profile appeared consistent with the previously-reported pembrolizumab toxicity, even though a higher risk of immune-mediated, low-grade, generally persistent hypothyroidism in pembrolizumab-treated subjects with R/M HNSCC was found. Most of the subjects experiencing hypothyroidism had received previous radiotherapy and showed an earlier onset of the event when compared to that in other pembrolizumab indications. A review all SAEs of haemorrhage with respect to associated carotid artery bleeding did not identify any new safety signal.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 16 is acceptable.

The CHMP endorsed the Risk Management Plan version 16 with the following content:

Safety concerns

Summary of safety concerns	

Important identified risks	Immune-Related Adverse Reactions
	• Immune-related pneumonitis
	• Immune-related colitis
	• Immune-related hepatitis
	• Immune-related nephritis
	• Immune-related endocrinopathies
	  • Hypophysitis (including hypopituitarism and secondary adrenal insufficiency)
	  • Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis)
	  • Type 1 diabetes mellitus
	• Severe skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
	Other Immune-Related Adverse Reactions
	• Uveitis
	• Myositis
	• Pancreatitis
	• Myocarditis
	• Guillain-Barre Syndrome
	• Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients
	• Encephalitis
	• Sarcoidosis
	Infusion-Related Reactions

Important potential risks	Immune-Related Adverse Events 1. Gastrointestinal perforation secondary to colitis Other Immune-Related Adverse Events 2. For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab 3. Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT) Immunogenicity
Missing information	Safety in patients with moderate or severe hepatic impairment Safety in patients with severe renal impairment Safety in patients with active systemic autoimmune disease Safety in patients with HIV or Hepatitis B or Hepatitis C Safety in pediatric patients Reproductive and lactation data Long term safety Safety in various ethnic groups Potential pharmacodynamic interaction with systemic immunosuppressants Safety in patients with previous hypersensitivity to another monoclonal antibody Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs

No changes to the list of safety concerns were made as a result of this extension of indication.

Pharmacovigilance plan *(changes in blue italic)*

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities					
Started	Clinical trial A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (KN010)	To examine the overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and long term efficacy and safety of MK-3475 in previously treated subjects with NSCLC whose tumors express PD-L1	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, Immunogenicity) -Long term safety	Final Study Report	Aug 2019
Started	Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (KN024)	To evaluate the overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) and the safety and tolerability profile of pembrolizumab in subjects with 1L metastatic NSCLC, whose tumors express PD-L1, treated with pembrolizumab compared to standard of care (SOC) chemotherapies	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic SCT; Immunogenicity) -Long term safety	Final Study Report	Sep 2018
Started	Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (KN042)	To evaluate the overall survival (OS) and progression free survival (PFS) and to examine the safety and tolerability profile of pembrolizumab in subjects with PD-L1 positive 1L advanced/metastatic NSCLC, treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, GVHD after pembrolizumab administration in patients with a history of allogeneic	Final Study Report	Dec 2019

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
			SCT;Immunogenicity) -Long term safety		
Started	Clinical Trial A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies (KN013)	To examine the safety and tolerability of pembrolizumab in subjects with hematologic malignancies including, Hodgkin lymphoma, mediastinal large B cell lymphoma (MLBCL), relapsed/refractory non-Hodgkin lymphoma (NHL), myelodysplastic syndrome (MDS) and multiple myeloma	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Mar 2019

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical Trial A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (KN087)	To determine the safety and tolerability of pembrolizumab in subjects with relapsed or refractory classical Hodgkin Lymphoma (cHL) and to evaluate overall response rate (ORR), progression free survival (PFS), duration of response (DOR) and overall survival (OS) of pembrolizumab in study subjects	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Aug 2021
Started	Clinical Trial A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204)	To compare overall survival (OS), progression free survival (PFS) and overall response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.	-Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT;Immunogenicity)	Final Study Report	Apr 2021

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical trial A Phase I/II Study of Pembrolizumab (MK-3475) in Children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma (KN051)	To define the toxicities and maximum tolerated, maximum administered dose of pembrolizumab when administered as monotherapy to children between 6 months to 18 years of age with advanced melanoma, advanced, relapsed or refractory solid tumors or lymphoma. Study is designed to determine the safety and tolerability of pembrolizumab in all children between 6 months to 18 years of age.	Important identified risks (Immune-related adverse reactions, Infusion-related reactions) -Important potential risks (Immune-related adverse events- GI perforation secondary to colitis); GVHD after pembrolizumab administration in patients with a history of allogeneic SCT; -Safety in pediatric patients	Final Study Report	July 2019
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risks of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Important identified risks of encephalitis, sarcoidosis; potiental risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	PSUR	2019
Started	*Clinical Trial* *A randomized, active-controlled, multicenter, open-label Phase III clinical trial to examine the efficacy and safety of Pembrolizumab versus the choice of 3 different standard treatment options in subjects with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) whose disease has progressed on or after prior*	*To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.*	*-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)* *-Important potential risks (Immune-related adverse events- GI perforation secondary to colitis, Immunogenicity)* *-Long term safety*	*Final Study Report*	*May 2020*

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	platinum-containing chemotherapy (KN040)				

Study KN040 which is supporting the new indication has been added to the Pharmacovigilance plan in order to investigate existing safety concerns but in the new target population.

Risk minimisation measures

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related Pneumonitis	Routine risk minimisation measures: The risk of the immune-related adverse reaction of pneumonitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Educational materials	Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Colitis	Routine risk minimisation measures: The risk of the immune-related adverse reaction of colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immune-related Hepatitis	Routine risk minimisation measures: The risk of the immune-related adverse reaction of hepatitis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Nephritis	Routine risk Minimisation measures: The risk of the immune-related adverse reaction of nephritis associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions

Safety Concern	**Risk minimisation Measures** Additional risk minimisation measures: Educational materials	**Pharmacovigilance Activities** Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Immune-related Endocrinopathies -Hypophysitis (including hypopituitarism and secondary adrenal insufficiency) - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis) - Type 1 Diabetes Mellitus	Routine risk Minimisation measures: The risk of the immune-related endocrinopathies [Hypophysitis (including hypopituitarism and secondary adrenal insufficiency); Thyroid Disorder (Hypothyroidism, Hyperthyroidism, thyroiditis); Type 1 Diabetes Mellitus] associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4 and 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Severe Skin Reactions including SJS and TEN	Routine risk Minimisation measures: The risk of severe skin reactions including SJS and TEN associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: Educational materials	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Other Immune-related adverse reactions -Uveitis, Myositis, Pancreatitis, Myocarditis, Guillain-Barre Syndrome, Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients, Encephalitis, Sarcoidosis	Routine risk Minimisation measures: The risk of other immune-related adverse reactions (uveitis, myositis, pancreatitis, myocarditis, Guillain-Barre syndrome, Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients, encephalitis, sarcoidosis) associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 (Guillain-Barre Syndrome, Myocarditis, Encephalitis are also described in Section 4.2) and appropriate advice is provided to the prescriber to minimize the risk.	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reaction

Safety Concern	**Risk minimisation Measures**	**Pharmacovigilance Activities**
	Additional risk minimisation measures: Educational materials	Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types Cumulative review of literature, clinical trial and post-marketing cases of encephalitis and sarcoidosis to be included with PSUR submission in 2019.
Important Identified Risks: Infusion-Related Reactions		
Infusion-Related Reactions	Routine risk Minimisation measures: The risk of infusion-related reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk Additional risk minimisation measures: Educational materials.	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks: Immune-Related Adverse Events		
Gastrointestinal perforation secondary to colitis	Routine risk Minimisation measures: The risk of the immune-related adverse event of gastrointestinal perforation secondary to colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Other Immune-related adverse events- For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk Minimisation measures: For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	**Routine pharmacovigilance activities**

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: Educational materials	**Additional pharmacovigilance including:** Safety monitoring in the ongoing HL trials (KN013, KN087, KN204).
Other Immune-related adverse events- GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk Minimisation measures: GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: Educational materials	Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001 (Cohort C&F), KN010, KN024, KN042), HL trials (KN013, KN087, KN204), ~~and~~ UC trials (KN045, KN052, KN361*) and HNSCC trial (KN040*). Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types Cumulative review of literature, clinical trial and post-marketing cases of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT with PSUR submission in 2019.
Important Potential Risks: Immunogenicity		

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immunogenicity	Routine risk Minimisation measures: The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 4.8.	**Routine pharmacovigilance activities** **Additional pharmacovigilance including:** Conducting anti-drug antibody (ADA) assessments in multiple MAH- sponsored clinical trials in different tumor types in the pembrolizumab program.
Missing Information		
Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment	Routine risk Minimisation measures: The missing information of safety in these patients is described in the SmPC, Section 4.2, 4.4.	**Routine pharmacovigilance activities**
Safety in patients with active systemic autoimmune disease	Routine risk Minimisation measures: The missing information of safety in patients with active systemic autoimmune disease is described in the SmPC, Section 4.4, 5.1.	**Routine pharmacovigilance activities**
Safety in patients with HIV or Hepatitis B or Hepatitis C	Routine risk Minimisation measures: The missing information of safety in patients with patients with HIV or Hepatitis B or Hepatitis C is described in the SmPC, Section 4.4, 5.1.	**Routine pharmacovigilance activities**

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Safety in Pediatric patients	Routine risk Minimisation measures: The missing information of safety in pediatric patients is described in the SmPC, Section 4.2.	**Routine pharmacovigilance activities** Additional pharmacovigilance including: Safety monitoring in the paediatric investigation plan (PIP): A Phase I/II Study of Pembrolizumab (MK-3475) in Children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma (KN051)
Reproductive and lactation data	Routine risk Minimisation measures: Use during pregnancy and use in nursing mothers is described in the SmPC, Section 4.6, 5.3.	**Routine pharmacovigilance activities**
Long term safety	No risk Minimisation warranted	**Routine pharmacovigilance activities** Additional pharmacovigilance including: Safety monitoring in the ongoing NSCLC trials (KN001, KN010, KN024, KN042) Safety monitoring in other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Safety in various ethnic groups	No risk Minimisation warranted	**Routine pharmacovigilance activities** **Additional pharmacovigilance including:** Safety monitoring in ongoing global MAH-sponsored clinical trials for pembrolizumab

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Potential pharmacodynamic interaction with systemic immunosuppressants	Routine risk Minimisation measures: The missing information of potential pharmacodynamic interaction with systemic immunosuppressants is described in the SmPC, Section 4.4, 4.5**.**	**Routine pharmacovigilance activities**
Safety in patients with previous hypersensitivity to another monoclonal antibody	Routine risk Minimisation measures: The missing information of safety in patients with previous hypersensitivity to another monoclonal antibody is described in the SmPC, Section 4.4, 5.1.	**Routine pharmacovigilance activities**
Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs	Routine risk Minimisation measures: The missing information of safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs is described in the SmPC, Section 4.4, 5.1.	**Routine pharmacovigilance activities** Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific questionnaire for spontaneous postmarketing reports of immune related reactions

No changes to the risk minimisation measures have been introduced as a result of the new indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to include treatment as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy based on the results from KEYNOTE-040 (KN040). The Package Leaflet is being updated accordingly. In addition, section 5.2 of the SmPC is being updated to include a description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure.

In addition, the existing obligation in the Annex II with regard to the further exploration of the value of biomarkers to predict the efficacy of pembrolizumab has been updated to include also the HNSCC study (KN040).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- A CHMP request was received during variation EMEA/H/C/003820/II/0023/G (new indications in urothelial carcinoma approved on 24-Aug-2017) to perform a new user testing considering that all sections of the package leaflet were affected since marketing authorization. The proposed revisions included in this variation for R/M HNSCC do not constitute significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The following extension of indication for pembrolizumab is sought: "KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy".

After the second RSI, the indication was restricted to include patients whose tumor express PD-L1 as follows:

"KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy (see section 5.1)."

3.1.2. Available therapies and unmet medical need

In the first-line treatment of R/M HNSCC, combination therapy with cetuximab plus cisplatin/carboplatin plus 5-fluorouracil followed by maintenance cetuximab (the "EXTREME" regimen) has shown the best results so far. Patients who progress on (or are ineligible for) the EXTREME regimen and other cetuximab-based first-line treatments can participate in a clinical trial, receive systemic therapy or best supportive care. Systemic therapies may include cisplatin/carboplatin, 5-FU, cetuximab, docetaxel, paclitaxel, gemcitabine, vinorelbine, methotrexate, capecitabine. Nivolumab has been recently approved in EU in the same indication pembrolizumab is applying for. Nivolumab was approved regardless PD-L1 expression.

Patients with R/M HNSCC have a poor prognosis with median overall survival of under 1 year. Treatment is dictated in large part by the patient's performance status, which is one of the most important factor associated with clinical outcome. The main treatment objectives are to prolong survival and/or provide symptom palliation.

3.1.3. Main clinical studies

Pivotal study: KEYNOTE-040, phase 3 open label randomized comparing pembrolizumab vs standard treatment (investigator's choice of methotrexate, docetaxel, or cetuximab) in R/M HNSCC progressed after prior platinum treatment.

Supportive studies: phase 2 single arm KEYNOTE-055 and phase Ib KEYNOTE-012.

3.2. Favourable effects

- HR for OS in the overall population was 0.80 (95%CI 0.65, 0.98), corresponding to a gain in median OS of 1.5 months (not adjusted for multiplicity).
- OS curves separate after month 4-5 and further tend to divide over time
- Efficacy results are partially enriched in PD-L1 CPS ≥1 (HR=0.74), but highest advantage is seen in strongly positive (TPS≥50%) tumours (HR=0.53)
- Median DOR and rate of patients with ≥6 months response duration notably in favour of pembrolizumab

3.3. Uncertainties and limitations about favourable effects

- Primary OS analysis (DBL 04-JUN-2017), the only p-value provided for statistical inference not statistically significant (HR 0.82). Despite the fact that the primary efficacy analysis has been performed based on a higher number of events than originally planned, it did not show statistically significant results.
- Pembrolizumab OS curve lies below/overlaps the one of the standard treatment arm up to month 4-5. A higher number of deaths within two months from randomization is seen in the pembrolizumab arm compared to the control arm. Further data have been requested to determine potential factors useful to select patients in clinical practice.
- Several protocol amendments modified the statistical component of the study design and sample size, having implications for the clinical interpretation of the results.
- Detrimental effect of pembrolizumab over standard treatment in the NA population, with OS overperformance of the standard treatment arm.
- Longer median time to response of pembrolizumab vs standard treatment in Keynote-040, longer compared also to pembrolizumab in the supportive studies.
- No subjects with ECOG PS ≥2 or active brain metastasis have been enrolled.

3.4. Unfavourable effects

- The overall exposure-adjusted AE rate was lower in the pembrolizumab-treated group than in the standard treatment group (1969.8 events/100 person-years versus 3245.7 events/100 person-years).
- Frequencies of SAEs were higher in pembrolizumab-treated subjects (44.7% vs 39.3%), mainly due to SAEs of hypercalcaemia and tumour haemorrhage. Proportions of drug-related SAEs were lower in pembrolizumab-treated subjects (8.9% vs 15.4%).
- Two deaths in the pembrolizumab-treated subjects resulted from carotid artery bleeding.

Among 246 pembrolizumab treated subjects, 4 deaths (1.6%) were assessed as study-drug associated (death, unspecified, large intestine perforation; malignant neoplasm progression, and Stevens-Johnson syndrome). SJS is a known adverse drug reaction associated with pembrolizumab, large intestine perforation is considered to be more likely associated with mesenteric ischemia.

- SOCs more frequently recorded in the standard treatment arm were: *General disorders and administration site conditions (52.8% vs 65.4%), Investigations (26.8% vs 39.3%), Skin and subcutaneous tissue disorders (30.1% vs 50%).* On the contrary, *Endocrine disorders* (17.5% *vs*

5.1%), and *Respiratory, thoracic and mediastinal disorders* (47.2% *vs* 38.5%) were more often registered with pembrolizumab.

- A higher rate of drug-related hypothyroidism seen in the KN040 pembrolizumab arm (13.4%) and in the Pooled HNSCC Dataset (11.2%), compared to both the KN040 standard treatment group (0.9%) and to the Reference Safety Dataset (7.6%).

3.5. Uncertainties and limitations about unfavourable effects

- Interpretation of safety in the elderly is limited by small numbers of subjects in the 75 to 84 years of age subgroup (n = 18) and the fact that there was only 1 treated subject ≥85 years of age. However, there were no indications of worse (or better) safety in the elderly ≥65 years (relative to younger subjects (< 65 years) in the Reference Safety Dataset comprising the data for the 2 approved indications. No data on very old subjects (75 years and older) were provided in the Reference Safety Dataset.
- Experience with pembrolizumab in HNSCC is, from a safety perspective, limited, and long-term safety is not well characterised. There is, however, a relatively large safety dataset of pembrolizumab monotherapy in other indications. The safety of pembrolizumab in HNSCC was generally consistent with the overall experience with pembrolizumab in 2 other tumour types.
- Interpretation of safety in female subjects is impacted by the limited dataset (n = 40 [16.3%]).

3.6. Effects Table

Table 105: Effects Table for KN040 Trial. Data cut-off: 15-MAY-2017 (database lock 13-OCT-2017) (references: CSR KN040)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
OS	Time from randomization to the date of death from any cause	Median (months)	8.4	6.9	- Primary analysis for OS not statistically significant - TPS was a stratification factor; - OS Crossing curves, with higher number of deaths associated with pembrolizumab vs standard treatmentin the first 4-5 months - OS curves separate at month 4-5 and further diverge over time;
		12 M rate	37%	26.5%	
		HR (95%CI)	0.80 (0.65-0.98)		
OS (TPS≥ 50%)	Time from randomization to the date of death from any cause	Median (months)	11.6	6.6	
		12 M rate	46.6%	25.4%	
		HR (95%CI)	0.53 (0.35, 0.81)		
PFS	Time to the first documented disease progression or to death due to any cause	Median (months)	2.1	2.3	
		HR (95%CI)	0.96 (0.79, 1.16)		
ORR	% of randomized subjects with best response of CR or PR (RECIST v1.1).	%	14.6	10.1	
DoR	based on confirmed response by BICR in months	median (range) months	18.4 (2.7,18.4)	5.0 (1.4+,18.8)	
Unfavourable Effects					
Tolerability	Adverse events regardless of causality	%	96.7	97.0	No new safety concerns with pembrolizumab treatment were identified in HNSCC/ Higher rate of earlier occurrence of hypothyroidism especially in subjects
	Anemia	%	26.8	22.6	
	Fatigue	%	19.5	26.9	
	Constipation	%	17.5	15.8	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Drug-related AEs	Serious adverse events regardless of causality	%	44.7	39.3	previously irradiated.
	All AEOSIs	%	25.6	12.0	
	Drug-related AEs	%	63.0	83.8	
	Hypothyroidism	%	13.4	0.9	
	Fatigue	%	12.6	18.4	
	Diarrhoea	%	8.1	10.3	
	Drug-related G 3-5 AEs	%	13.4	36.3	
	Drug-related SAEs	%	8.9	15.4	
	Discontinuation due to drug-related AEs	%	6.1	5.1	
	Discontinuation due to drug-related SAEs	%	4.5	2.1	

Abbreviations: AE (adverse event), AEOSI (adverse event of special interest), AR (assessment report), CR (complete response), HR (hazard ratio), PFS (progression free survival), ORR (objective response rate), OS (overall survival), PR (partial response), HNSCC (squamous cell carcinoma of the head and neck) SAE (serious adverse event)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the fact that the primary efficacy analysis has been performed based on a higher number of events than originally planned, the pivotal trial KEYNOTE-040 did not show statistically significant OS result. As seen with other anti-PD1 (nivolumab) in the same setting, as well as with pembrolizumab in other indication, pembrolizumab OS curve lies below/overlap with the one of the standard treatment arm.

The OS curves appear to cross at month 4-5, then the clinical advantage of pembrolizumab is seen in the separation of the curves which tend to further divide over time. Increased risk of early death with pembrolizumab over standard treatment within the first two months from randomization has been investigated, showing that the PD-L1 expression is one of the factor to take into account.

Evaluation of PD-L1 expression in tumour- and immune cells (CPS) has not been implemented as stratification factor at randomization (but TPS <50% vs. ≥50%), since the clinical relevance of CPS has been only identified during the conduct of the study based on phase II data.

The positive results seem to be driven by subjects whose tumor has PD-L1 CPS score ≥1, with highest advantage for strongly positive PD-L1 expressing tumours (TPS ≥ 50%). Response rate appears not outstanding, although the benefit of pembrolizumab is primarily laying on the longer median duration of response and durable response rate, which is confirmed in the supportive studies. However, no benefit is seen in OS and PFS, if not even a detrimental effect in ORR, in the subgroup of patients with PD-L1 CPS<1 expression.

The highest advantage of pembrolizumab compared to standard treatment is seen in strongly positive PD-L1 expressing tumours (i.e. TPS≥50%) comprising about 25% of the overall population (and approximately 33% of CPS≥1 subjects). In the TPS≥50% population, the benefit of pembrolizumab vs standard treatment is clear and observed in all efficacy endpoints. OS curves do not overlap, clearly separating from the beginning, with OS HR=0.53 (95%CI 0.35-0.81).

In the subgroup of patients with CPS≥1 but TPS<50%, the benefit has not been convincingly demonstrated.

The drug-related toxicity appears to compare quite favourably with the standard treatment. No new safety issues have been highlighted.

3.7.2. Balance of benefits and risks

Based on the overall data provided an indication of pembrolizumab in R/M HNSCC tumour with PD-L1 TPS score ≥50% is deemed appropriate.

Even taking into account the methodological limitations, and the results in the ITT population, in patients whose tumour has a PD-L1 TPS score ≥50% a strong treatment effect with a separation of the KM OS curves from the beginning is observed supporting the beneficial effect of pembrolizumab over standard treatment, combined with an overall more favourable safety profile compared to standard treatment.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Keytruda for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ⩾ 50% TPS and progressing on or after platinum-containing chemotherapy is positive.

4. Recommendations

Outcome

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

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

Extension of Indication to include treatment as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy based on the results from KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012/ KEYNOTE-055). KN040 is a randomized, multi-center, pivotal phase III study investigating KEYTRUDA as a monotherapy versus standard treatment (methotrexate, docetaxel or cetuximab) in 495 patients with recurrent or metastatic HNSCC who have previously progressed on prior platinum. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include in SmPC section 5.2 the description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure.

Furthermore, the existing obligation in the Annex II with regard to the further exploration of the value of biomarkers to predict the efficacy of pembrolizumab has been updated to include also the HNSCC study (KN040).

An updated RMP version 16 was agreed during the procedure.

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

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

Description	Due date
4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing NSCLC studies (P001, P010, P024 and P042) and urothelial carcinoma studies (KN045, KN052) and HNSCC study (KN040): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling	 2Q 2020 2Q 2019 4Q 2021