17 October 2019
EMA/CHMP/591139/2019/corr.
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0065

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First-line therapy (patients/participants who have not received any prior therapy for R/M disease)
2L	Second-line therapy (patients/participants who have received 1 prior therapy for R/M disease)
2L+	Second-line or later therapy (patients/participants who have received 1 or more prior therapies for R/M disease)
5-FU	5 fluorouracil
AE	Adverse event(s)
AEOSI	Adverse event(s) of special interest
ASaT	All Subjects as Treated
BICR	Blinded independent central review
cHL	Classic Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPS	Combined positive score
CSR	Clinical Study Report
CR	Complete response
DMC	Data monitoring committee
DOR	Duration of response
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EHNS	European Head and Neck Society
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
IA	Interim analysis
IFN	Interferon
IgG	Immunoglobulin
IL-2	Interleukin-2
ITT	Intention to Treat
KM	Kaplan-Meier

mAb	Monoclonal antibody
MAH	Marketing Authorization Holder
MSI-H	Microsatellite instability high
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcomes
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
R/M	Recurrent/metastatic
RSD	Reference Safety Dataset
SAE	Serious adverse event(s)
SOC	System organ class
TNF	Tumour necrosis factor
TPS	Tumour proportion score
US	United States
USPI	United states prescribing information
WBC	White blood cell

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 28 November 2018 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, II and IIIB

Extension of indication to include, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) Chemotherapy, first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults for Keytruda; based on the results from KEYNOTE-048, a randomized, multi-center, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated version of the RMP (Version 22.1) is also submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II 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/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0043/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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

The MAH received Scientific Advice from the CHMP in 2014 on the design elements of the clinical trial KEYNOTE-048 (EMEA/H/SA/2437/5/2014/II).

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	28 November 2018
Start of procedure:	29 December 2018
CHMP Co-Rapporteur's preliminary assessment report circulated on	22 February 2019
CHMP Rapporteur's preliminary assessment report circulated on	27 February 2019
PRAC Rapporteur's preliminary assessment report circulated on	28 February 2019
PRAC RMP advice and assessment overview adopted by PRAC on	14 March 2019
CHMP Rapporteurs' updated joint assessment report circulated on	22 March 2019
Request for supplementary information adopted by the CHMP on	28 March 2019
MAH's responses submitted to the CHMP on	25 April 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	3 June 2019
2nd Request for supplementary information adopted by the CHMP on	27 June 2019
MAH's responses submitted to the CHMP on	18 July 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	20 August 2019
3rd Request for supplementary information adopted by the CHMP on	19 September 2019
MAH's responses submitted to the CHMP on	24 September 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	3 October 2019
CHMP Opinion	17 October 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Head and neck squamous cell carc inoma (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.

Epidemiology and risk fac tors, screening tools/prevention

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]. 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].

Biologic features, Aetiology and pathogenesis

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.

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.

Clinical presentation, diagnosis and stage/prognosis

Tumours have different clinical behaviour, 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. A significant number of patients with HNSCC initially present with locoregionally advanced disease (American Joint Committee on Cancer stages I-IVB) and the rate of recurrence is up to 50%. Common sites of metastases include lymph nodes, bone, and lung. The challenges of recurrent or metastatic (R/M) HNSCC include pain, speech, swallowing, breathing, and social function. Survival is predicted primarily by stage, anatomical site and HPV status. Patients with recurrent or metastatic (R/M) HNSCC have a poor prognosis with median overall survival of under 1 year[7].

Management

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). In the first-line treatment of R/M HNSCC, combination therapy with cetuximab plus cisplatin/carboplatin plus 5-fluorouracil followed by maintenance cetuximab (the

[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 carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000 Mar 18;355(9208):949-55.
[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

"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 HNSCC 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 nivolumab and pembrolizumab.

The table below summarises the available published data on 1st line treatment in patients with R/M HNSCC.

Table 1: Published studies of 1st line treatment in patients with R/M HNSCC

Study/Author	Study Design	Population	Treatment	ORR	DCR	Median DOR	Median PFS/TTP	Median OS
Combination Studies								
Liverpool Head and Neck Oncology Group (1990) [Ref. 5.4: 03YXPF]	Phase 3, randomized study	200 patients with no prior treatment for R/M HNSCC	Cisplatin+5-FU Cisplatin+methotrexate Methotrexate Cisplatin	24% 22% 12% 28%	-	-	-	388 days for patients with CR or PR (p<0.001) 165 days for patients with SD 79 days for patients with PD Median OS not stated but the figure within the publications shows the med survival would be within 9 month range
Jacobs 1992 [Ref. 5.4: 03YXN5]	Phase 3, randomized study	249 patients with no prior treatment for R/M HNSCC	Cisplatin+5-FU Cisplatin 5-FU	32% 17% 13%	-	-	2.4 months 2.0 months 1.7 months	5.5 months 5.0 months 6.1 months
Forastiere 1992 [Ref. 5.4: 03WN8M]	Phase 3, randomized study	277 patients with no prior treatment for R/M HNSCC	Cisplatin+5-FU Carboplatin+5-FU Methotrexate	32% 21% 10%	-	4.2 months 5.1 months 4.1 months	-	6.6 months 5.0 months 5.6 months
Clavel 1994 [Ref. 5.4: 052TLG]	Phase 3, randomized study	382 patients	Cisplatin+methotrexate+bleomycin+vincristine Cisplatin+5-FU Cisplatin	34% 31% 15%	-	-	Overall no difference between the treatment groups in PFS and OS	
Schrijver 1998 [Ref. 5.4: 03YXNC]	Phase 3, randomized study	244 patients with no prior treatment for R/M HNSCC	Cisplatin+5-FU+IFN2b Cisplatin+5-FU	38.4% 47.1%	-	-	-	6.02 months 6.28 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.

Forastiere 2001 [Ref. 5.4: 03YXNJ]	Phase 3, randomized study	210 patients with no prior treatment for R/M HNSCC	Cisplatin+paclitaxel (low dose) Cisplatin+paclitaxel (high dose)	36% 35%			4.0 months* 4.1 months* *EFS	6.8 months 7.6 months
Gibson 2005 (ECOG) [Ref. 5.4: 03YXQS]	Phase 3, randomized study	218 patients with no prior treatment for R/M HNSCC	Cisplatin+5-FU Cisplatin+paclitaxel	29.8% 26%	-	-	-	8.7 months 8.1 months
EXTREME, Vermorken 2008 [Ref. 5.4: 03WNBF]	Phase 3, randomized study	442 patients with no prior treatment for R/M HNSCC	Cisplatin or carboplatin+5-FU Cisplatin or carboplatin+5-FU+ cetuximab	20% 36% (p<0.001)	60% 81% (p<0.001)	4.7 months 5.6 months (p=0.21)	3.3 months 5.6 months (p<0.001)	7.4 months 10.1 months (p=0.04)
ECOG (Burtness 2005) [Ref. 5.4: 0425Y6]	Phase 3, randomized, placebo-controlled study	123 patients with no prior treatment for R/M HNSCC	Cisplatin+placebo Cisplatin+cetuximab	10% 26% (p=0.03)			2.7 months 4.2 months	8.0 months 9.2 months
Monotherapy studies								
Catimel 1994a [Ref. 5.4: 052TKT]		43 patients with no prior treatment for R/M HNSCC	Docetaxel	32%	-	-	-	-
Dreyfuss 1996 [Ref. 5.4: 052TLT]	Phase 2	31 patients with no prior treatment for R/M HNSCC	Docetaxel	42%	-	5.0 months (2 to 14)	-	7 patients alive with a median FU of 12 months
Forastiere 1998 [Ref. 5.4: 052TNR]	Phase 2	34 patients with no prior treatment for R/M HNSCC	Paclitaxel	40%	-	4.5 months (2 to 20)	-	9.2 months
Martin 1993 [Ref. 5.4: 052TPT]		37 male patients with no prior treatment for R/M HNSCC	Ifosfamide	26%	-	3.0 months (3 to 5)	-	-

Study/Author	Study Design	Population	Treatment	ORR	DCR	Median DOR	Median PFS/TTP	Median OS
Gilbert 2007 [Ref. 5.4: 052YW8]	Phase 2	22 evaluable patients with no prior treatment for R/M HNSCC	Irinotecan	20.0% at 125 mg/m^2 dose and 12.5% at 75 mg/m^2 dose	-	-	-	6.7 months
Sandler 1998 [Ref. 5.4: 052TPX]	Phase 2	24 patients with no prior treatment for R/M HNSCC	Ifosfamide	4.3%	-	-	-	-
Degardin 1998 [Ref. 5.4: 04W7H2]	Phase 2	71 patients with no prior treatment for R/M HNSCC (56 evaluable)	Vinorelbine	16%	32% (SD for a minimum of 8 weeks)	19 weeks	12 weeks	32 weeks
Samlowski 2001 [Ref. 5.4: 04W7HK]	Phase 2	29 patients with no prior treatment for R/M HNSCC (26 evaluable)	Gemcitabine	0%	-	-	2 months	6 months

Abbreviations: 5-FU=5-fluorouracil; CR=Complete response; DCR=Disease control rate; DOR=Duration of response; EFS=Event-free survival; FU=follow-up; HNSCC=Head and neck squamous cell carcinoma; IFN=Interferon; ORR=Objective response rate; OS=Overall survival; PD=Progressive disease; PFS=Progression-free survival; PR=Partial response; R/M=Recurrent/metastatic; SD=Stable disease; TTP=Time to progression.

About the product

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 tumour microenvironment to overcome active antitumour-specific T cell immune surveillance. A variety of cancers, unlike healthy organs, express abundant levels of PD-1 ligands, PD-L1 and PD-L2. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. The high expression of PD-L1 on tumour cells has been found to correlate with poor prognosis and survival in various cancers and suggests that the PD-1/PD-L1 pathway plays a critical role in tumour evasion and is, thus, an attractive target for therapeutic intervention.

Keytruda was recently approved as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) in adults whose tumours express PD-L1 TSP ≥ 50% and progressing on or after

platinum-containing chemotherapy (EMEA/H/C/003820/II/0042).

The scope of this variation is to include a new indication for Keytruda for the first-line treatment of R/M HNSCC in adults, as monotherapy or in combination with chemotherapy. The proposed indication is based on the results from KEYNOTE-048, a randomized, multi-center, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC. A total of 882 patients were randomized to one of the 3 treatment arms.

The MAH applied for the following indications:

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults.

The CHMP agreed to the following indications:

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1).

Type of Application and aspects on development

The MAH received Scientific Advice from the CHMP in 2014 on the design elements of the clinical trial KEYNOTE-048 (EMEA/H/SA/2437/5/2014/II). The MAH did follow some of the advice given (e.g. OS as most convincing proof of benefit (later upgraded from secondary to dual primary endpoint), pre-planned subgroup analyses by PD-L1 status).

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. As an unaltered protein, being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, pembrolizumab is unlikely to result in a significant environmental exposure. 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 submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

No new nonclinical data has been provided to support this application. The applicant did not submit studies for the ERA. According to the relevant guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), this 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

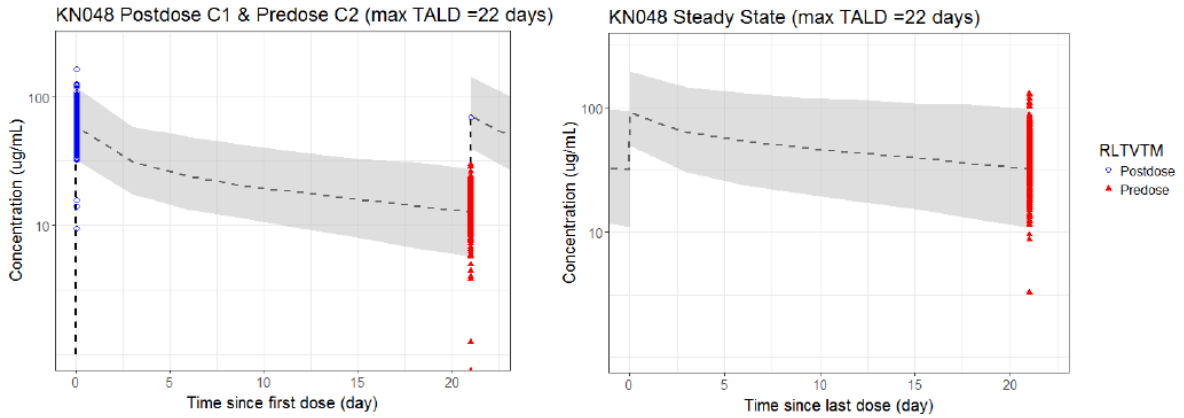
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-048 KEYNOTE-048	3	Worldwide, US, EU, Rest of World (ROW)	A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma	Randomized active-controlled multi-site open-label	Pembrolizumab 200 mg IV, Q3W Cisplatin 100 mg/m^2 IV, Q3W Carboplatin AUC 5 IV, Q3W 5-FU 1000 mg/m^2/day IV continuous from Day 1-4 of each cycle, Q3W Cetuximab: initial dose 400 mg/m^2 IV over 2 hours on Day 1, followed by 250 mg/m^2 IV over 1 hour weekly	Males/females Age: ≥18 of age on the day of consent Subjects with recurrent or metastic head and neck cancer	Received at least 1 dose: Pembrolizumab monotherapy: 300 Pembrolizumab plus chemotherapy: 276 Cetuximab plus chemotherapy: 287

2.3.2. Pharmacokinetics

Pharmacokinetic data from KEYNOTE-048 suggest that pembrolizumab exposures in 1L HNSCC participants administered with 200 mg Q3W pembrolizumab as monotherapy or in combination with platinum and 5-FU are consistent with the historical reference PK dataset from melanoma and NSCLC participants (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024) in Cycle 1 and at steady state (Figure 1). This supports the use of the recommended pembrolizumab dose of 200 mg Q3W. Additional justifications for the use of the newly proposed dosing regimen of 400 mg Q6W in 1L HNSCC participants are provided below.



Postdose cycle 1, predose before cycle 2 dosing and predose at steady state (at and after Cycle 8) on log scale. Red and blue symbols are individual observed data (nominal time) from subjects with Head and Neck Cancer in KEYNOTE-048; 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.

Figure 1: Observed concentration data with a cut-off of 22 days after last dosing of KEYNOTE-048 subjects receiving 200 mg Q3W pembrolizumab with reference model-predicted pharmacokinetic profile for 200 mg Q3W dose regimen

Moreover, observed pembrolizumab serum concentration values in KEYNOTE-048 are found to be consistent with other approved studies in different tumour types (KEYNOTE-024 in NSCLC, KEYNOTE-045 and KEYNOTE-052 in UC, KEYNOTE-055 in HNSCC, KEYNOTE-087 in HL, KEYNOTE-158 and KEYNOTE-164 in MSI-H) following the fixed dose administration of 200 mg Q3W as shown in (Table 2).

Table 2: Summary statistics of pembrolizumab observed serum concentration values following administration of multiple I.V. doses of 200 mg Q3W in studies KEYNOTE-024, KEYNOTE-045, KEYNOTE-048, KEYNOTE-052, KEYNOTE-055, KEYNOTE-087, KEYNOTE-158 and KEYNOTE-164

Time point	Study/Indication	N	GM (%CV) (µg/mL)	AM (SD) (µg/mL)	Min	Median	Max
Cycle 1 Postdose	KN024 NSCLC	147	67.5 (23)	69.27 (16)	36.6	66.8	132
	KN045 UC	247	65.7 (26)	67.93 (18)	33.9	65.9	144
	KN048 1L HNSCC	495	61.8 (29)	64.15 (18)	9.48	61.7	165
	KN052 UC	298	58 (28)	60.18 (17)	22.8	57.4	148
	KN055 HNSCC	43	56.5 (28)	58.94 (21)	33.1	54.9	162
	KN087 HL	195	60.7 (28)	63.06 (18)	31.2	61.3	183
	KN158 MSIH	90	64.4 (27)	66.65 (18)	31.2	65.2	133
	KN164 MSIH	56	62.2 (28)	64.59 (19)	34.9	61.2	150
Cycle 2 Predose	KN024 NSCLC	132	11.1 (54)	12.26 (5)	0.535	12.2	28.5
	KN045 UC	233	13.1 (47)	14.18 (5)	0.475	13.9	29.3
	KN048 1L HNSCC	458	N.A.	13.37 (5)	0.00	13.2	29.6
	KN052 UC	286	11.1 (42)	11.91 (4)	2.07	11.5	26.2
	KN055 HNSCC	40	10.7 (47)	11.76 (5)	3.45	11.6	33.1
	KN087 HL	200	14.4 (40)	15.36 (5)	3.06	15.3	30.0
	KN164 MSIH	56	12.5 (35)	13.23 (5)	5.44	12.4	25.6
Cycle 8 Predose	KN024 NSCLC	82	30.6 (50)	33.61 (13)	5.26	32.7	64.1
	KN045 UC	104	33.4 (64)	37.83 (17)	1.13	37.5	95.6
	KN048 1L HNSCC	235	34.2 (50)	37.51 (15)	1.77	34.8	127
	KN052 UC	59	28 (38)	29.86 (10)	8.15	27.9	59.8
	KN055 HNSCC	7	27.8 (41)	29.64 (11)	16.8	24.5	43.3
	KN087 HL	68	43.9 (43)	47.37 (17)	13.9	47.5	92.4
	KN164 MSIH	34	33.6 (43)	36.23 (14)	8.40	33.7	78.8

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

An additional dosing regimen of 400 mg Q6W has been approved in the EU on 28 March 2019 for all monotherapy indications approved at the time based on PK and exposure-response bridging using modeling and simulations analyses (procedure number EMEA/H/C/003820/II/0062). The inferences from these analyses support the dosing regimen of 400 mg Q6W across indications, including 1L HNSCC, given the similarity in PK (as outlined above) and based on the following additional rationale:

- Pembrolizumab acts via binding to PD-1 on immune cells, not tumour cells; hence meaningful differences in exposure/dose-response are not expected across cancer types.
- Consistent, flat exposure-response relationships are seen for pembrolizumab in multiple tumour types
    - Efficacy is seen at the same dosing regimen across multiple indications (melanoma, NSCLC, HNSCC, UC, cHL, GC, MSI-H cancers, PMBCL, HCC and cervical cancer).
- Clearance is similar across tumour types, suggesting saturation of the target on immune cells in circulation is achieved at the clinical dose, which is the same across tumour types; this further supports that PK/exposures and exposure-response are consistent across indications.

2.3.3. Discussion on clinical pharmacology

A dosing regimen of 200 mg Q3W is recommended for pembrolizumab treatment in patients with R/M HNSCC, as pharmacokinetic and clinical pharmacology properties remain similar across indications.

A robust characterization of the PK and immunogenicity of pembrolizumab has been provided in previous submissions in other monotherapy indications in the non-adjuvant settings. A description of the clinical pharmacology of pembrolizumab in subjects with previously treated HNSCC was included in the KEYNOTE-040 submission to support 200 mg Q3W as the recommended dose of pembrolizumab in this patient population (see EPAR for EMEA/H/C/003820/II/0042).

A description of the pharmacology of pembrolizumab in combination with chemotherapy was included in the KEYNOTE-021-G/KEYNOTE-189 submission (see EPAR for EMEA/H/C/003820/II/0043). This analysis demonstrated that the PK and immunogenicity of pembrolizumab are not impacted by concomitant chemotherapy.

Considering the consistency in exposure between subjects with 1L HNSCC tumour treated with pembrolizumab 200 mg Q3W in monotherapy and subjects with other tumour type treated with the same regimen, the use of 400 mg Q6W as additional dosing option for pembrolizumab as monotherapy in the 1L HNSCC is supported by the already proposed modelling and simulation approach.

2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology data and rationale submitted support the use of the currently authorised dosing regimens for the first-line treatment of metastatic or unresectable recurrent HNSCC as monotherapy or in combination with platinum and 5 FU chemotherapy.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No specific dose-response study was conducted. The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W dose is justified by:

• Clinical data from eight randomized studies demonstrating flat dose- and exposure- efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W)

• Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

• Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumour (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC. All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. Subsequently, flat dose-/exposure-response relationships were also observed in other tumour types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumour type.

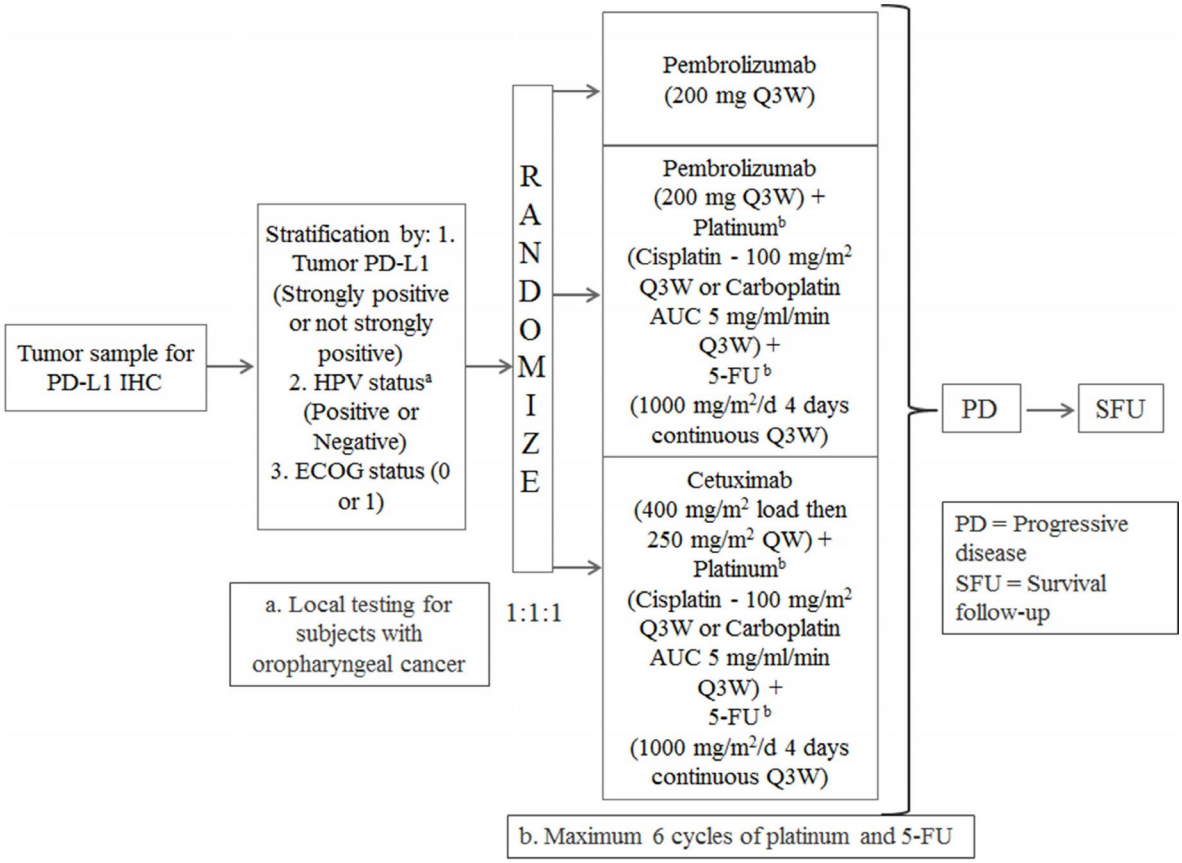
Additionally, pharmacology data show target saturation at 200 mg Q3W.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed–dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose.

Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

2.4.2. Main study

A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (KEYNOTE-048)



Methods

Study participants

Key inclusion criteria included:

1. Histologically or cytologically-confirmed R/M HNSCC that was considered incurable by local therapies.
    - No prior systemic therapy in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months prior to signing consent if given as part of combination therapy for locally advanced disease was allowed.
    - The eligible primary tumour locations were oropharynx, oral cavity, hypopharynx, and larynx.
    - Participants may not have had a primary tumour site of nasopharynx (any histology).
2. Written informed consent
3. ≥18 years of age
4. Measurable disease based on RECIST 1.1 as determined by the site. Tumour lesions situated in a previously irradiated area were considered measurable if progression had been demonstrated in such lesions.
5. ECOG performance status of 0 or 1.

6. Adequate organ function
7. Had results from testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point. If HPV status was previously tested using this method, no additional testing was required.
8. Had provided tissue for PD-L1 biomarker analysis from a core or excisional biopsy. Repeat samples may be required if adequate tissue was not provided. A newly obtained biopsy (within 90 days prior to start of study treatment) was strongly preferred, but an archival sample was acceptable.
9. Female participants of childbearing potential had a negative blood pregnancy test within 72 hours prior to receiving the first dose of study medication.

Key exclusion criteria included:

1. Had disease that was suitable for local therapy administered with curative intent.
2. Had PD within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.
3. Had radiation therapy (or other non-systemic therapy) within 2 weeks prior to randomization or participant had not fully recovered (ie, ≤Grade 1 or at baseline) from AEs due to a previously administered treatment.
4. Had a life expectancy of less than 3 months and/or had rapidly progressing disease (e.g. tumor bleeding, uncontrolled tumour pain) in the opinion of the treating investigator.
5. Had a diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention. Corticosteroid use as pre-medication for allergic reactions (e.g. IV contrast), or as a prophylactic management of AEs related to the chemotherapies specified in the protocol was allowed.
6. Had a diagnosed and/or treated 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, curatively resected *in situ* cervical cancer, and curatively resected *in situ* breast cancer.
7. Had known active CNS metastases and/or carcinomatous meningitis.
8. Active autoimmune disease that had required systemic treatment in past 2 year. Replacement therapy was not considered a form of systemic treatment.
9. Had had an allogeneic tissue/solid organ transplant.
10. Had a history of (noninfectious) pneumonitis that required steroids or current pneumonitis; active infection requiring systemic therapy; known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study; known history of HIV; known active Hepatitis B or C.
11. Was pregnant or breastfeeding
12. Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
13. Had received a live vaccine within 30 days of planned start of study therapy.

Treatments

Pembrolizumab plus chemotherapy group (pembro combo): pembrolizumab + cisplatin/carboplatin + 5-FU

Pembrolizumab monotherapy group (pembro mono): pembrolizumab

Standard treatment group (control): cetuximab + cisplatin/carboplatin + 5-FU (EXTREME regimen)

Intervention	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles)	Experimental
Cisplatin	100 mg/m^2	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
Carboplatin	AUC 5 mg/mL/min	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
5-FU	1000 mg/m^2/day 1-4 of each cycle	Every 3 weeks	Intravenous	Day 1-4 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
Cetuximab	Initial dose on day 1 is 400 mg/m^2 followed by weekly doses of 250 mg/m^2	Every week	Intravenous	Days 1, 8, and 15 of each cycle (3 week cycles)	Comparator regimen

Subjects may receive a maximum of 6 cycles (infusions) of the chemotherapy agents (carboplatin, cisplatin, and 5-FU).

After platinum and 5-FU are discontinued, for subjects with at least stable disease, cetuximab monotherapy may continue until disease progression or unacceptable toxicity occurs.

Treatment on trial continued until disease progression is verified by the central imaging vendor, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision, noncompliance, subject receives 24 months of study medication (pembrolizumab arms only), pregnancy, or administrative reasons. Subjects on either pembrolizumab arm who attain a complete response (CR) may consider stopping trial treatment if they meet criteria for holding therapy. Subjects receiving pembrolizumab who stop trial treatment after receiving 24 months of study medication for reasons other than disease progression or intolerability, or subjects who attain a CR and stop trial treatment may be eligible for up to one year of retreatment upon experiencing centrally-verified disease progression at investigator's discretion.

Investigators may switch subjects from cisplatin to carboplatin during the course of the study if toxicities occur. If the cisplatin dose was modified prior to switching, the subject may start at a carboplatin dose of AUC 5 and will be eligible to receive an additional 2 dose modifications of carboplatin.

If subjects on the cetuximab + platinum + 5-FU arm are required to have the platinum and/or 5-FU discontinued for toxicity, the subject and may continue to receive cetuximab alone. In the case of cetuximab toxicity, subjects may continue on chemotherapy alone.

The first on-study imaging was performed at 9 weeks after the date of randomization and then every 6 weeks thereafter or more frequently if clinically indicated. After 1 year, imaging time point will occur every 9 weeks. Progressive disease should be verified by the central imaging vendor prior to subject discontinuation from treatment. Local reading (investigator assessment with site radiology reading) were used to determine eligibility and for subject management.

Objectives

Primary objectives:

- To compare PFS per RECIST 1.1 as assessed by BICR in first line R/M HNSCC subjects, treated with pembrolizumab monotherapy versus standard treatment.
- To compare PFS per RECIST 1.1 as assessed by BICR in first line R/M HNSCC subjects, treated with pembrolizumab in combination with chemotherapy versus standard treatment.
- To evaluate OS in first line R/M HNSCC subjects, treated with pembrolizumab monotherapy versus standard treatment.
- To evaluate OS in first line R/M HNSCC subjects, treated with pembrolizumab in combination with chemotherapy versus standard treatment.

Secondary objectives:

- To evaluate the safety and tolerability profile of pembrolizumab monotherapy or a combination of pembrolizumab with chemotherapy in all first line R/M HNSCC subjects.

The following secondary objectives were evaluated in (1) PD-L1 ≥20 CPS, (2) PD-L1 ≥1 CPS and (3) all participants for both pembrolizumab in combination with chemotherapy and pembrolizumab monotherapy compared to standard treatment:

- To evaluate proportion progression-free at 6 months and 12 months per RECIST 1.1 by BICR of first line R/M HNSCC subjects.
- To evaluate ORR per RECIST 1.1 by BICR in first line R/M HNSCC subjects.
- To evaluate mean change from baseline in global health status/quality of life in 1L R/M HNSCC subjects.
- To evaluate time to deterioration (TTD) in global health status/quality of life, pain and swallowing in first line R/M HNSCC subjects.

Exploratory Objectives:

- To evaluate DOR per RECIST 1.1 by BICR in 1L R/M HNSCC participants.
- To evaluate ORR, DOR, and PFS using irRECIST as assessed by BICR in 1L R/M HNSCC participants.
- To evaluate changes in health-related quality-of-life assessments from baseline in participants with R/M HNSCC using the EORTC QLQ-C30 and EORTC QLQ-H&N35.
- To characterize utilities in participants with R/M HNSCC cancer using the EuroQol EQ-5D.
- To evaluate changes in opioid analgesic use from baseline in participants with R/M HNSCC, based on reported concomitant medications, supplemented with a daily Pain Medication Log.
- To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (eg, PD-L1, genetic variation, serum soluble PD-L1) utilizing archival tumour tissue, and blood sampling.
- To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

Outcomes/endpoints

Table 3: KEYNOTE-048 Efficacy Endpoints

Endpoints		Populations	Definitions
Primary	OS	ITT (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) ITT (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	Time from randomization to death due to any cause
	PFS	ITT (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) ITT (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	Time from randomization to first PD (per RECIST 1.1 based on BICR) or death due to any cause
Secondary	ORR	ITT (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) ITT (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	Proportion of participants who had CR or PR (per RECIST 1.1 based on BICR)
	PFS at 6 months and 12 months	ITT (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) ITT (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	Proportion of participants who have duration of PFS ≥6 months and 12 months, respectively.
	Mean change from baseline in QLQ-C30 global QOL score	FAS (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) FAS (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	EORTC QLQ-C30 global health status/quality of life scores at baseline and week 15
	TTD in global QOL, pain, and swallowing	FAS (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) FAS (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	Time from baseline to first onset of patient reported outcomes (PRO) deterioration with confirmation (true deterioration*).
Exploratory	DOR	ITT (Combo) PD-L1 ≥1 CPS (Combo) PD-L1 ≥20 CPS (Combo) ITT (Mono) PD-L1 ≥1 CPS (Mono) PD-L1 ≥20 CPS (Mono)	Time from first documented evidence of CR or PR until PD (per RECIST 1.1 based on BICR) or death

Abbreviations: BICR= Blinded central radiology review; Combo=pembrolizumab plus chemotherapy; CPS=Combined Positive Score; CR=complete response; DOR=Duration of response; HRQoL=Health related quality of life; Mono=pembrolizumab monotherapy; ORR=Objective response rate; OS=Overall survival; PD=Progressive disease; PD L1=Programmed cell death ligand-1; PFS=Progression-free survival; PR=Partial response; QLQ-C30=Quality of Life Core Questionnaire, Version 3.0;QOL=Quality of life; RECIST 1.1=Response Evaluation Criteria in Solid Tumours, version 1.1; TTD=Time to deterioration.
*defined in the global health status/quality of life, pain, and swallowing endpoints as a 10 points or greater worsening from baseline for each multi-item scale and confirmed by a second adjacent 10 or more deterioration from baseline under a right-censoring rule.

Sample size

A total of 825 participants with a 1:1:1 ratio were planned to be randomized into 3 treatment groups: pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and standard treatment.

KEYNOTE-048 is an event and time driven trial. The sample size was chosen to achieve the required number of PFS and OS events at the time of the 1st planned analysis, followed by time driven analysis at a 2nd interim and final timepoints, as summarized in the following table:

Table 4: Summary of PFS and OS Analysis Strategies

PFS and OS Analyses	Key Endpoints	Timing of Analysis	Expected Number of Events at the Time of Analysis	Primary Purpose of Analysis
Interim analysis 1	PFS OS	~30 months from study start	~423 PFS events between pembrolizumab plus chemotherapy and standard treatment in all participants	Demonstrate PFS and OS superiority
Interim analysis 2	OS	~38 months from study start	~421 deaths between pembrolizumab plus chemotherapy and standard treatment in all participants	Demonstrate PFS (if not significant at IA1) and OS superiority
Final analysis	OS	~44 months from study start	≥222 deaths between one experimental treatment and standard treatment in PD-L1 CPS ≥20 ≥359 deaths between one experimental treatment and standard treatment in PD-L1 CPS ≥1 ≥455 deaths between one experimental treatment and standard treatment in all participants Note: if the expected number of deaths for a hypothesis is not observed by the time that the trial is open for 44 months, the timing of the final analysis may be delayed for up to 2 months or when the target death event numbers are observed, whichever occurs first.	Demonstrate OS superiority
For the interim analyses, the actual timing is determined by the minimum follow-up; and for the final analysis, the actual timing is determined by both the expected event numbers and minimum follow-up. However, to prevent the trial form continuing to an unreasonable duration, if the the expected number of deaths for a hypothesis is not observed by the time that the trial is open for 44 months, the timing of the final analysis may be delayed for up to 2 months or when the target death event numbers are observed, whichever occurs first. The table only lists the timing and the required event numbers of the hypotheses that drive the analysis.				

In particular, at the time of the **final PFS** analysis (interim analysis 2 for OS):

- for subjects with PD-L1 CPS≥20, it was expected to observe approximately 237 PFS events between one experimental treatment and standard treatment. The study had 90% power with each experimental treatment (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) to detect a hazard ratio of 0.58 vs. standard treatment at alpha = 0.19% (one-sided).
- for subjects with PD-L1 CPS≥1, it was expected to observe approximately 378 PFS events between one experimental treatment and standard treatment. The study had 98.6% power with each experimental treatment (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) to detect a hazard ratio of 0.59 vs. standard treatment at alpha = 0.19% (one-sided).
- for all subjects, it was expected to observe approximately 474 PFS events between pembrolizumab monotherapy and standard treatment. The study had 99.6% power with pembrolizumab monotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.19% (one-sided).
- for all subjects, it was expected to observe approximately 474 PFS events between pembrolizumab in combination with chemotherapy and standard treatment. The study had 97.7% power with pembrolizumab in combination with chemotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.02% (one-sided).

The PFS sample size calculation was based on the following assumptions: 1) progression-free survival following an exponential distribution with a median of 6 months in the standard treatment arm; 2) hazard ratios equal to 0.58 for subjects with PD-L1 CPS ≥20, 0.59 for subjects with PD-L1 CPS ≥1 and 0.6 for all subjects; 3) an enrolment period of 21 months; 4) at least 9 months follow-up at interim analysis 1, and 17 months follow-up at interim analysis 2; and 5) a yearly dropout rate of 5%.

At the time of the **final OS** analysis:

- for subjects with PD-L1 CPS≥20, it is expected that approximately 222 deaths will have been observed between one experimental treatment and standard treatment. The study has 90.5% power with each experimental treatment (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.7% (one-sided).
- for subjects with PD-L1 CPS≥1, it is expected that approximately 359 deaths will have been observed between one experimental treatment and standard treatment. The study has 94.3% power with each experimental treatment (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) to detect a hazard ratio of 0.65 vs. standard treatment at alpha = 0.7% (one-sided).
- for all subjects, it is expected that approximately 455 deaths will have been observed between one experimental treatment and standard treatment. The study has 87.85% power with a hazard ratio of 0.85 to establish non-inferiority (NI margin = 1.2) for each experimental treatment (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) vs. standard treatment at alpha = 0.7% (one-sided) (that is, the treatment could be considered as non-inferior to the standard treatment arm in terms of OS if the upper bound of the CI, based on the alpha level allocated to the analysis for the HR is <1.2).
- for all subjects, it is expected that approximately 455 deaths will have been observed between one experimental treatment and standard treatment. The study has 90.4% power with each experimental treatment (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) to detect a hazard ratio of 0.7 vs. standard treatment at alpha = 0.7% (one-sided).

The OS sample size calculation was based on the following assumptions: 1) overall survival following an exponential distribution with a median of 10 months in the standard treatment arm; 2) the hazard ratios equal to 0.6 for subjects with PD-L1 CPS ≥20, 0.65 for subjects with PD-L1 CPS ≥1, 0.7 for all subjects for the superiority hypotheses, and 0.85 for all subjects for the non-inferiority hypotheses; 3) an enrollment period of 21 months; 4) at least 23 months follow-up at the final analysis; and 5) a yearly dropout rate of 2%.

The assumptions for median PFS of 6 months and median OS of 10 months in the standard treatment arm were based on the median PFS and median OS estimates from the EXTREME trial. The assumptions do not take into account potential prognostic implications in a biomarker selected population. As such, the median of the standard treatment arm for the PD-L1 positive subgroups may be more or less than 6 months for PFS and more or less than 10 months for OS.

Randomisation

Randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects were assigned randomly in a 1:1:1 ratio to one of the 3 treatment arms.

Randomization was stratified according to the following factors:

1. PD-L1 tumour expression by TPS (≥50% vs not ≥50%)

2. HPV status (positive vs. negative); HPV status for oropharynx cancer was determined by p16 IHC. HPV status for subjects without oropharynx cancer (e.g. cancers of the oral cavity, hypopharynx and larynx) was considered HPV negative.
3. ECOG Performance Scale (0 vs. 1)

Blinding (masking)

Study was open-label.

PD-L1 status of all participants was blinded to both Investigators and the Sponsor.

Statistical methods

Efficacy population

The analysis of primary efficacy endpoints were based on the intention-to-treat (ITT) population, i.e., subjects were included in the treatment group to which they were randomized.

Statistical methods

Table 5: Efficacy analysis methods

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Censored according to rules in Table 18
OS	Testing: Stratified Log-rank test (for superiority hypotheses only) Estimation: Stratified Cox model with Efron's tie handling method	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Censored at last known alive date
Secondary Analyses:			
PFS at 6 months/12 months (RECIST 1.1) by BICR	Kaplan-Meier estimation with CI	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Censored according to primary censoring rule in Table 18
ORR (RECIST 1.1) by BICR	Stratified Miettinen and Nurminen method	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Subjects with missing data are considered non-responders
Exploratory Analyses:			
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis
Sensitivity analyses will be performed for PFS, ORR and DOR based on investigator's assessment.			

The non-parametric Kaplan-Meier method was used to estimate the PFS/OS curve in each treatment group. The treatment difference in PFS/OS 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 (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate was reported.

The same stratification factors used for randomization were used as the stratification factors in both the stratified log-rank test and the stratified Cox model (as well as in the stratified Miettinen and Nurminen method) for the analyses in all subjects and in subjects with PD-L1 CPS ≥1. For analyses in the PD-L1 CPS ≥20 subgroup, HPV status and ECOG status were used as the stratification factors. In case the event count in any stratum is <5, for the analysis purpose, stratification factors would be combined in the order of ECOG->HPV status->PD-L1 status (defined by TPS) until event count in every stratum is ≥5.

Sensitivity analyses

To account for the possible non-proportional hazards effect associated with immunotherapies, two sensitivity analyses were conducted, the first based on the weighted log-rank test with parameter (0,1), the other using the restricted mean survival time (RMST) method.

Adjustment for the effect on OS of crossover (of subjects in the standard therapy arm that may switch to another anti PD-1 treatment following confirmation of progressive disease) is planned based on methods such as Rank Preserving Structural Failure Time (RPSFT) model, two stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

Sensitivity analyses were performed for PFS, ORR and DOR based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, two sensitivity analyses with a different set of censoring rules were performed. The censoring rules for PFS primary endpoint and sensitivity analyses are summarized in the following table:

Table 6: Censoring rules for Primary and Sensitivity Analyses of 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
No PD and no death; ≥ 2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
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 at any time 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

Interim analyses

Two interim efficacy analyses and a final analysis are planned in this study. A summary table of PFS and OS analysis strategy is shown in section "sample size".

At first interim analysis (IA1), PFS/OS analyses took place when all subjects have been followed up for at least 9 months. Assuming 21 months enrolment period for 825 all subjects, interim analysis 1 was

projected to occur ~30 months after study start, with the primary objective to demonstrate PFS superiority of pembrolizumab (monotherapy or in combination with chemotherapy).

The second interim analysis (IA2), which is the final PFS analysis, took place when all subjects have been followed up for at least 17 months. Assuming 21 months enrolment period for 825 all subjects, interim analysis 2 was projected to occur ~38 months after study start, with the primary objective to demonstrate OS superiority of pembrolizumab (monotherapy or in combination with chemotherapy). A PFS hypothesis was to be tested only if superior PFS was not declared for that hypothesis at interim analysis 1 (IA1).

Subgroup analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted by treatment group within each category of the following classification variables:

- Stratification factors
- PD-L1 expression level defined by CPS (≥20 vs. not ≥20; and ≥1 vs. not ≥1)
- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)
- Race (white vs. all others)
- Region (North America [NA] vs European Union [EU] vs Rest of the World [ROW])
- Smoking status (never vs. former vs. current)
- Disease status (recurrent vs. metastatic)

Subgroup analyses did not use stratified analyses. The consistency of the treatment effect was assessed descriptively.

Multiplicity

The overall type I error rate was strongly controlled at 2.5% (one-sided) with:

- 0.19% allocated to each PFS hypothesis of pembrolizumab monotherapy vs. standard treatment (H1) and pembrolizumab in combination with chemotherapy vs. standard treatment (H4) in subjects with PD-L1 CPS ≥20;
- 0.02% allocated to PFS hypothesis of pembrolizumab in combination with chemotherapy vs. standard treatment in all subjects (H6);
- 0.7% allocated to each OS hypothesis of pembrolizumab monotherapy vs. standard treatment (H7) and pembrolizumab in combination with chemotherapy vs. standard treatment (H11) in subjects with PD-L1 CPS ≥20;
- 0.7% allocated to OS non-inferiority hypothesis of pembrolizumab in combination with chemotherapy vs. standard treatment in all subjects (H13).

The alpha reallocation strategy followed the graphical approach of Maurer and Bretz, as reported in the following figure:

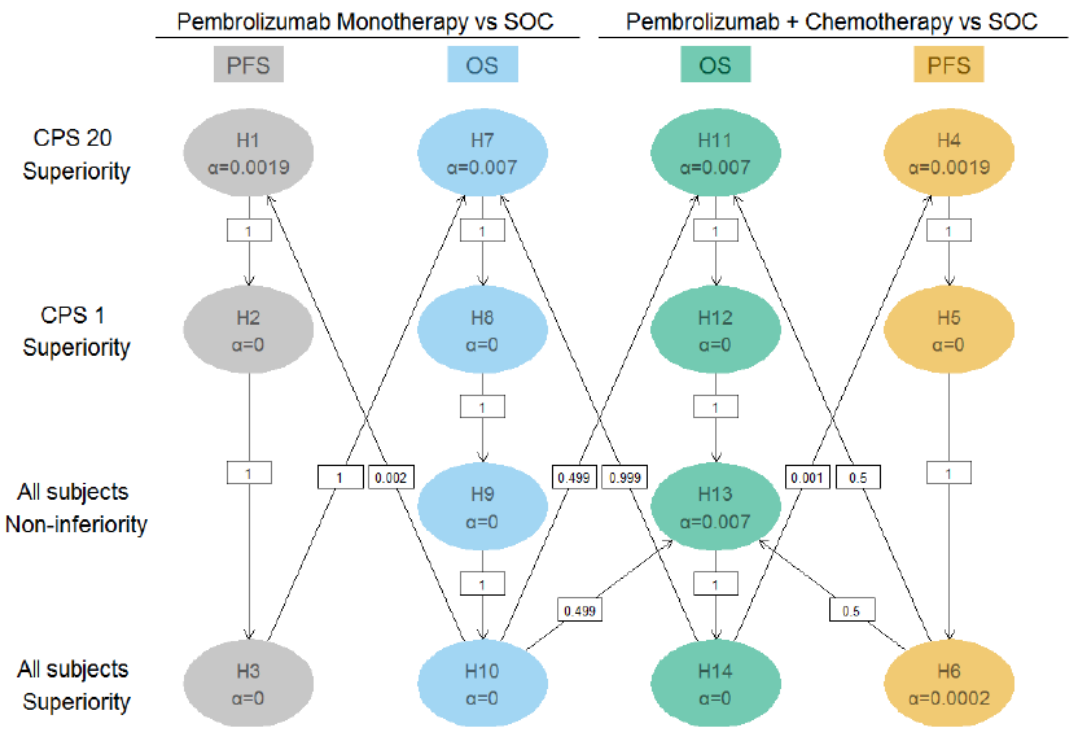


Figure 2: multiplicity strategy

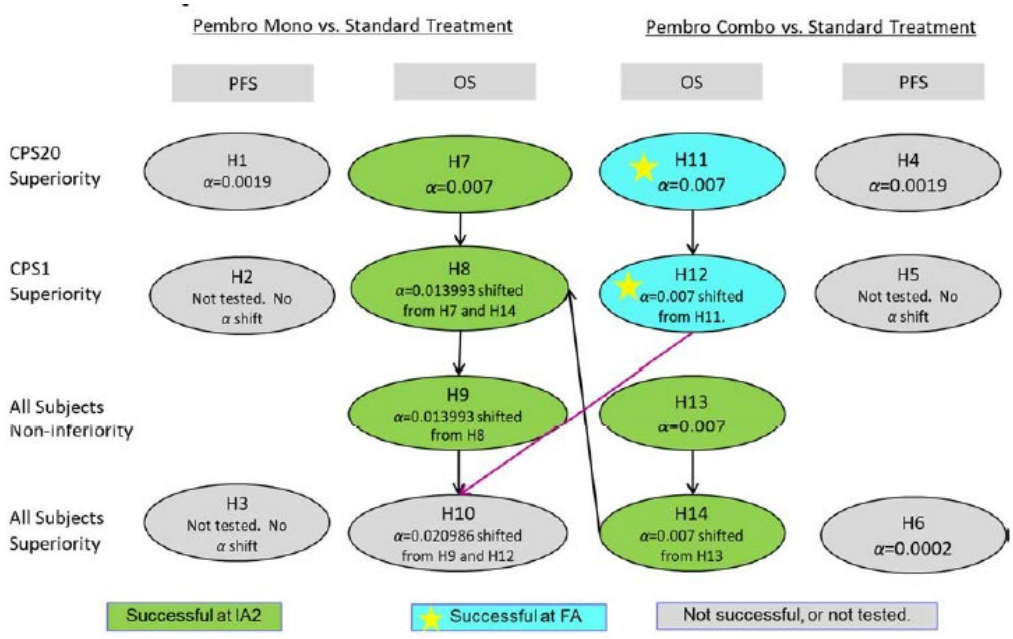


Figure 3: Alpha Re-allocation Schema at IA2 and FA for KEYNOTE-048

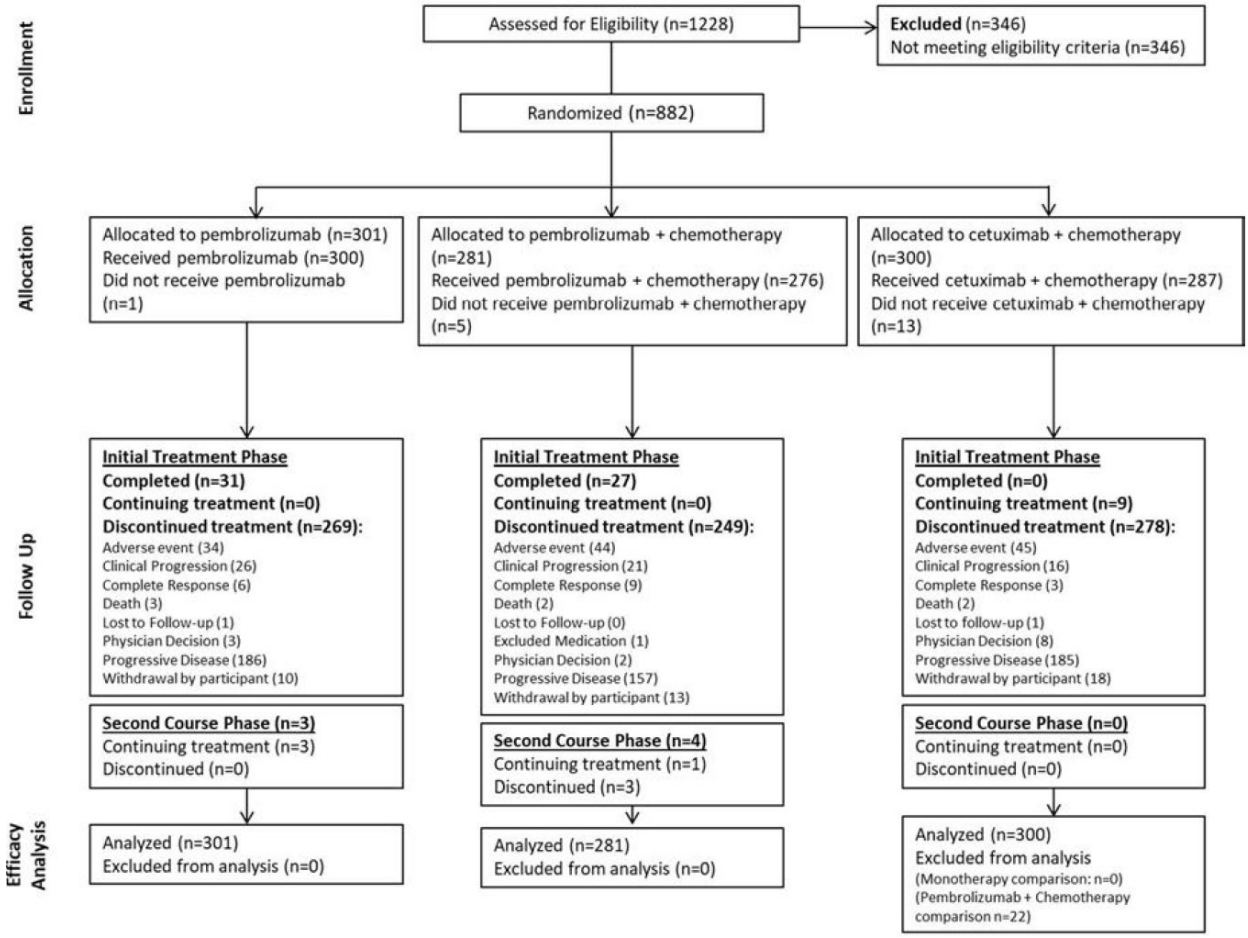
The stratified Miettinen and Nurminen's method was used for comparison of the objective response rates between the treatment groups.

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR was assessed using RECIST 1.1 separately by BICR and by investigator's assessment.

The PRO analyses are based on the PRO FAS population, defined as all randomized participants who have at least 1 PRO assessment available and have received at least 1 dose of the study medication. PROs were evaluated using the EORTC QLQ-30, EORTC QLQ-H&N35 and the EQ-5D questionnaires.

Results

Participant flow



Note: "Completed" in the Follow-up phase indicates the participant completed 24 months (initial treatment phase) of treatment with pembrolizumab.

Recruitment

This study was conducted at 228 centres in 37 countries. First participant first visit was on 01-APR-2015, last patient was randomized on 17-JAN-2017.

Enrolment in the pembrolizumab plus chemotherapy group was paused on 13 August 2015 and reopened on 2 October 2015, based on the external DMC recommendation after 20 participants were randomized to that group, following the review of the first 3 death events in 14 participants enrolled in that group as of 24-JUL-2015. After the DMC completed their safety assessment of those 20 subjects who had completed 2 cycles of study treatment, the DMC recommended lifting the enrolment pause.

Interim Analysis 2 (IA2): data cut-off is 13-JUN-2018, data-base lock is 29-JUN-2018.

At the IA2, the median duration of follow-up was 13.0 months (range: 0.1, 36.6) in the pembrolizumab plus chemotherapy group and 10.7 months (range: 0.1, 35.3) in the standard treatment group. The

median follow-up duration for all subjects was 11.7 months (range: 0.2, 37.3) in the pembrolizumab monotherapy group and 10.7 months (range: 0.1, 35.3) in the standard treatment group.

Final Analysis (FA): data cut-off is 25-FEB-2019, data-base lock is 25-MAR-2019. The median duration of follow-up was 13.0 months (range: 0.1, 43.4) in the pembrolizumab plus chemotherapy group and 10.7 months (range: 0.1, 40.7) in the standard treatment group. The median follow-up duration for all subjects was 11.5 months (range: 0.2, 45.7) in the pembrolizumab monotherapy group and 10.7 months (range: 0.1, 41.8) in the standard treatment group.

Conduct of the study

Protocol amendments

The main protocol changes are summarized below:

Table 7: Summary of MK-3475 KEYNOTE-048 Protocol Amendments

Protocol or Amendment	Rationale
Protocol (05-DEC-2014)	Original protocol.
Amendment 01 (26-JUN-2015) Global (all countries)	Increased sample size from 750 to 780 subjects, including the first 600 subjects with any level of PD-L1 expression and the remaining 180 subjects with strongly positive PD-L1 expression
Amendment 05 (05-AUG-2016) Global (all countries)	Enrollment target was updated from 780 to 825 subjects, OS was added to the primary objectives and hypotheses, and the description of the biomarker selected population was updated. In addition, the SAP was updated to: 1. Move OS from a secondary efficacy endpoint to primary, 2. For PD-L1 positive sub-populations, updated strongly positive and positive as defined by tumour proportion score (TPS) to PD-L1 ≥20% CPS, PD-L1 ≥10% CPS, and PD-L1 ≥ 1% CPS. 3. Updated analysis populations, statistical methods, power and sample size calculation, multiplicity strategy, interim analysis plan, and subgroup analyses, accordingly.
Amendment 07 (17-MAR-2017) Global (all countries)	CPS 10% was removed from the analyses plan. Only the 20% and 1% CPS cutpoints will be analyzed. Therefore, references to PD-L1 10% CPS were removed. Hypothesis numbering was modified accordingly.
Amendment 08 (24-AUG-2017) Global (all countries)	Increased follow-up time at the interim and final analyses by 3 months, and updated timing of each analysis. Power calculations and analysis plan (expected timing, required number of events and boundary properties) were updated accordingly.
Amendment 09 (09-NOV-2017) Global (all countries)	Updated the dose modifications table for pembrolizumab including the addition of guidelines for the management of myocarditis based upon health authority feedback; added hypotheses for PFS and OS superiority in the biomarker positive subpopulation for comparison of pembrolizumab in combination with chemotherapy versus standard treatment; increased the follow-up period by 3 months for the second interim analysis and final analysis with power calculations and analysis plan updated accordingly, moved DOR to an exploratory endpoint; added OS and PFS hypotheses in the biomarker-positive subpopulation for pembrolizumab combination therapy, and updated the multiplicity strategy accordingly; and added language to allow for collection of survival status for subjects in all phases of the study at time points specified by the Sponsor.
Amendment 10 (11-JAN-2019) Global (all countries)	Modified to indicate the number of expected events, rather than required events; references to "event-driven" were removed and text was modified to describe the timing of the final analysis to account for the scenario if the number of deaths for 1 hypothesis accumulates slower than expected to prevent the trial continuing for an unreasonable period for the final analysis.

Change from TPS to CPS score

TPS is defined by the percentage of neoplastic cells expressing PD-L1 at any intensity (weak, moderate, or strong), and only takes into account the expression of PD-L1 on neoplastic cells.

CPS is defined by the number of tumour cells and mononuclear inflammatory cells within the tumourtumour nests and the adjacent supporting stroma expressing PD-L1 at any intensity divided by number of tumourtumour cells, then multiplied by 100.

In KEYNOTE-048, with protocol amendment 05 (dated 05-AUG-2016), the pre-specified biomarker scoring method for the analysis of efficacy was updated from TPS to CPS, and the biomarker cut point for efficacy analyses was changed from strongly positive PD-L1 (TPS ≥50%) to CPS ≥20, CPS ≥10, and CPS ≥1 (and subsequently limited to CPS ≥20 and CPS ≥1 in protocol amendment 07, dated 17-MAR-2017).

Similarly, the PD-L1 biomarker analysis population and cutoff in KEYNOTE-040 (2L HNSCC study) was changed from TPS ≥50% to CPS ≥1 during the study (protocol amendment 10, dated 10-MAR-2016).

Based on data from KEYNOTE-012 for BOR, PFS, and OS, the MAH considered that PD-L1 expression in both tumour and infiltrating immune cells (CPS scoring) showed improved association with clinical outcome under pembrolizumab treatment when compared with PD-L1 expression in tumour cells alone (TPS scoring). In KEYNOTE-012, patients whose tumours were CPS ≥1 showed increased response rates relative to patients whose tumours were CPS<1. In contrast, the 1% and 50% TPS cutoffs showed fairly similar response rates above and below the cutoff and there seemed to be poor sensitivity in general when scoring tumour alone.

In addition, based on clinical utility, sensitivity, specificity, as well as the prevalence of patients associated with various PD-L1 cut points evaluated in this analysis, the MAH selected CPS ≥1 and CPS ≥20 as the biomarker cutoffs for PD-L1 assessment in KEYNOTE-048. The CPS assay was analytically validated and the testing site personnel appropriately trained on CPS ≥20 and ≥1 before implementation to determine PD-L1 status in the KEYNOTE-048 study. Furthermore, the MAH considered that the survival benefit in CPS ≥1 and CPS ≥20 populations at the IA2 of KEYNOTE-048 demonstrated clinical validation for the scoring method. Additionally, the MAH reported that the method has been extensively analytically validated in HNSCC by the MAH's IHC partner, Agilent, to demonstrate sensitivity, robustness and reproducibility.

PD-L1 expression was based on the PD-L1 IHC 22C3 pharmDxTM Kit.

Protocol deviations

A total of 308 (34.9%) of the 882 randomized participants had one or more important protocol deviations (ie, those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or wellbeing): 85 patients (28.2%) in the pembro mono, 116 (41.3%) in the pembro combo, and 107 (35.7%) in the control arm.

Important protocol deviations were reported across the following categories:

- Had no documented initial consent to enter the trial, or did not have their consent form updated per the Informed Consent implementation plan following a significant safety change to the Risk Language/Informed Consent (following site/regional approval of the ICF),
- Entered into the study (ie, progressed beyond screening) and did not meet key inclusion/exclusion criteria,
- Received incorrect study intervention and/or were administered improperly stored study intervention,
- Received prohibited concomitant intervention,

- Experienced an SAE/ECI/pregnancy and information was not reported as required per the protocol,
- Missed key safety or efficacy procedures which may impact participant safety or data integrity.

No important protocol deviations were classified as GCP compliance issues.

Changes Following Study Unblinding

Following the DMC review on 23-JUL-2018 and the unblinding of the study team and program statisticians on 26-JUL-2018, it was identified that one participant randomized to the pembrolizumab plus chemotherapy group was erroneously excluded from the analyses comparing the efficacy of pembrolizumab plus chemotherapy to standard treatment. After the discovery and following confirmation of the error, the analysis dataset was updated to subsequently include this participant. No data points were altered in the clinical database or the SDTM source data to fix this error, and that the change was implemented only in the analysis dataset.

On 11-OCT-2018, several cases of measurement discrepancy were reported by independent reviewers and PAREXEL Medical Imaging (PXL) staff, where the value presented in ALICE (Medical Imaging proprietary viewing software) differed from the value captured in the ANALYSIS eCRF. A decision was made to remediate measurement discrepancies through a modified re-review in a consistent manner for all MSD studies where PXL was utilized as the central imaging vendor. In KEYNOTE-048, 16 participants were identified by PXL's assurance tool with measurement discrepancies in scope for the remediation process. Following remediation, a change in assessment occurred with 4 participants. A sensitivity analysis performed with these 4 new assessments showed minimal impact to IA2 PFS assessment for KEYNOTE-048. The findings do not impact the OS outcomes.

Baseline data

Pembrolizumab plus chemotherapy (platinum+5-FU) vs chemotherapy (EXTREME regimen)

Table 8: Subject Characteristics (Pembro Combo vs Control) (ITT Population)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	281		278		559	
Gender						
Male	224	(79.7)	242	(87.1)	466	(83.4)
Female	57	(20.3)	36	(12.9)	93	(16.6)
Age (Years)						
<65	180	(64.1)	181	(65.1)	361	(64.6)
>=65	101	(35.9)	97	(34.9)	198	(35.4)
Mean	60.7		60.9		60.8	
SD	9.8		10.0		9.9	
Median	61.0		61.0		61.0	
Range	20 to 85		24 to 84		20 to 85	
Race						
American Indian Or Alaska Native	3	(1.1)	6	(2.2)	9	(1.6)
Asian	60	(21.4)	49	(17.6)	109	(19.5)
Black Or African American	11	(3.9)	6	(2.2)	17	(3.0)
Multi-Racial	4	(1.4)	9	(3.2)	13	(2.3)
White	203	(72.2)	207	(74.5)	410	(73.3)
Missing	0	(0.0)	1	(0.4)	1	(0.2)

Ethnicity						
Hispanic Or Latino	45	(16.0)	44	(15.8)	89	(15.9)
Not Hispanic Or Latino	213	(75.8)	211	(75.9)	424	(75.8)
Not Reported	18	(6.4)	14	(5.0)	32	(5.7)
Unknown	5	(1.8)	9	(3.2)	14	(2.5)
Region Group						
NA	60	(21.4)	59	(21.2)	119	(21.3)
EU	88	(31.3)	94	(33.8)	182	(32.6)
ROW	133	(47.3)	125	(45.0)	258	(46.2)
Smoking Status						
Never Smoker	57	(20.3)	61	(21.9)	118	(21.1)
Ex Smoker	168	(59.8)	179	(64.4)	347	(62.1)
Current Smoker	56	(19.9)	36	(12.9)	92	(16.5)
Missing	0	(0.0)	2	(0.7)	2	(0.4)
ECOG						
0	110	(39.1)	108	(38.8)	218	(39.0)
1	171	(60.9)	170	(61.2)	341	(61.0)
HPV Status						
Positive	60	(21.4)	61	(21.9)	121	(21.6)
Negative	221	(78.6)	217	(78.1)	438	(78.4)
PD-L1 TPS Status						
Strongly Positive	66	(23.5)	62	(22.3)	128	(22.9)
Not Strongly Positive	215	(76.5)	216	(77.7)	431	(77.1)
PD-L1 CPS Status (CPS>=1)						
CPS >=1	242	(86.1)	235	(84.5)	477	(85.3)
CPS <1	39	(13.9)	43	(15.5)	82	(14.7)
PD-L1 CPS Status (CPS>=20)						
CPS >=20	126	(44.8)	110	(39.6)	236	(42.2)
CPS <20	154	(54.8)	165	(59.4)	319	(57.1)
Missing	1	(0.4)	3	(1.1)	4	(0.7)
PD-L1 CPS Status						
CPS<1	39	(13.9)	43	(15.5)	82	(14.7)
1<=CPS<20	116	(41.3)	125	(45.0)	241	(43.1)
CPS>=20	126	(44.8)	110	(39.6)	236	(42.2)
Baseline Tumour Size (mm) (Grouping by ITT Median)						
>=Median	146	(52.0)	124	(44.6)	270	(48.3)
<Median	114	(40.6)	135	(48.6)	249	(44.5)
Missing	21	(7.5)	19	(6.8)	40	(7.2)
Subjects with data	260		259		519	
Mean	82.3		78.7		80.5	
SD	61.6		67.7		64.7	
Median	67.3		58.7		63.6	
Range	12 to 385		10 to 419		10 to 419	
Disease Status						
Metastatic	201	(71.5)	187	(67.3)	388	(69.4)
Recurrent	76	(27.0)	88	(31.7)	164	(29.3)
Neither	4	(1.4)	3	(1.1)	7	(1.3)
Primary Tumour Staging						

T0	42	(14.9)	34	(12.2)	76	(13.6)
T1	22	(7.8)	12	(4.3)	34	(6.1)
T1A	1	(0.4)	0	(0.0)	1	(0.2)
T2	40	(14.2)	48	(17.3)	88	(15.7)
T3	37	(13.2)	36	(12.9)	73	(13.1)
T3B	0	(0.0)	1	(0.4)	1	(0.2)
T4	38	(13.5)	52	(18.7)	90	(16.1)
T4A	54	(19.2)	47	(16.9)	101	(18.1)
T4B	13	(4.6)	22	(7.9)	35	(6.3)
TX	34	(12.1)	26	(9.4)	60	(10.7)
Regional Lymph Nodes Staging						
N0	76	(27.0)	77	(27.7)	153	(27.4)
N1	37	(13.2)	47	(16.9)	84	(15.0)
N2	134	(47.7)	118	(42.4)	252	(45.1)
N3	22	(7.8)	29	(10.4)	51	(9.1)
NX	12	(4.3)	7	(2.5)	19	(3.4)
Metastatic Staging						
M0	80	(28.5)	91	(32.7)	171	(30.6)
M1	201	(71.5)	187	(67.3)	388	(69.4)
Overall Cancer Staging						
III	15	(5.3)	13	(4.7)	28	(5.0)
IVA	50	(17.8)	58	(20.9)	108	(19.3)
IVB	15	(5.3)	20	(7.2)	35	(6.3)
IVC	201	(71.5)	187	(67.3)	388	(69.4)
Primary Tumour Location-Oral Cavity						
Yes	82	(29.2)	84	(30.2)	166	(29.7)
No	199	(70.8)	194	(69.8)	393	(70.3)
Primary Tumour Location-Larynx						
Yes	46	(16.4)	56	(20.1)	102	(18.2)
No	235	(83.6)	222	(79.9)	457	(81.8)
Primary Tumour Location-Hypopharynx						
Yes	44	(15.7)	36	(12.9)	80	(14.3)
No	237	(84.3)	242	(87.1)	479	(85.7)
Primary Tumour Location-Oropharynx						
Yes	113	(40.2)	107	(38.5)	220	(39.4)
No	168	(59.8)	171	(61.5)	339	(60.6)
Time from Latest Platinum Therapy (days)						
Subjects with data	130		130		260	
Mean	795.0		893.5		844.3	
SD	954.8		920.1		937.1	
Median	457.5		585.5		513.5	
Range	146 to 6278		119 to 6817		119 to 6817	
Time from Prior Systemic Therapy (days)						
Subjects with data	141		138		279	
Mean	760.0		871.3		815.0	
SD	922.1		894.8		908.8	
Median	449.0		571.5		502.0	
Range	146 to 6278		119 to 6817		119 to 6817	
Database Cutoff Date: 13JUN2018.						

Table 9: Summary of Prior Line of Systemic Therapy (Pembro Combo vs Control) (ITT Population)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	281		278		559	
Subjects with no prior systemic therapy	140	(49.8)	140	(50.4)	280	(50.1)
Primary/Locally Advanced/With Curative Intent	**136**	**(48.4)**	**136**	**(48.9)**	**272**	**(48.7)**
Cetuximab	19	(6.8)	16	(5.8)	35	(6.3)
Platinum	125	(44.5)	128	(46.0)	253	(45.3)
Recurrent/With Curative Intent	**10**	**(3.6)**	**4**	**(1.4)**	**14**	**(2.5)**
Cetuximab	0	(0.0)	0	(0.0)	0	(0.0)
Platinum	9	(3.2)	3	(1.1)	12	(2.1)

A subject can have multiple prior systemic therapies and be counted in different rows that are applicable. But every subject is counted a single time for each applicable row and column.
Database Cutoff Date: 13JUN2018.

Table 10: Subject Characteristics (Pembro Combo vs Control) (ITT population) (CPS≥1 and CPS≥20)

	CPS>=1				CPS>=20			
	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	242		235		126		110	
Gender								
Male	188	(77.7)	203	(86.4)	90	(71.4)	96	(87.3)
Female	54	(22.3)	32	(13.6)	36	(28.6)	14	(12.7)
Age (Years)								
<65	153	(63.2)	152	(64.7)	77	(61.1)	77	(70.0)
>=65	89	(36.8)	83	(35.3)	49	(38.9)	33	(30.0)
Mean	60.6		60.8		61.1		59.8	
SD	9.9		10.3		9.6		10.2	
Median	61.0		61.0		62.0		60.0	
Range	20 to 85		24 to 84		28 to 85		24 to 80	
Race								
American Indian Or Alaska Native	2	(0.8)	6	(2.6)	1	(0.8)	3	(2.7)
Asian	48	(19.8)	43	(18.3)	24	(19.0)	20	(18.2)
Black Or African American	10	(4.1)	3	(1.3)	3	(2.4)	1	(0.9)
Multi-Racial	4	(1.7)	9	(3.8)	3	(2.4)	4	(3.6)
White	178	(73.6)	173	(73.6)	95	(75.4)	82	(74.5)
Missing	0	(0.0)	1	(0.4)	-			
Ethnicity								
Hispanic Or Latino	39	(16.1)	34	(14.5)	24	(19.0)	15	(13.6)
Not Hispanic Or Latino	185	(76.4)	181	(77.0)	96	(76.2)	82	(74.5)
Not Reported	14	(5.8)	13	(5.5)	4	(3.2)	8	(7.3)
Unknown	4	(1.7)	7	(3.0)	2	(1.6)	5	(4.5)
Region Group								
NA	53	(21.9)	51	(21.7)	30	(23.8)	30	(27.3)
EU	76	(31.4)	82	(34.9)	39	(31.0)	35	(31.8)
ROW	113	(46.7)	102	(43.4)	57	(45.2)	45	(40.9)
Smoking Status								

Never Smoker	50	(20.7)	58	(24.7)	30	(23.8)	28	(25.5)
Ex Smoker	143	(59.1)	142	(60.4)	75	(59.5)	63	(57.3)
Current Smoker	49	(20.2)	33	(14.0)	21	(16.7)	18	(16.4)
Missing	0	(0.0)	2	(0.9)	0	(0.0)	1	(0.9)
ECOG								
0	92	(38.0)	94	(40.0)	47	(37.3)	47	(42.7)
1	150	(62.0)	141	(60.0)	79	(62.7)	63	(57.3)
HPV Status								
Positive	53	(21.9)	50	(21.3)	27	(21.4)	25	(22.7)
Negative	189	(78.1)	185	(78.7)	99	(78.6)	85	(77.3)
PD-L1 TPS Status								
Strongly Positive	66	(27.3)	62	(26.4)	65	(51.6)	58	(52.7)
Not Strongly Positive	176	(72.7)	173	(73.6)	61	(48.4)	52	(47.3)
PD-L1 CPS Status (CPS>=20)								
CPS >=20	126	(52.1)	110	(46.8)	-		-	
CPS <20	115	(47.5)	123	(52.3)				
Missing	1	(0.4)	2	(0.9)				
Baseline Tumour Size (mm) (Grouping by ITT Median)								
>=Median	128	(52.9)	102	(43.4)	63	(50.0)	42	(38.2)
<Median	95	(39.3)	116	(49.4)	54	(42.9)	59	(53.6)
Missing	19	(7.9)	17	(7.2)	9	(7.1)	9	(8.2)
Subjects with data	223		218		117		101	
Mean	82.7		73.0		74.7		65.8	
SD	59.8		58.6		47.6		55.0	
Median	68.1		56.0		64.7		51.2	
Range	12 to 385		10 to 419		13 to 206		10 to 320	
Disease Status								
Metastatic	173	(71.5)	154	(65.5)	87	(69.0)	69	(62.7)
Recurrent	65	(26.9)	78	(33.2)	38	(30.2)	40	(36.4)
Neither	4	(1.7)	3	(1.3)	1	(0.8)	1	(0.9)
Primary Tumour Staging								
T0	33	(13.6)	33	(14.0)	16	(12.7)	20	(18.2)
T1	18	(7.4)	9	(3.8)	11	(8.7)	4	(3.6)
T1A	1	(0.4)	0	(0.0)	-		-	
T2	38	(15.7)	42	(17.9)	15	(11.9)	20	(18.2)
T3	33	(13.6)	31	(13.2)	20	(15.9)	11	(10.0)
T3B	0	(0.0)	1	(0.4)	-		-	
T4	31	(12.8)	43	(18.3)	14	(11.1)	18	(16.4)
T4A	48	(19.8)	39	(16.6)	30	(23.8)	21	(19.1)
T4B	11	(4.5)	20	(8.5)	7	(5.6)	7	(6.4)
TX	29	(12.0)	17	(7.2)	13	(10.3)	9	(8.2)
Regional Lymph Nodes Staging								
N0	64	(26.4)	63	(26.8)	38	(30.2)	34	(30.9)
N1	33	(13.6)	41	(17.4)	11	(8.7)	27	(24.5)
N2	114	(47.1)	102	(43.4)	61	(48.4)	36	(32.7)
N3	20	(8.3)	23	(9.8)	10	(7.9)	11	(10.0)
NX	11	(4.5)	6	(2.6)	6	(4.8)	2	(1.8)
Metastatic Staging								
M0	69	(28.5)	81	(34.5)	39	(31.0)	41	(37.3)
M1	173	(71.5)	154	(65.5)	87	(69.0)	69	(62.7)

Overall Cancer Staging								
III	14	(5.8)	10	(4.3)	11	(8.7)	6	(5.5)
IVA	42	(17.4)	54	(23.0)	22	(17.5)	26	(23.6)
IVB	13	(5.4)	17	(7.2)	6	(4.8)	9	(8.2)
IVC	173	(71.5)	154	(65.5)	87	(69.0)	69	(62.7)
Primary Tumour Location-Oral Cavity								
Yes	77	(31.8)	73	(31.1)	51	(40.5)	44	(40.0)
No	165	(68.2)	162	(68.9)	75	(59.5)	66	(60.0)
Primary Tumour Location-Larynx								
Yes	37	(15.3)	48	(20.4)	14	(11.1)	16	(14.5)
No	205	(84.7)	187	(79.6)	112	(88.9)	94	(85.5)
Primary Tumour Location-Hypopharynx								
Yes	33	(13.6)	30	(12.8)	17	(13.5)	7	(6.4)
No	209	(86.4)	205	(87.2)	109	(86.5)	103	(93.6)
Primary Tumour Location-Oropharynx								
Yes	98	(40.5)	88	(37.4)	45	(35.7)	43	(39.1)
No	144	(59.5)	147	(62.6)	81	(64.3)	67	(60.9)
Time from Latest Platinum Therapy (days)								
Subjects with data	109		113		53		50	
Mean	734.4		866.8		813.7		951.0	
SD	939.9		883.0		1137.9		1157.3	
Median	441.0		575.0		430.0		502.0	
Range	146 to 6278		201 to 6817		146 to 6278		224 to 6817	
Time from Prior Systemic Therapy (days)								
Subjects with data	118		118		57		52	
Mean	705.3		851.8		764.6		933.9	
SD	905.8		863.8		1100.4		1135.7	
Median	440.0		601.0		421.0		521.5	
Range	146 to 6278		201 to 6817		146 to 6278		224 to 6817	
Database Cutoff Date: 13JUN2018.								

The choice of platinum compound in KEYNOTE-048 was made by the investigator before randomization, which was documented in IVRS. Overall, approximately 60% received carboplatin and 40% received cisplatin at first dose in the pembrolizumab + chemo group and standard treatment group. In the pembrolizumab plus chemotherapy group and standard treatment group, 119 (43.1%) and 119 (41.5%) participants were assigned to receive cisplatin, respectively. During the study, 33.6% (40 of 119 participants) and 30.3% (36 of 119 participants) switched from cisplatin to carboplatin in the pembrolizumab plus chemotherapy and standard treatment groups, respectively. For participants who switched from cisplatin to carboplatin, the median number of cycles of cisplatin and carboplatin received in the pembrolizumab plus chemotherapy group was 2 cycles and 2 cycles, respectively, and in the standard treatment group was 2 cycles and 3 cycles, respectively.

Pembrolizumab vs chemotherapy (EXTREME regimen)

Table 11: Subject Characteristics (Pembro Mono vs Control) (ITT Population)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	301		300		601	
Gender						
Male	250	(83.1)	261	(87.0)	511	(85.0)
Female	51	(16.9)	39	(13.0)	90	(15.0)
Age (Years)						
<65	190	(63.1)	195	(65.0)	385	(64.1)
>=65	111	(36.9)	105	(35.0)	216	(35.9)
Mean	61.2		61.0		61.1	
SD	9.4		10.0		9.7	
Median	62.0		61.0		61.0	
Range	22 to 94		24 to 84		22 to 94	
Race						
American Indian Or Alaska Native	5	(1.7)	6	(2.0)	11	(1.8)
Asian	58	(19.3)	54	(18.0)	112	(18.6)
Black Or African American	4	(1.3)	6	(2.0)	10	(1.7)
Multi-Racial	12	(4.0)	9	(3.0)	21	(3.5)
White	219	(72.8)	224	(74.7)	443	(73.7)
Missing	3	(1.0)	1	(0.3)	4	(0.7)
Ethnicity						
Hispanic Or Latino	46	(15.3)	44	(14.7)	90	(15.0)
Not Hispanic Or Latino	233	(77.4)	231	(77.0)	464	(77.2)
Not Reported	19	(6.3)	16	(5.3)	35	(5.8)
Unknown	3	(1.0)	9	(3.0)	12	(2.0)
Region Group						
NA	75	(24.9)	62	(20.7)	137	(22.8)
EU	87	(28.9)	105	(35.0)	192	(31.9)
ROW	139	(46.2)	133	(44.3)	272	(45.3)
Smoking Status						
Never Smoker	62	(20.6)	64	(21.3)	126	(21.0)
Ex Smoker	186	(61.8)	193	(64.3)	379	(63.1)
Current Smoker	53	(17.6)	41	(13.7)	94	(15.6)
Missing	0	(0.0)	2	(0.7)	2	(0.3)
ECOG						
0	118	(39.2)	117	(39.0)	235	(39.1)
1	183	(60.8)	183	(61.0)	366	(60.9)
HPV Status						
Positive	63	(20.9)	67	(22.3)	130	(21.6)
Negative	238	(79.1)	233	(77.7)	471	(78.4)
PD-L1 TPS Status						
Strongly Positive	67	(22.3)	66	(22.0)	133	(22.1)
Not Strongly Positive	234	(77.7)	234	(78.0)	468	(77.9)

PD-L1 CPS Status (CPS>=1)						
CPS >=1	257	(85.4)	255	(85.0)	512	(85.2)
CPS <1	44	(14.6)	45	(15.0)	89	(14.8)
PD-L1 CPS Status (CPS>=20)						
CPS >=20	133	(44.2)	122	(40.7)	255	(42.4)
CPS <20	167	(55.5)	175	(58.3)	342	(56.9)
Missing	1	(0.3)	3	(1.0)	4	(0.7)
PD-L1 CPS Status						
CPS<1	44	(14.6)	45	(15.0)	89	(14.8)
1<=CPS<20	124	(41.2)	133	(44.3)	257	(42.8)
CPS>=20	133	(44.2)	122	(40.7)	255	(42.4)
Baseline Tumour Size (mm) (Grouping by ITT Median)						
>=Median	128	(42.5)	134	(44.7)	262	(43.6)
<Median	148	(49.2)	145	(48.3)	293	(48.8)
Missing	25	(8.3)	21	(7.0)	46	(7.7)
Subjects with data	276		279		555	
Mean	75.9		78.2		77.1	
SD	62.1		66.7		64.4	
Median	54.1		58.7		57.1	
Range	10 to 430		10 to 419		10 to 430	
Disease Status						
Metastatic	216	(71.8)	203	(67.7)	419	(69.7)
Recurrent	82	(27.2)	94	(31.3)	176	(29.3)
Neither	3	(1.0)	3	(1.0)	6	(1.0)
Primary Tumour Staging						
T0	26	(8.6)	38	(12.7)	64	(10.6)
T1	14	(4.7)	15	(5.0)	29	(4.8)
T1A	1	(0.3)	0	(0.0)	1	(0.2)
T2	40	(13.3)	53	(17.7)	93	(15.5)
T3	47	(15.6)	37	(12.3)	84	(14.0)
T3A	1	(0.3)	0	(0.0)	1	(0.2)
T3B	0	(0.0)	1	(0.3)	1	(0.2)
T4	58	(19.3)	52	(17.3)	110	(18.3)
T4A	63	(20.9)	48	(16.0)	111	(18.5)
T4B	17	(5.6)	25	(8.3)	42	(7.0)
TX	34	(11.3)	31	(10.3)	65	(10.8)
Regional Lymph Nodes Staging						
N0	88	(29.2)	81	(27.0)	169	(28.1)
N1	44	(14.6)	48	(16.0)	92	(15.3)
N2	133	(44.2)	131	(43.7)	264	(43.9)
N3	23	(7.6)	31	(10.3)	54	(9.0)
NX	13	(4.3)	9	(3.0)	22	(3.7)
Metastatic Staging						
M0	85	(28.2)	97	(32.3)	182	(30.3)
M1	216	(71.8)	203	(67.7)	419	(69.7)

Overall Cancer Staging						
II	1	(0.3)	1	(0.3)	2	(0.3)
III	11	(3.7)	14	(4.7)	25	(4.2)
IVA	60	(19.9)	61	(20.3)	121	(20.1)
IVB	13	(4.3)	21	(7.0)	34	(5.7)
IVC	216	(71.8)	203	(67.7)	419	(69.7)
Primary Tumour Location-Oral Cavity						
Yes	82	(27.2)	91	(30.3)	173	(28.8)
No	219	(72.8)	209	(69.7)	428	(71.2)
Primary Tumour Location-Larynx						
Yes	74	(24.6)	61	(20.3)	135	(22.5)
No	227	(75.4)	239	(79.7)	466	(77.5)
Primary Tumour Location-Hypopharynx						
Yes	38	(12.6)	39	(13.0)	77	(12.8)
No	263	(87.4)	261	(87.0)	524	(87.2)
Primary Tumour Location-Oropharynx						
Yes	113	(37.5)	114	(38.0)	227	(37.8)
No	188	(62.5)	186	(62.0)	374	(62.2)
Time from Latest Platinum Therapy (days)						
Subjects with data	132		137		269	
Mean	766.3		887.0		827.8	
SD	666.0		902.7		796.2	
Median	518.5		596.0		553.0	
Range	193 to 4620		119 to 6817		119 to 6817	
Time from Prior Systemic Therapy (days)						
Subjects with data	151		146		297	
Mean	809.8		862.7		835.8	
SD	980.9		877.0		930.1	
Median	511.0		571.5		530.0	
Range	35 to 9264		119 to 6817		35 to 9264	
Database Cutoff Date: 13JUN2018.						

Table 12: Summary of Prior Line of Systemic Therapy (Pembro Mono vs Control) (ITT Population)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	301		300		601	
Subjects with no prior systemic therapy	150	(49.8)	154	(51.3)	304	(50.6)
Primary/Locally Advanced/With Curative Intent	**143**	**(47.5)**	**143**	**(47.7)**	**286**	**(47.6)**
Cetuximab	20	(6.6)	18	(6.0)	38	(6.3)
Platinum	125	(41.5)	134	(44.7)	259	(43.1)
Recurrent/With Curative Intent	**11**	**(3.7)**	**5**	**(1.7)**	**16**	**(2.7)**
Cetuximab	3	(1.0)	0	(0.0)	3	(0.5)
Platinum	9	(3.0)	4	(1.3)	13	(2.2)

A subject can have multiple prior systemic therapies and be counted in different rows that are applicable. But every subject is counted a single time for each applicable row and column.

Database Cutoff Date: 13JUN2018.

Table 13: Subject Characteristics (Pembro Mono vs Control) (ITT population) (CPS≥1 and CPS≥20)

	CPS>=1				CPS>=20			
	Pembrolizumab		Cetuximab + Chemotherapy		Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	257		255		133		122	
Gender								
Male	209	(81.3)	220	(86.3)	104	(78.2)	108	(88.5)
Female	48	(18.7)	35	(13.7)	29	(21.8)	14	(11.5)
Age (Years)								
<65	163	(63.4)	166	(65.1)	80	(60.2)	85	(69.7)
>=65	94	(36.6)	89	(34.9)	53	(39.8)	37	(30.3)
Mean	60.8		60.8		60.5		59.8	
SD	9.7		10.2		10.2		10.2	
Median	62.0		61.0		62.0		60.0	
Range	22 to 94		24 to 84		22 to 83		24 to 81	
Race								
American Indian Or Alaska Native	4	(1.6)	6	(2.4)	2	(1.5)	3	(2.5)
Asian	50	(19.5)	47	(18.4)	24	(18.0)	22	(18.0)
Black Or African American	3	(1.2)	3	(1.2)	2	(1.5)	1	(0.8)
Multi-Racial	10	(3.9)	9	(3.5)	7	(5.3)	4	(3.3)
White	188	(73.2)	189	(74.1)	98	(73.7)	92	(75.4)
Missing	2	(0.8)	1	(0.4)	-		-	
Ethnicity								
Hispanic Or Latino	35	(13.6)	34	(13.3)	22	(16.5)	15	(12.3)
Not Hispanic Or Latino	204	(79.4)	199	(78.0)	101	(75.9)	93	(76.2)
Not Reported	16	(6.2)	15	(5.9)	10	(7.5)	9	(7.4)
Unknown	2	(0.8)	7	(2.7)	0	(0.0)	5	(4.1)
Region Group								
NA	68	(26.5)	54	(21.2)	32	(24.1)	31	(25.4)
EU	74	(28.8)	92	(36.1)	44	(33.1)	42	(34.4)
ROW	115	(44.7)	109	(42.7)	57	(42.9)	49	(40.2)
Smoking Status								
Never Smoker	59	(23.0)	61	(23.9)	34	(25.6)	30	(24.6)
Ex Smoker	154	(59.9)	156	(61.2)	82	(61.7)	71	(58.2)
Current Smoker	44	(17.1)	36	(14.1)	17	(12.8)	20	(16.4)
Missing	0	(0.0)	2	(0.8)	0	(0.0)	1	(0.8)
ECOG								
0	104	(40.5)	101	(39.6)	58	(43.6)	52	(42.6)
1	153	(59.5)	154	(60.4)	75	(56.4)	70	(57.4)
HPV Status								
Positive	54	(21.0)	55	(21.6)	24	(18.0)	28	(23.0)
Negative	203	(79.0)	200	(78.4)	109	(82.0)	94	(77.0)
PD-L1 TPS Status								
Strongly Positive	67	(26.1)	66	(25.9)	66	(49.6)	62	(50.8)
Not Strongly Positive	190	(73.9)	189	(74.1)	67	(50.4)	60	(49.2)

PD-L1 CPS Status (CPS>=20)								
CPS >=20	133	(51.8)	122	(47.8)				
CPS <20	123	(47.9)	131	(51.4)	-		-	
Missing	1	(0.4)	2	(0.8)				
Baseline Tumour Size (mm) (Grouping by ITT Median)								
>=Median	102	(39.7)	111	(43.5)	54	(40.6)	48	(39.3)
<Median	133	(51.8)	125	(49.0)	67	(50.4)	64	(52.5)
Missing	22	(8.6)	19	(7.5)	12	(9.0)	10	(8.2)
Subjects with data	235		236		121		112	
Mean	74.3		73.2		74.3		67.2	
SD	60.4		58.2		61.2		55.8	
Median	52.7		56.0		52.5		51.4	
Range	10 to 338		10 to 419		11 to 338		10 to 320	
Disease Status								
Metastatic	179	(69.6)	168	(65.9)	88	(66.2)	79	(64.8)
Recurrent	75	(29.2)	84	(32.9)	42	(31.6)	42	(34.4)
Neither	3	(1.2)	3	(1.2)	3	(2.3)	1	(0.8)
Primary Tumour Staging								
T0	23	(8.9)	37	(14.5)	14	(10.5)	23	(18.9)
T1	11	(4.3)	11	(4.3)	6	(4.5)	4	(3.3)
T2	33	(12.8)	47	(18.4)	19	(14.3)	22	(18.0)
T3	41	(16.0)	32	(12.5)	17	(12.8)	12	(9.8)
T3A	1	(0.4)	0	(0.0)	-		-	
T3B	0	(0.0)	1	(0.4)	-		-	
T4	51	(19.8)	43	(16.9)	26	(19.5)	18	(14.8)
T4A	55	(21.4)	40	(15.7)	31	(23.3)	22	(18.0)
T4B	13	(5.1)	23	(9.0)	3	(2.3)	9	(7.4)
TX	29	(11.3)	21	(8.2)	17	(12.8)	12	(9.8)
Regional Lymph Nodes Staging								
N0	71	(27.6)	67	(26.3)	34	(25.6)	37	(30.3)
N1	37	(14.4)	42	(16.5)	20	(15.0)	27	(22.1)
N2	119	(46.3)	113	(44.3)	61	(45.9)	44	(36.1)
N3	18	(7.0)	25	(9.8)	9	(6.8)	11	(9.0)
NX	12	(4.7)	8	(3.1)	9	(6.8)	3	(2.5)
Metastatic Staging								
M0	78	(30.4)	87	(34.1)	45	(33.8)	43	(35.2)
M1	179	(69.6)	168	(65.9)	88	(66.2)	79	(64.8)
Overall Cancer Staging								
II	1	(0.4)	1	(0.4)	-		-	
III	10	(3.9)	11	(4.3)	8	(6.0)	6	(4.9)
IVA	56	(21.8)	57	(22.4)	33	(24.8)	28	(23.0)
IVB	11	(4.3)	18	(7.1)	4	(3.0)	9	(7.4)
IVC	179	(69.6)	168	(65.9)	88	(66.2)	79	(64.8)
Primary Tumour Location-Oral Cavity								
Yes	75	(29.2)	80	(31.4)	49	(36.8)	49	(40.2)
No	182	(70.8)	175	(68.6)	84	(63.2)	73	(59.8)
Primary Tumour Location-Larynx								
Yes	57	(22.2)	53	(20.8)	25	(18.8)	19	(15.6)
No	200	(77.8)	202	(79.2)	108	(81.2)	103	(84.4)

Primary Tumour Location-Hypopharynx								
Yes	34	(13.2)	32	(12.5)	16	(12.0)	8	(6.6)
No	223	(86.8)	223	(87.5)	117	(88.0)	114	
Primary Tumour Location-Oropharynx								
Yes	97	(37.7)	94	(36.9)	46	(34.6)	46	(37.7)
No	160	(62.3)	161	(63.1)	87	(65.4)	76	(62.3)
Time from Latest Platinum Therapy (days)								
Subjects with data	112		120		56		56	
Mean	754.6		860.9		840.1		940.4	
SD	676.3		864.3		803.3		1102.8	
Median	510.0		585.5		512.5		529.5	
Range	193 to 4620		201 to 6817		193 to 4620		224 to 6817	
Time from Prior Systemic Therapy (days)								
Subjects with data	130		125		63		58	
Mean	810.8		847.0		971.1		925.4	
SD	1029.7		846.5		1373.3		1084.3	
Median	507.5		627.0		509.0		582.5	
Range	35 to 9264		201 to 6817		35 to 9264		224 to 6817	
Database Cutoff Date: 13JUN2018.								

Numbers analysed

Two comparisons were made in the study:

- pembrolizumab plus chemotherapy versus standard treatment
- pembrolizumab monotherapy versus standard treatment.

No comparisons were conducted between the pembrolizumab monotherapy and pembrolizumab plus chemotherapy group.

A total of 882 participants were randomized to either pembro mono (301) or pembro combo (281) or to the control arm (300).

Due to an enrolment pause in the pembro combo arm recommended by the external DMC that occurred between 13-AUG-2015 and 02-OCT-2015, 22 subjects enrolled in the control arm during the pause were excluded for the comparison between the pembro combo vs control, according to ITT principle. As a result, the primary efficacy analyses were based on the ITT population which included:

- 559 participants in the pembro combo (n=281) versus control (n=278) analysis;
- 601 participants in the pembro mono (n=301) versus control (n=300)

Efficacy endpoints have been analyzed for three populations:

- ITT (all participants regardless of PD-L1 status),
- PD-L1 CPS ≥1 population,
- PD-L1 CPS ≥20 population.

Quality-of-life endpoints in the treatment group comparisons have been analyzed for three populations:

- patient reported outcomes FAS population (referred to as the "PRO FAS" population and consisting of all participants regardless of PD-L1 status who were randomized and treated and had at least one PRO assessment)

- PD-L1 CPS ≥1 population,
- PD-L1 CPS ≥20 population.

Table 14: Study Population (Pembro Combo vs Control)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects Randomized	281		300		581	
Intention-to-Treat (ITT)	281	(100.0)	278	(92.7)	559	(96.2)
Intention-to-Treat (ITT) (CPS >=1)	242	(86.1)	235	(78.3)	477	(82.1)
Intention-to-Treat (ITT) (CPS >=20)	126	(44.8)	110	(36.7)	236	(40.6)
All-Subjects-as-Treated (ASaT)	276	(98.2)	287	(95.7)	563	(96.9)
Database Cutoff Date: 13JUN2018.						

Table 15: Study Population (Pembro Mono vs Control)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects Randomized	301		300		601	
Intention-to-Treat (ITT)	301	(100.0)	300	(100.0)	601	(100.0)
Intention-to-Treat (ITT) (CPS >=1)	257	(85.4)	255	(85.0)	512	(85.2)
Intention-to-Treat (ITT) (CPS >=20)	133	(44.2)	122	(40.7)	255	(42.4)
All-Subjects-as-Treated (ASaT)	300	(99.7)	287	(95.7)	587	(97.7)
Database Cutoff Date: 13JUN2018.						

Outcomes and estimation

The MAH provided the results of the **second interim analysis** (IA2) of this study, which was a time-driven analysis, occurring approximately 38 months from study start (**data cut-off 13-Jun-2018**, all participants were followed for at least 17 months) (results are from IA2 unless differently indicated).

During the procedure, the MAH provided the **final analysis (FA)** data (**data cut-off 25-Feb-2019**). At FA, only Hypotheses 11, 12, and 10 were tested for statistical significance and the corresponding p-values were used for statistical inference. For the other tables in this section, p-values were provided for descriptive purpose only.

Table 16: Overall alpha level, nominal p-value and p-value at boundary for each hypothesis at IA2

Hypothesis	Population	Test	Overall alpha	Nominal p-value	p-value boundary	Outcome
H1: PFS (M vs. S)	CPS ≥20	Superiority	0.0019	0.45625	0.0016	Not yet successful
H2: PFS (M vs. S)	CPS ≥1	Superiority	NA	0.93303	NA	Not tested
H3: PFS (M vs. S)	All participants	Superiority	NA	0.99951	NA	Not tested
H4: PFS (C vs. S)	CPS ≥20	Superiority	0.0019	0.01622	0.0017	Not yet successful
H5: PFS (C vs. S)	CPS ≥1	Superiority	NA	0.02286	NA	Not tested
H6: PFS (C vs. S)	All participants	Superiority	0.0002	0.16971	0.0002	Not tested
H7: OS (M vs. S)	**CPS ≥20**	**Superiority**	**0.007**	**0.00074**	**0.0024**	**Successful with initial alpha allocation**
H8: OS (M vs. S)	**CPS ≥1**	**Superiority**	**0.013993†**	**0.00855**	**0.0109**	**Successful with alpha shifted from H7 and H14**
H9: OS (M vs. S)	**All participants**	**Non-inferiority**	**0.013993†**	**0.0001399**	**0.0117**	**Successful with alpha shifted from H8**
H10: OS (M vs. S)	All participants	Superiority	0.013993†	0.04563	0.0117	Not yet successful
H11: OS (C vs. S)	CPS ≥20	Superiority	0.007	0.00984	0.0018	Not yet successful
H12: OS (C vs. S)	CPS ≥1	Superiority	NA	0.00072	NA	Not tested
H13: OS (C vs. S)	**All participants**	**Non-inferiority**	**0.007**	**0.0000040**	**0.0041**	**Successful with initial alpha allocation**
H14: OS (C vs. S)	**All participants**	**Superiority**	**0.007†**	**0.00335**	**0.0041**	**Successful with alpha shifted from H13**

Abbreviations: C = pembrolizumab plus chemotherapy; CPS = Combined positive score; H = hypothesis; M = pembrolizumab monotherapy; NA = not applicable; PFS = progression-free survival; OS = overall survival; S = standard treatment; vs = versus.
NA = Not applicable, no alpha allocated to the hypothesis due to multiplicity strategy.
† Alpha shifted from other hypotheses due to a positive outcome at IA2.

Table 17: Overall Alpha Level and p-value at Boundary for Hypotheses Tested at FA - KEYNOTE-048

Hypothesis	Population	Test	Overall alpha	p-value boundary§	Observed p-value
H11: OS (C vs. S)	CPS≥20	Superiority	0.007	0.0023	0.00044
H12: OS (C vs. S)	CPS≥1	Superiority	0.007	0.0026	0.00002
H10: OS (M vs. S)	All participants	Superiority	0.020986	0.0059	0.01985

§ Alpha spending at IA1 and IA2 was determined using the spending function, and the information fraction (ratio of the actual number of events at the interim analyses relative to the targeted events at the final analysis as specified in the protocol). The final analysis used the remaining Type I error not spent at earlier analyses, regardless of the number of events observed at the final analysis. The p-value boundary at final analysis was calculated by considering the correlation between the test statistics as determined by the actual number of OS events at the previous and current analysis.

Note: results of KEYNOTE-048 study are presented below separately for the two comparisons:

- Pembro combo vs control
- Pembro mono vs control

Pembrolizumab plus chemotherapy (platinum+5-FU) vs chemotherapy (EXTREME regimen)

Final analysis (cut-off date 25 Feb 2019, DBL 25-MAR-2019)

During the procedure, the MAH provided the results of the Final analysis for KEYNOTE-048 study.

Table 18: Key Efficacy Results Pembrolizumab Plus Chemotherapy vs Standard Treatment ITT, CPS ≥1 and CPS ≥20 Population Findings KEYNOTE-048 (FA)

	ITT (All Participants)		PD-L1 CPS ≥1		PD-L1 CPS ≥20	
	Pembrolizumab Plus Chemotherapy N=281	Std Treatment N=278	Pembrolizumab Plus Chemotherapy N=242	Std Treatment N=235	Pembrolizumab Plus Chemotherapy N=126	Std Treatment N=110
OS						
Number of events (%)	213 (75.8)	247 (88.8)	177 (73.1)	213 (90.6)	84 (66.7)	98 (89.1)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)
HR (95% CI)	0.72 (0.60, 0.87)		0.65 (0.53, 0.80)		0.60 (0.45, 0.82)	
P-value (superiority statistic)	0.00025		0.00002		0.00044	
OS rate at 12 months (95% CI)	53.0 (47.0, 58.7)	43.9 (38.0, 49.7)	55.0 (48.5, 61.0)	43.5 (37.0, 49.7)	57.1 (48.0, 65.2)	46.1 (36.6, 55.1)
OS rate at 18 months (95% CI)	37.6 (32.0, 43.3)	27.2 (22.1, 32.6)	39.1 (33.0, 45.2)	26.7 (21.2, 32.5)	43.5 (34.7, 51.9)	27.7 (19.6, 36.3)
OS rate at 24 months (95% CI)	29.4 (24.2, 34.8)	18.2 (13.9, 22.9)	30.8 (25.1, 36.7)	16.8 (12.3, 21.9)	35.4 (27.2, 43.8)	19.4 (12.6, 27.3)
PFS (BICR per RECIST 1.1)						
Number of events (%)	250 (89.0)	260 (93.5)	212 (87.6)	221 (94.0)	106 (84.1)	104 (94.5)
Median in months (95% CI)	4.9 (4.7, 6.1)	5.1 (4.9, 6.1)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)	5.8 (4.7, 7.6)	5.3 (4.9, 6.3)
HR (95% CI)[b]	0.93 (0.78, 1.11)		0.84 (0.69, 1.02)		0.76 (0.58, 1.01)	
P-value	0.21211		0.03697		0.02951	
PFS rate at 6 months (95% CI)	44.7 (38.8, 50.5)	44.9 (38.9, 50.8)	44.9 (38.5, 51.1)	43.3 (36.9, 49.6)	49.4 (40.3, 57.9)	47.2 (37.5, 56.2)
PFS rate at 9 months (95% CI)	26.9 (21.8, 32.3)	20.5 (15.9, 25.6)	28.0 (22.4, 33.9)	19.4 (14.5, 24.8)	35.4 (27.0, 43.8)	21.7 (14.4, 29.9)
PFS rate at 12 months (95% CI)	17.2 (13.0, 21.9)	13.6 (9.8, 18.1)	19.7 (14.8, 25.0)	12.5 (8.6, 17.3)	23.9 (16.7, 31.7)	14.0 (8.2, 21.3)
ORR (BICR per RECIST 1.1, with confirmation)						
% (95% CI)	35.6 (30.0, 41.5)	36.3 (30.7, 42.3)	36.4 (30.3, 42.8)	35.7 (29.6, 42.2)	42.9 (34.1, 52.0)	38.2 (29.1, 47.9)
Complete Responses (CR)	17 (6.0%)	8 (2.9%)	16 (6.6%)	7 (3.0%)	12 (9.5%)	4 (3.6%)
Partial Responses (PR)	83 (29.5%)	93 (33.5%)	72 (29.8%)	77 (32.8%)	42 (33.3%)	38 (34.5%)
Stable Disease (SD)	78 (27.8%)	95 (34.2%)	64 (26.4%)	77 (32.8%)	29 (23.0%)	38 (34.5%)
Progressive Disease (PD)	48 (17.1%)	33 (11.9%)	42 (17.4%)	29 (12.3%)	19 (15.1%)	9 (8.2%)
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Number of responders	100	101	88	84	54	42
Median in months (range)	6.7 (1.6+ - 39.0+)	4.3 (1.2+ - 31.5+)	6.7 (1.6+ - 39.0+)	4.3 (1.2+ - 31.5+)	7.1 (2.1+ - 39.0+)	4.2 (1.2+ - 31.5+)
Median time to response (range)	2.1 (1.4 - 13.7)	2.1 (1.3 – 10.4)	2.1 (1.4 - 13.7)	2.1 (1.3 – 10.4)	2.1 (1.4 - 13.7)	2.1 (1.9 - 6.0)
Number (Kaplan-Meier %) With Extended Response Duration (≥6 months)	49 (53.5)	28 (36.8)	44 (54.3)	21 (34.3)	31 (60.2)	11 (34.0)

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; 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 Tumours Version 1.1; Std=Standard. Database cutoff date: 25-FEB-2019

Primary endpoints

OS – pembro combo vs control

At IA2 in the ITT population, treatment with pembrolizumab plus chemotherapy resulted in a statistically significant and clinically meaningful benefit in OS over standard treatment (HR 0.77 [0.63, 0.93], p = 0.00335). The OS results at the FA confirmed the results at IA2 (HR 0.72 [0.60, 0.87]). In the population of participants whose tumors express PD-L1 CPS ≥1 or PD-L1 CPS ≥20, at the final analysis, statistically significant superiority in OS was demonstrated for pembrolizumab plus chemotherapy over standard treatment. Overall, OS HR point estimates improved compared to the IA2 in the ITT population and all CPS subgroups, with the exception of CPS<1 population (from 1.07 to 1.21).

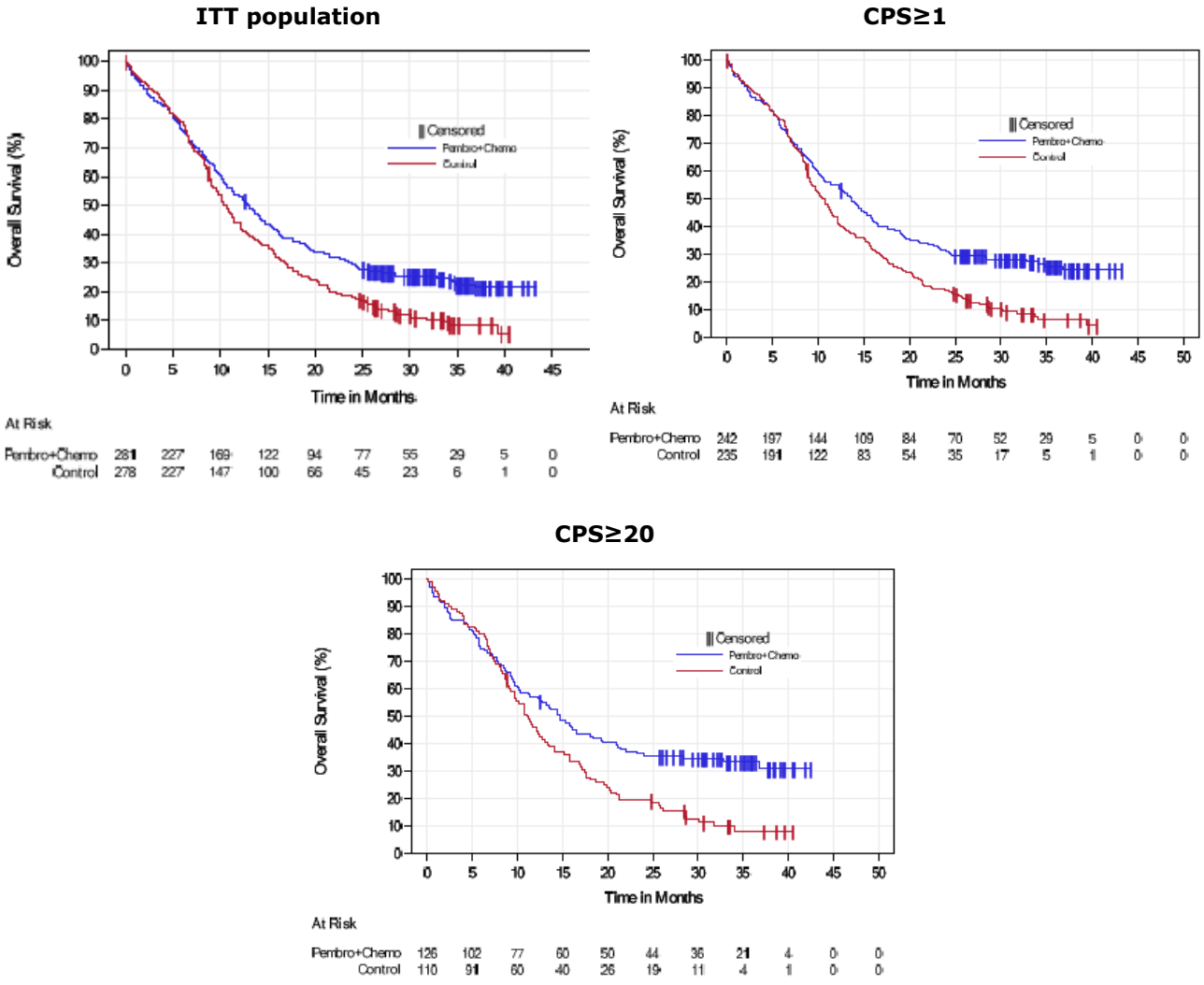


Figure 4: Kaplan-Meier estimates of Overall survival (ITT, CPS≥1, CPS≥20) - Pembro Combo vs Control (FA)

Table 19: Summary of Timing of Overall Survival Events (Pembro Combo vs Control) - ITT Population

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	281		278	
Subjects With OS Event	213	(75.8)	247	(88.8)
<30 Days Following Randomization	16	(5.7)	13	(4.7)
30-60 Days Following Randomization	10	(3.6)	7	(2.5)
>60 Days Following Randomization	187	(66.5)	227	(81.7)
Subjects Without OS Event	68	(24.2)	31	(11.2)
(Database Cutoff Date: 25FEB2019).				

PFS - pembro combo vs control

PFS was not tested at FA, as prespecified in the protocol. PFS did not show improvement; however, PFS rates at 9 and 12 months were higher in pembrolizumab combination compared to control.

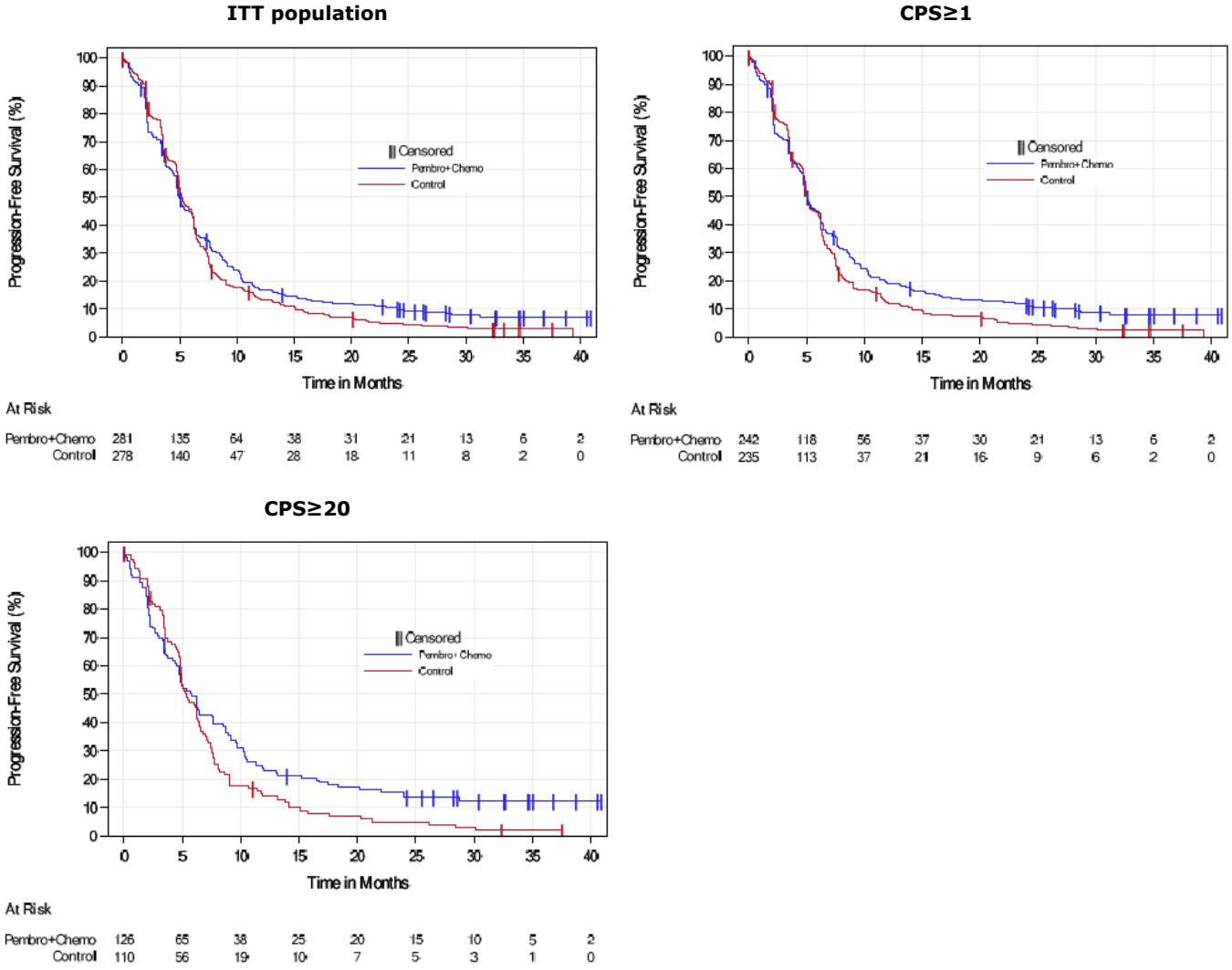


Figure 5: Kaplan-Meier estimates of PFS, based on BICR assessment per RECIST 1.1 (ITT, CPS≥1, CPS≥20), Pembro Combo vs Control (IA2)

PFS sensitivity analysis 1 and PFS sensitivity analysis 2, yielded results similar to the primary analysis for the overall population. A comparison of PFS based on investigator's assessment for the overall population performed as sensitivity analyses yielded similar results as the analyses based on BICR.

Secondary endpoints - Interim analysis 2 (data cut-off 13-JUN-2018, DBL 29-JUN-2018)

ORR – pembro combo vs control

ORR results based on BICR assessment per RECIST 1.1 for the ITT, CPS≥1 and CPS≥20 are reported in tables below. Objective responses are confirmed.

Table 20: Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1 (Pembro Combo vs Control) – ITT population (IA2)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembrolizumab + Chemotherapy	281	100	35.6 (30.0,41.5)	-0.8 (-8.7,7.2)	0.5740
Cetuximab + Chemotherapy	278	101	36.3 (30.7,42.3)		

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with 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); in case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is >=5; 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: 13JUN2018.

Source: [P048V01MK3475: adam-adsl; adrs]

Table 21: Summary of best objective response with confirmation based on BICR assessment per RECIST 1.1 (Pembro Combo vs Control) – ITT population

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	281		278	
Complete Response (CR)	17	(6.0)	8	(2.9)
Partial Response (PR)	83	(29.5)	93	(33.5)
Objective Response (CR+PR)	**100**	**(35.6)**	**101**	**(36.3)**
Stable Disease (SD)	78	(27.8)	94	(33.8)
Progressive Disease (PD)	48	(17.1)	34	(12.2)
Non-CR/Non-PD (NN)	13	(4.6)	9	(3.2)
Not Evaluable (NE)	5	(1.8)	2	(0.7)
No Assessment	37	(13.2)	38	(13.7)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Source: [P048V01MK3475: adam-adsl; adrs]

Table 22: Summary of best objective response with confirmation based on BICR assessment per RECIST 1.1 (Pembro Combo vs Control) – CPS≥1

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	242		235	
Complete Response (CR)	16	(6.6)	7	(3.0)
Partial Response (PR)	72	(29.8)	77	(32.8)
Objective Response (CR+PR)	**88**	**(36.4)**	**84**	**(35.7)**
Stable Disease (SD)	64	(26.4)	76	(32.3)
Progressive Disease (PD)	42	(17.4)	30	(12.8)
Non-CR/Non-PD (NN)	11	(4.5)	9	(3.8)
Not Evaluable (NE)	4	(1.7)	2	(0.9)
No Assessment	33	(13.6)	34	(14.5)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Source: [P048V01MK3475: adam-adsl; adrs]

Table 23: Summary of Best Objective Response with Confirmation Based on BICR per RECIST 1.1 (Pembro Combo vs Control) (ITT Population) (CPS≥20)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	126		110	
Complete Response (CR)	12	(9.5)	4	(3.6)
Partial Response (PR)	42	(33.3)	38	(34.5)
Objective Response (CR+PR)	**54**	**(42.9)**	**42**	**(38.2)**
Stable Disease (SD)	29	(23.0)	37	(33.6)
Progressive Disease (PD)	19	(15.1)	10	(9.1)
Non-CR/Non-PD (NN)	4	(3.2)	5	(4.5)
Not Evaluable (NE)	2	(1.6)	0	(0.0)
No Assessment	18	(14.3)	16	(14.5)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Source: [P048V01MK3475: adam-adsl: adrsl

Analysis of objective response with both confirmed and unconfirmed responses yielded similar results as analysis with confirmed responses, in all three populations analysed.

Overall, no relevant changes in ORR are observed at the updated cut-off date for the final analysis compared to the results at the IA2.

Patients Reported Outcomes - pembro combo vs control

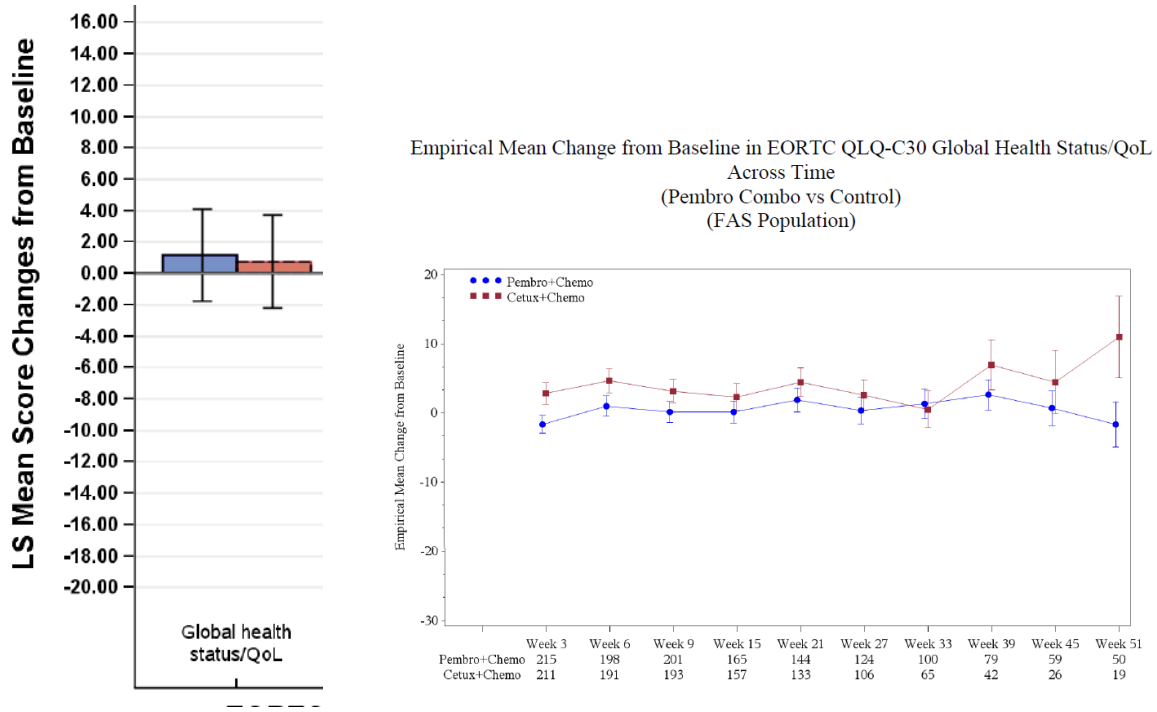
The PRO FAS population (i.e. all participants regardless of PD-L1 status who were randomized and treated and had at least one PRO assessment) included 270 participants in the pembrolizumab plus chemotherapy group and 260 participants in the standard treatment group who completed the EORTC QLQ-C30 questionnaire. The compliance rates for the EORTC QLQ-30 were similar in both pembro combo and control arm at baseline (94.4% vs 93.8%) and remained high at Week 15 (82% vs 78.9%). Compliance rates at baseline through Week 15 were similar for the EORTC QLQ H&N35 and EQ-5D.

Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/Quality of Life Score (secondary endpoint)

Table 24: Analysis of change from baseline of EORTC QLQ-C30 Global health status/QoI scales at Week 15 (Pembro combo vs Control) – FAS population

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab + Chemotherapy	255	62.19 (21.184)	173	64.60 (21.096)	268	1.17 (-1.79, 4.12)
Cetuximab + Chemotherapy	244	59.97 (21.863)	167	63.27 (18.727)	259	0.77 (-2.22, 3.76)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					0.40 (-3.46, 4.26)	0.839

[†] 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: 13JUN2018



Time to Deterioration in EORTC QLQ-C30 Global Health Status/Quality of Life (secondary endpoint)

In the PRO FAS population, TTD in the EORTC QLQ-C30 global health status/QoL score for pembrolizumab plus chemotherapy was HR = 1.37 (95% CI: 0.94, 2.00) (see figure below):

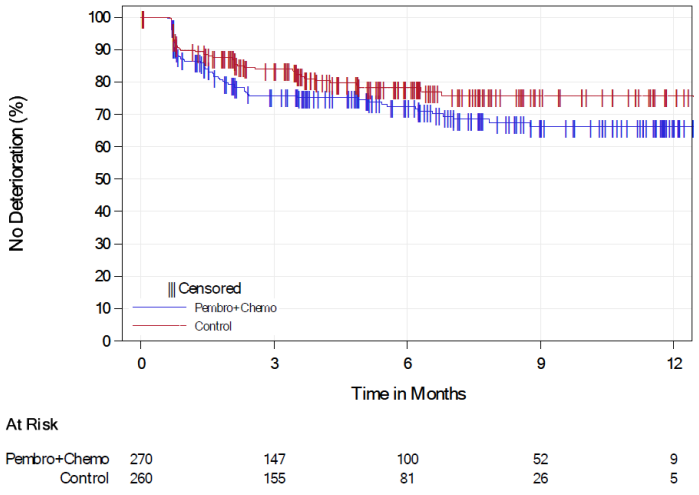
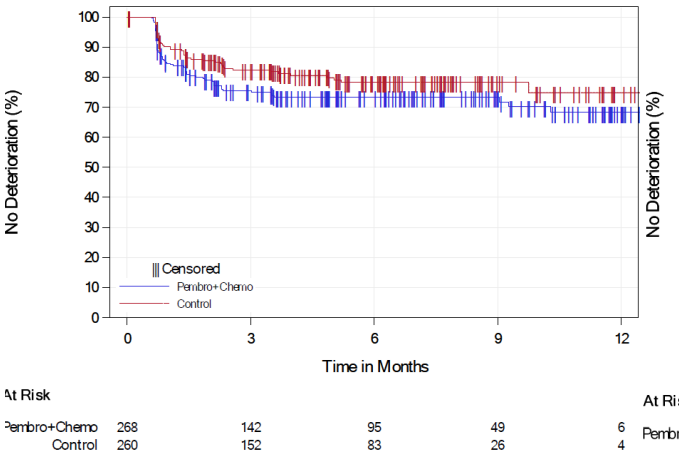
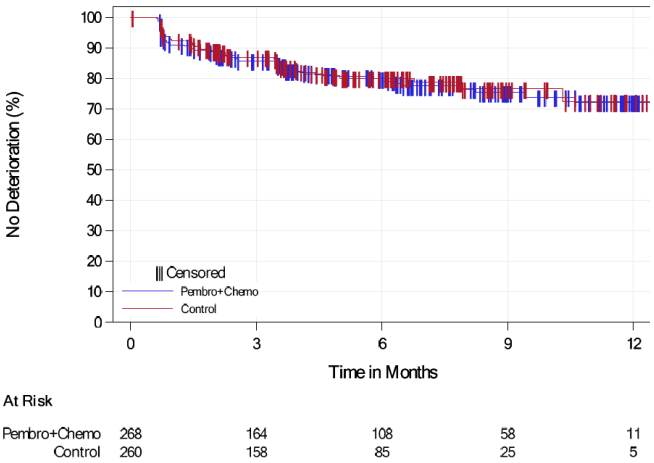


Figure 6: Kaplan-Meier plot of time to true deterioration for EORTC QLQ-C30 global health status/QoL (Pembro combo vs control) – FAS population (Cutoff date 13JUN2018)

Time to Deterioration EORTC QLQ-H&N35 Pain and Swallowing Scores (secondary endpoints)

In the PRO FAS population, TTD in the EORTC QLQ-H&N35 pain score was HR = 1.37 (95% CI: 0.93, 2.02) and swallowing score was HR = 1.05 (95% CI: 0.69, 1.59) for pembrolizumab plus chemotherapy when compared with standard treatment (see figures below):





FAS population – Cutoff date: 13 Jun 2018

Figure 7: Kaplan-Meier plot of time to deterioration for EORTC QLQ-H&N35 Pain (Pembro combo vs control)

Figure 8: Kaplan-Meier plot of time to deterioration for EORTC QLQ-H&N35 Swallowing (Pembro combo vs control)

Exploratory endpoints

- Time to response and duration of response

Table 25: Summary of time to response and duration of response based on BICR per RECIST 1.1 in subjects with confirmed response (Pembro combo vs control) - ITT

	Pembrolizumab + Chemotherapy (N=281)	Cetuximab + Chemotherapy (N=278)
Number of subjects with response[†]	100	101
Time to Response (months)		
Mean (SD)	2.6 (1.6)	2.5 (0.8)
Median (Range)	2.1 (1.4-13.7)	2.1 (1.3-6.2)
Response Duration[‡] (months)		
Median (Range)	6.7 (1.6+ - 30.4+)	4.3 (1.2+ - 27.9+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	49 (53.5)	28 (36.8)

[†]Includes subjects with 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: 13JUN2018.

Source: [P048V01MK3475: adam-adsl; adrs; adtte]

Table 26: Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1 (Pembro combo vs control) – ITT population

	Pembrolizumab + Chemotherapy (N=281)	Cetuximab + Chemotherapy (N=278)
Number of Subjects with Response[†]	100	101
Subjects Who Progressed or Died[‡] (%)	**71 (71.0)**	**74 (73.3)**
Range of DOR (months)	2.4 to 21.8	2.0 to 15.5
Censored Subjects (%)	**29 (29.0)**	**27 (26.7)**
Subjects who missed 2 or more consecutive disease assessments	4 (4.0)	11 (10.9)
Subjects who started new anti-cancer treatment	4 (4.0)	5 (5.0)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	1 (1.0)	2 (2.0)
Ongoing response[§]	20 (20.0)	9 (8.9)
≥6 months	20 (20.0)	9 (8.9)
Range of DOR (months)	14.1+ to 30.4+	16.0+ to 27.9+

[†] Includes subjects with a confirmed complete response or partial response.
[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
[§] Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.
'+' indicates there was no progressive disease by the time of last disease assessment.
Database Cutoff Date: 13JUN2018

Source: [P048V01MK3475: adam-adsl; adtte]

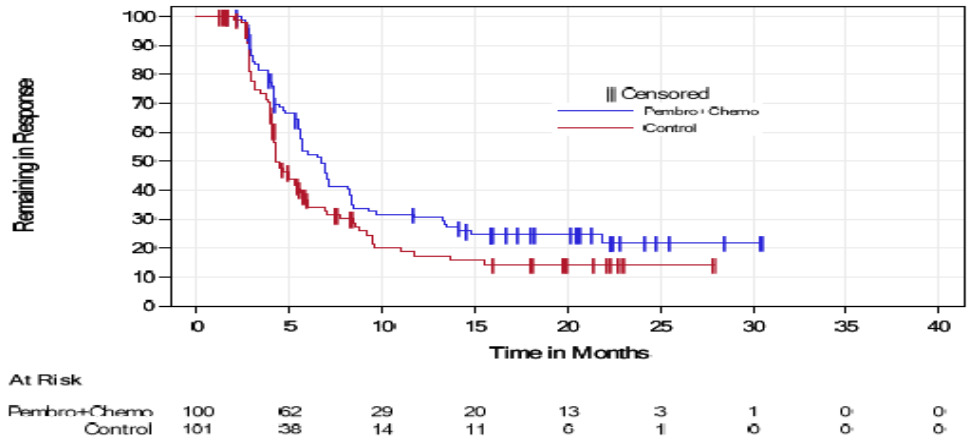


Figure 9: Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per Recist 1.1 (Pembro combo vs control) – ITT population

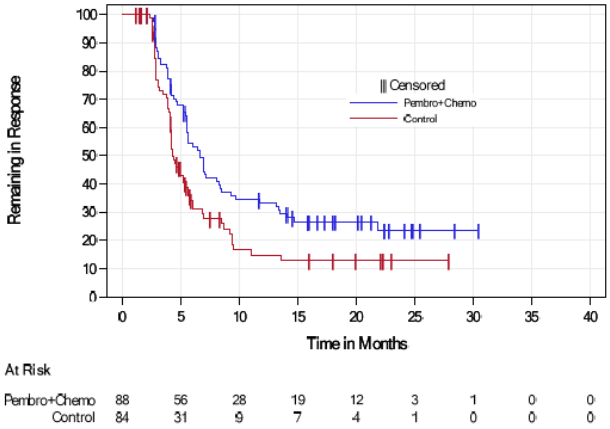


Figure 10: Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per Recist 1.1 (Pembro combo vs control) – CPS≥1

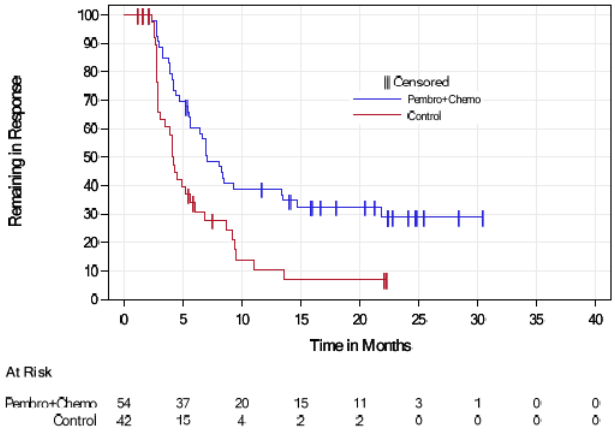


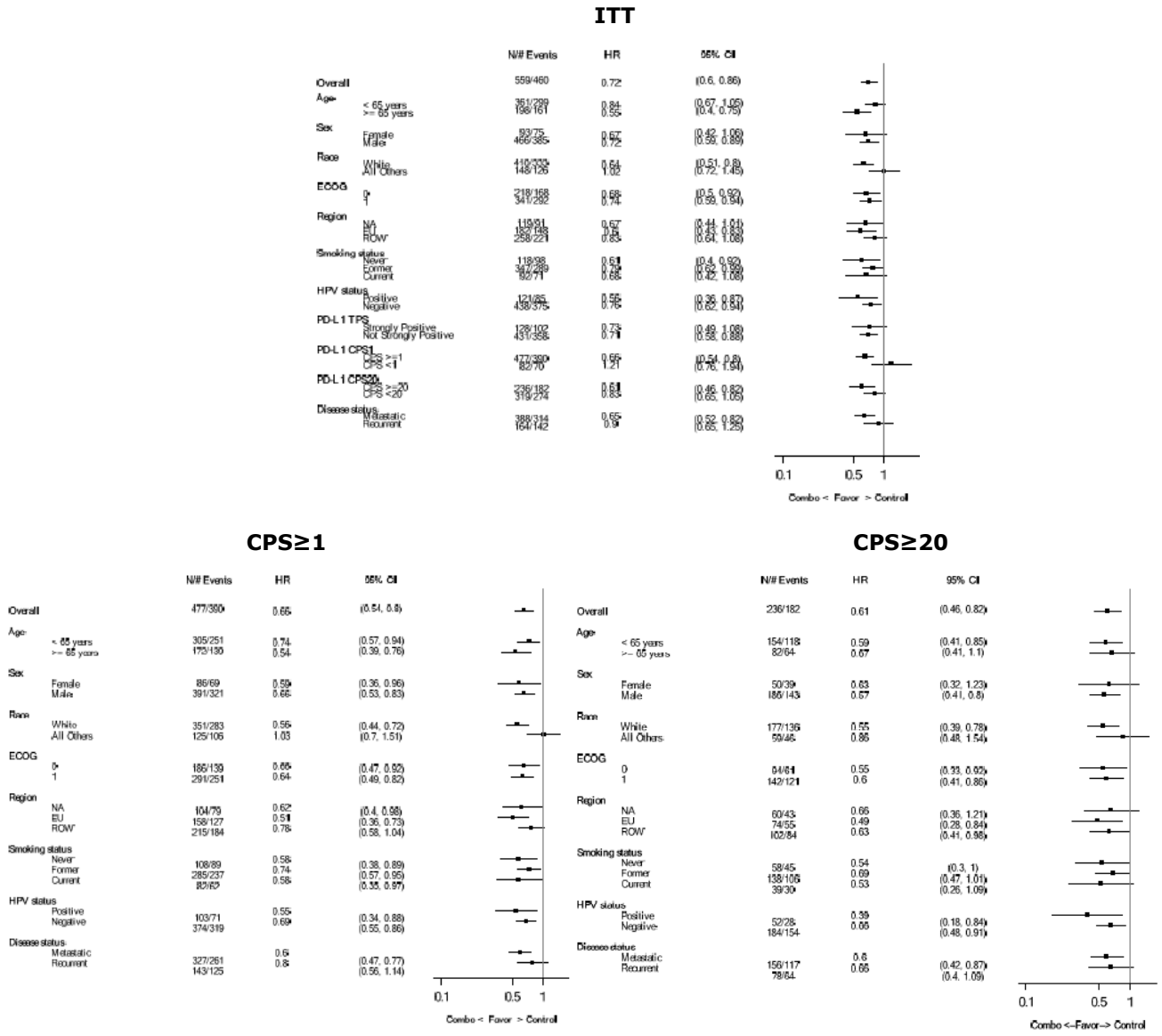
Figure 11: Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per Recist 1.1 (Pembro combo vs control) – CPS≥20

DOR and TTR results at the FA were consistent with prior data at IA2. Median time to response was similar, median DOR was longer, and more participants had a response duration ≥6 months (KM estimation) in pembrolizumab combination.

Ancillary analyses

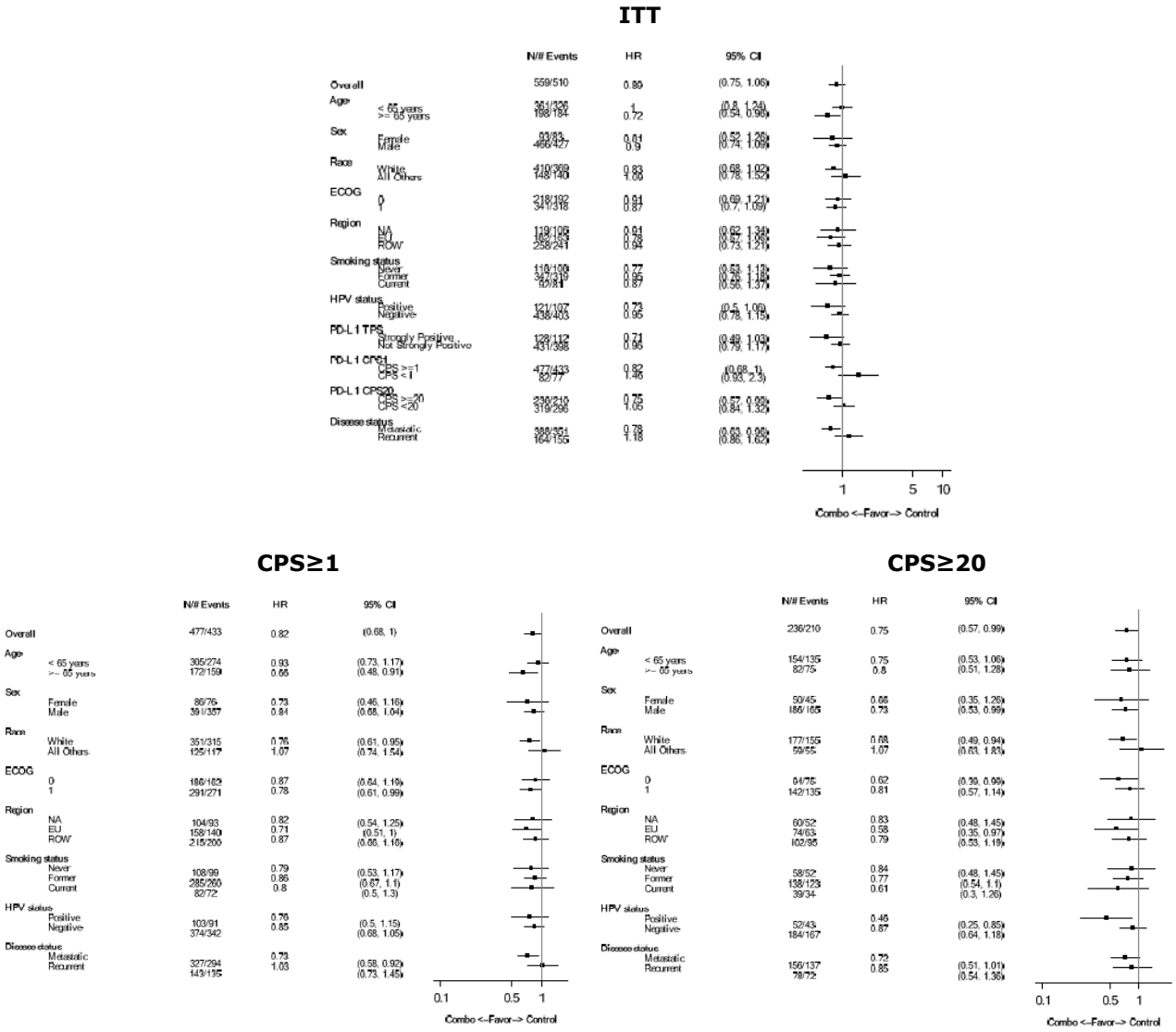
- Subgroup analyses – Pembro combo vs Control

Forest Plots of OS, PFS and ORR by subgroup factors are reported in the figures below:



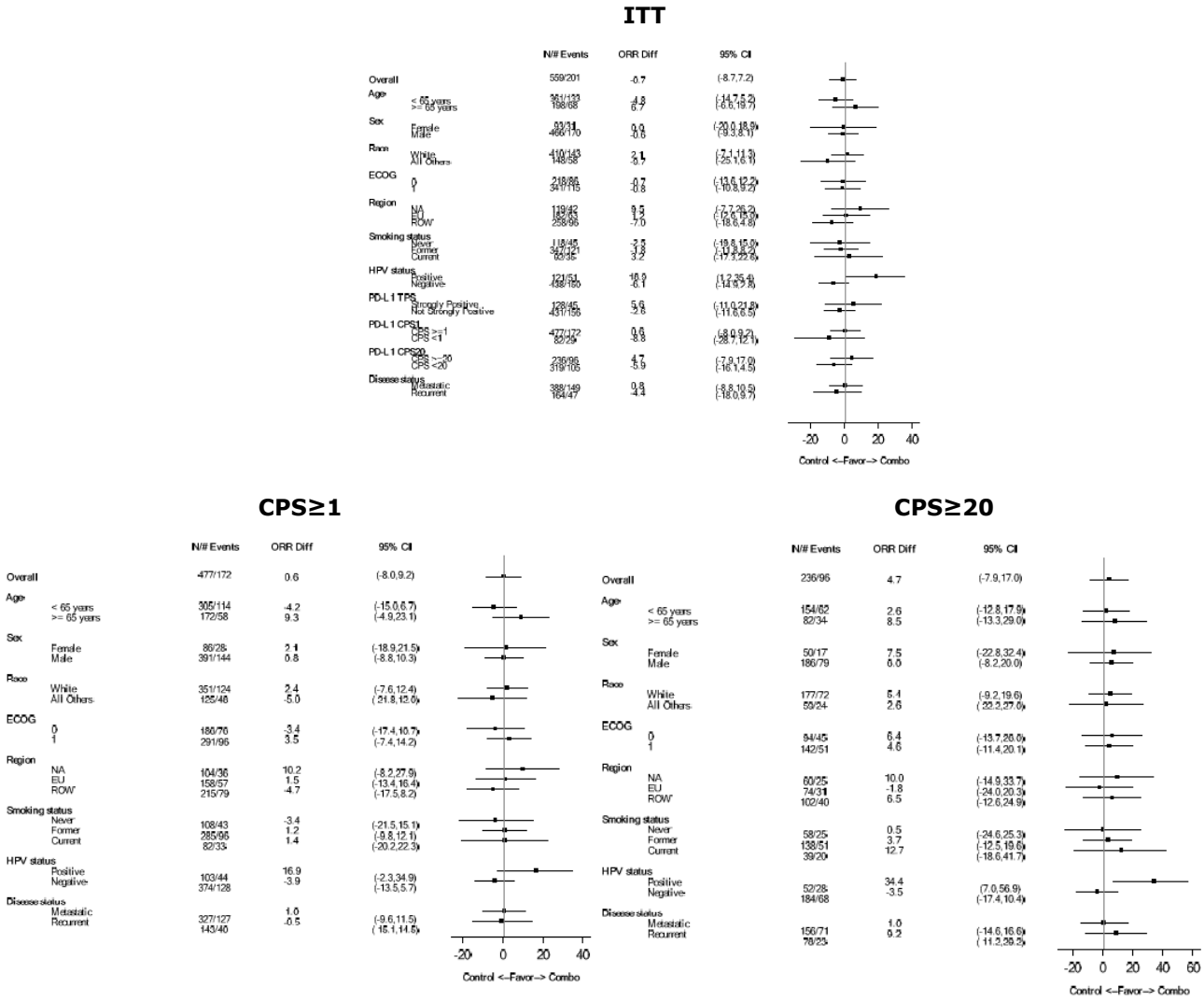
(database cut-off 25 Feb 2019)

Figure 12: Forest plots of OS Hazard Ratio in the ITT, CPS≥1 and CPS≥20 populations – pembro combo vs control



(database cut-off 25 Feb 2019)

Figure 13: Forest plots of PFS Hazard Ratio based on BICR per RECIST 1.1 in the ITT, CPS≥1 and CPS≥20 populations – pembro combo vs control



(database cut-off 25 Feb 2019)

Figure 14: Forest plots of Best objective response (confirmed) rate based on BICR per RECIST 1.1 in the ITT, CPS≥1 and CPS≥20 populations – pembro combo vs control

Analyses in the CPS <1, CPS <20, and CPS ≥1 to <20 Populations – pembro combo vs control

The subset analyses described in the three populations CPS <1, CPS <20, and CPS ≥1 to <20 were requested by the CHMP. These analyses are exploratory analyses, not adequately powered to test statistical significance, and should be interpreted with caution and considered hypothesis generating.

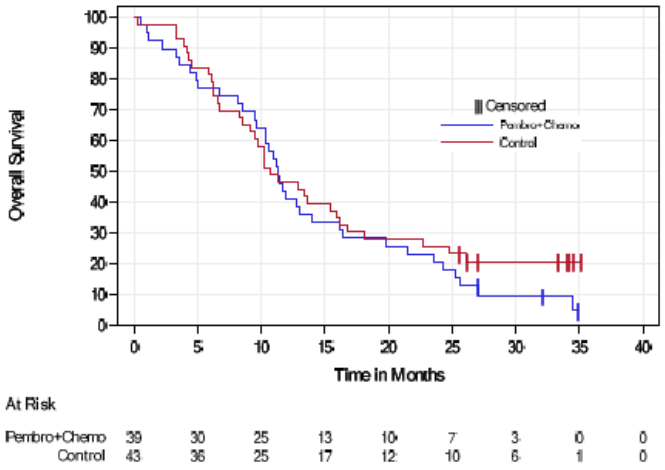
Table 27: Key Efficacy Results Pembrolizumab Plus Chemotherapy vs Standard Treatment CPS <1, CPS <20, and CPS ≥1 to CPS <20 Population Findings KEYNOTE-048 (FA)

	PD-L1 CPS <1		PD-L1 CPS <20		PD-L1 CPS ≥1 to CPS <20	
	Pembrolizumab Plus Chemotherapy N=39	Std Treatment N=43	Pembrolizumab Plus Chemotherapy N=154	Std Treatment N=165	Pembrolizumab Plus Chemotherapy N=116	Std Treatment N=125
OS						
Number of events (%)	36 (92.3)	34 (79.1)	128 (83.1)	146 (88.5)	93 (80.2)	115 (92.0)
Median in months (95% CI)	11.3 (9.5, 14.0)	10.7 (8.5, 15.9)	11.8 (10.4, 14.0)	10.2 (8.9, 12.1)	12.7 (9.4, 15.3)	9.9 (8.6, 11.5)
HR (95% CI)	1.21 (0.76, 1.94)		0.83 (0.65, 1.05)		0.71 (0.54, 0.94)	
P-value (superiority statistic)	0.78932		0.05693		0.00726	
OS rate at 12 months (95% CI)	41.0 (25.7, 55.8)	46.5 (31.2, 60.4)	49.4 (41.2, 56.9)	43.3 (35.6, 50.7)	52.6 (43.1, 61.2)	41.1 (32.4, 49.6)
OS rate at 18 months (95% CI)	28.2 (15.3, 42.7)	30.2 (17.4, 44.1)	33.1 (25.8, 40.6)	27.4 (20.9, 34.4)	34.5 (26.0, 43.1)	25.8 (18.5, 33.7)
OS rate at 24 months (95% CI)	20.5 (9.6, 34.2)	25.6 (13.8, 39.1)	24.7 (18.2, 31.7)	17.7 (12.3, 23.9)	25.9 (18.3, 34.1)	14.5 (9.0, 21.3)
PFS (BICR per RECIST 1.1)						
Number of events (%)	38 (97.4)	39 (90.7)	143 (92.9)	153 (92.7)	106 (91.4)	117 (93.6)
Median in months (95% CI)	4.7 (3.4, 6.2)	6.2 (5.0, 7.3)	4.9 (4.3, 5.3)	5.2 (4.8, 6.2)	4.9 (4.2, 5.3)	4.9 (3.7, 6.0)
HR (95% CI)b	1.46 (0.93, 2.30)		1.05 (0.84, 1.32)		0.93 (0.71, 1.21)	
P-value	0.94898		0.66834		0.29189	
PFS rate at 6 months (95% CI)	43.6 (27.9, 58.3)	53.8 (37.6, 67.6)	41.3 (33.4, 49.0)	44.3 (36.5, 51.8)	40.1 (31.0, 49.0)	40.0 (31.2, 48.5)
ORR (BICR per RECIST 1.1)						
% (95% CI)	30.8 (17.0, 47.6)	39.5 (25.0, 55.6)	29.9 (22.8, 37.8)	35.8 (28.5, 43.6)	29.3 (21.2, 38.5)	33.6 (25.4, 42.6)
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Number of responders	12	17	46	59	34	42
Median in months (range)	5.7 (2.6 – 20.6+)	4.3 (2.0 – 31.2+)	5.7 (1.6+ - 25.6+)	4.6 (1.4+ - 31.4+)	5.6 (1.6+ - 25.6+)	4.6 (1.4+ - 31.4+)
Median time to response (range)	2.2 (2.1-3.4)	2.1 (1.9-4.9)	2.1 (1.9-6.1)	2.1 (1.3-10.4)	2.1 (1.9-6.1)	2.1 (1.3-10.4)
Number (Kaplan-Meier %) With Extended Response Duration (≥6 months)	5 (46.9)	7 (49.0)	18 (45.1)	17 (38.5)	13 (44.3)	10 (34.0)

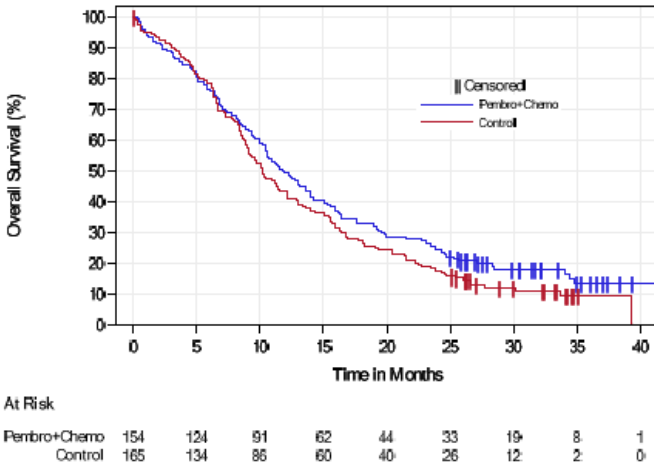
Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CPS=Combined positive score; CR=Complete response; DOR=Duration of response; HR=Hazard ratio; ITT=Intention to treat; NR=Not reached; ORR=Objective response rate; OS=Overall survival; PD-L1=Programmed cell death ligand 1; PFS=Progression-free survival; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1; Std=Standard.
Database cutoff date: 25-FEB-2019

Overall survival

CPS<1



CPS<20



1≤CPS<20

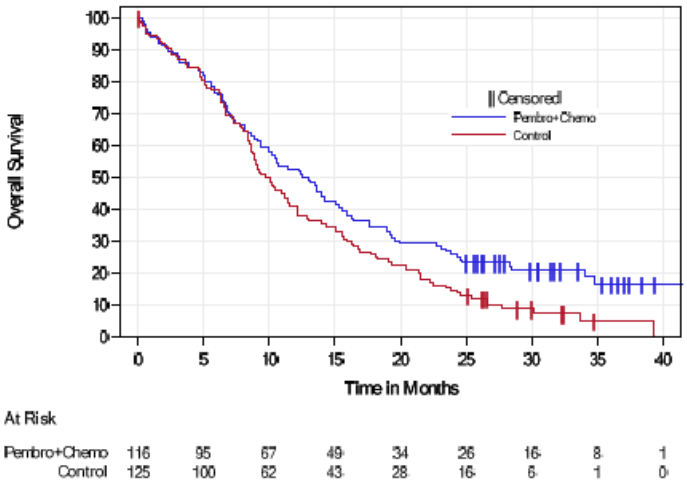
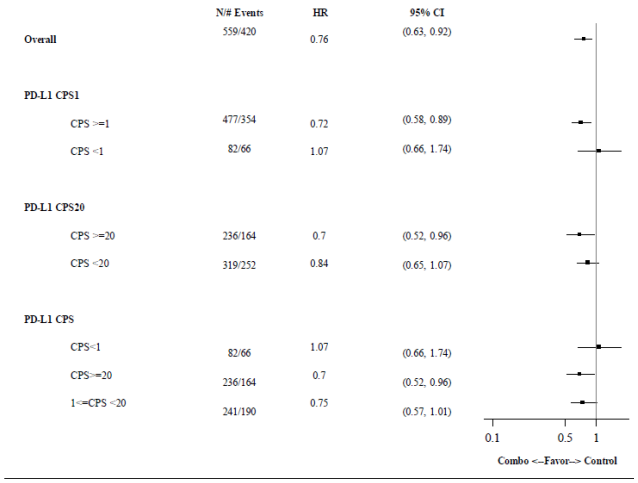


Figure 15: Kaplan-Meier of OS – Pembro combo vs control (Final analysis)



(Database Cutoff Date: 13JUN2018)

Figure 16: Forest plot of OS Hazard Ratio by PD-L1 subgroup (Pembro combo vs control) – ITT population (IA2)

PFS

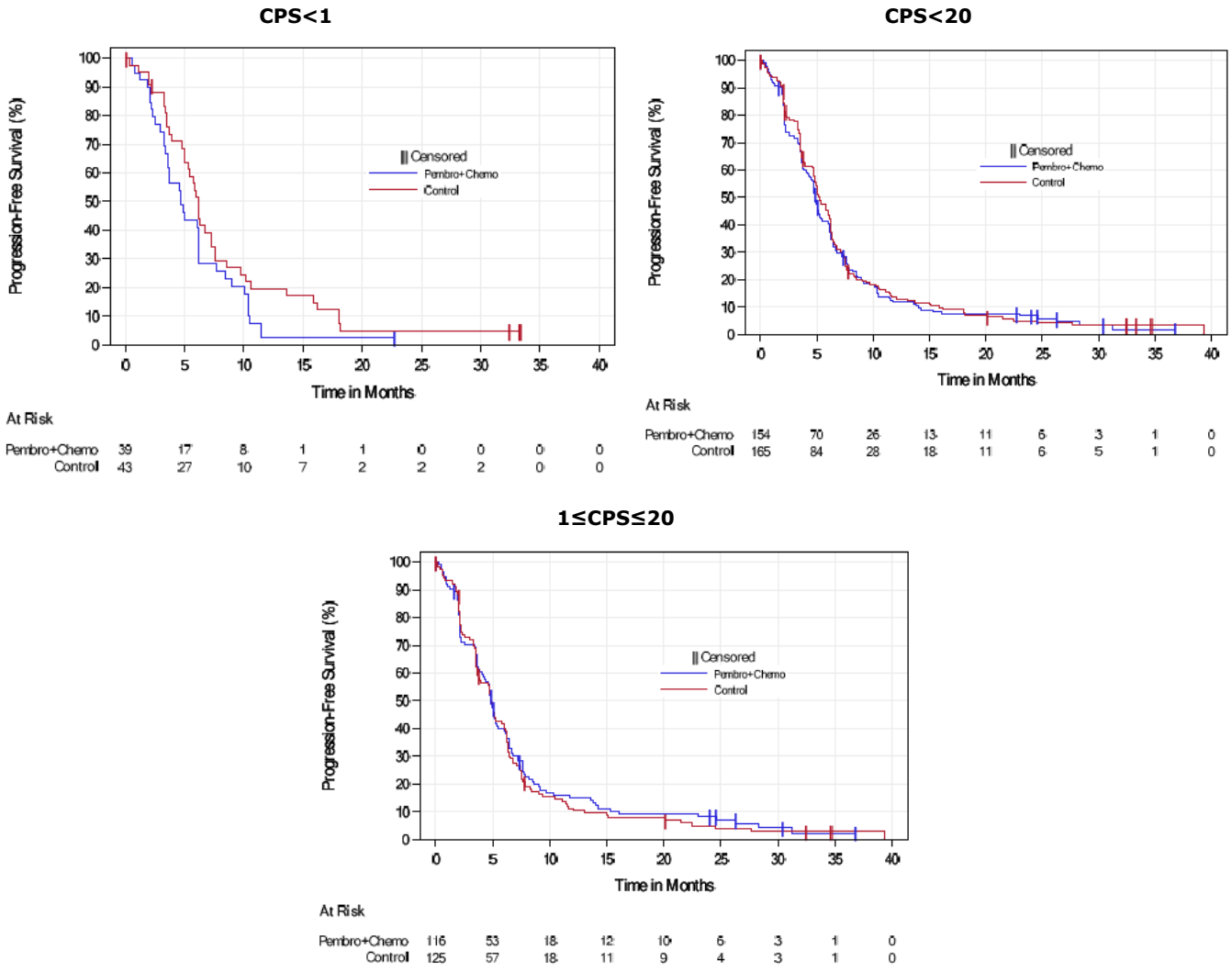


Figure 17: Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1 (primary analysis) – Pembro combo vs control

Analyses in the TPS<50% and TPS≥50% Populations – pembro combo vs control

Table 28: Key Efficacy Results OS/PFS/ORR/DOR Findings for Pembrolizumab Plus Chemotherapy versus Standard Treatment for TPS <50%, TPS ≥50% Populations - KEYNOTE-048 IA2 Analysis

	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	Pembrolizumab Plus Chemotherapy N=215	**Std Treatment N=216**	**Pembrolizumab Plus Chemotherapy N=66**	**Std Treatment N=62**
OS				
Number of events (%)	153 (71.2)	178 (82.4)	44 (66.7)	45 (72.6)
Median in months (95% CI)	12.8 (10.6, 15.0)	10.3 (9.0, 11.4)	13.5 (9.3, 16.6)	12.2 (8.9, 15.9)
HR (95% CI)	0.74 (0.59, 0.92)		0.88 (0.58, 1.35)	
P-value (superiority statistic)	0.00291§		0.28508§	
OS rate at 12 months (95% CI)	52.1 (45.2, 58.5)	41.9 (35.2, 48.3)	56.1 (43.3, 67.0)	51.3 (38.2, 62.9)
PFS (BICR per RECIST 1.1)				
Number of events (%)	192 (89.3)	197 (91.2)	52 (78.8)	56 (90.3)

	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	Pembrolizumab Plus Chemotherapy N=215	**Std Treatment N=216**	**Pembrolizumab Plus Chemotherapy N=66**	**Std Treatment N=62**
Median in months (95% CI)	4.9 (4.6, 5.8)	5.2 (4.9, 6.1)	5.7 (3.4, 9.7)	4.9 (3.6, 6.2)
HR (95% CI)	0.99 (0.81, 1.21)		0.67 (0.45, 1.01)	
P-value	0.45725§		0.02785§	
PFS rate at 6 months (95% CI)	13.8 (9.5, 18.8)	12.8 (8.6, 17.8)	49.7 (36.9, 61.2)	42.6 (29.9, 54.7)
ORR (BICR per RECIST 1.1)				
(%) (95% CI)	34.9 (28.5,41.7)	37.5 (31.0,44.3)	37.9 (26.2,50.7)	32.3 (20.9,45.3)
DOR (Confirmed CR or PR, BICR per RECIST 1.1)				
Number of responders	75	81	25	20
Median in months (range)	6.0 (1.6+ - 30.4+)	4.3 (1.4+ - 27.9+)	8.3 (2.1+ - 25.5+)	4.5 (1.2+ - 22.3+)
Median time to response (range)	2.1 (1.8-13.7)	2.1 (1.3-6.2)	2.1 (1.4-10.6)	2.2 (2.0-6.0)
Number (Kaplan-Meier %) With Extended Response Duration (≥6 months)	35 (50.6)	22 (38.3)	14 (62.5)	6 (31.6)

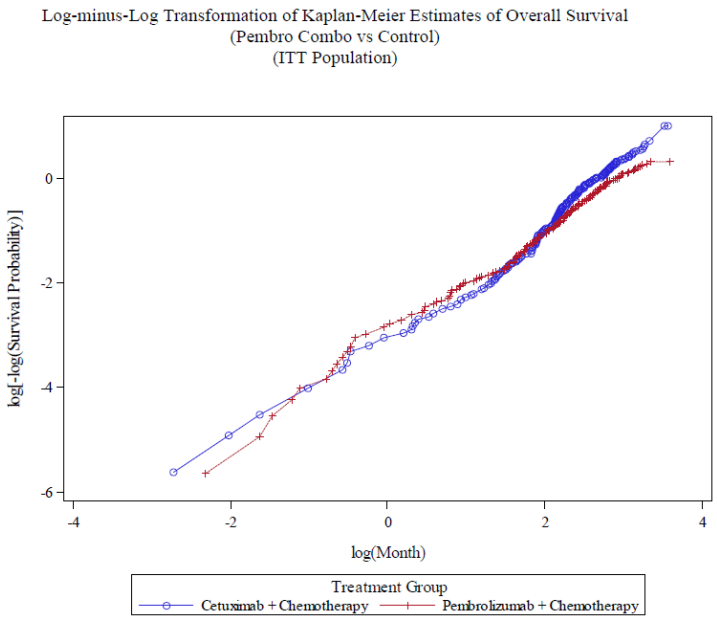
Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; DOR=Duration of response; HR=Hazard ratio; ORR=Objective response rate; OS=Overall survival; PD-L1=Programmed cell death ligand 1; PFS=Progression-free survival; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1; Std=Standard.
§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1) and HPV status (Positive vs. Negative).

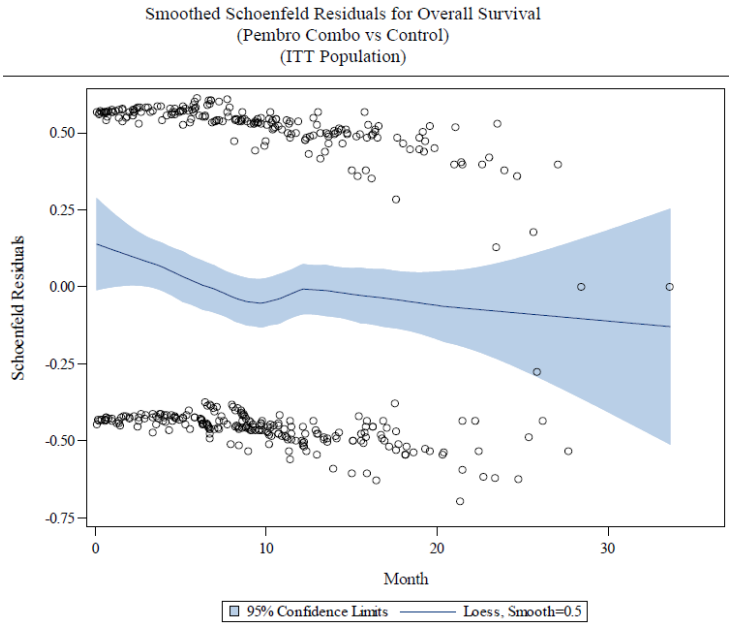
Database Cutoff Date: 13JUN2018

Proportional Hazards (PH) assumption for OS

The PH assumption for OS was examined using both graphical and analytical methods. From both the plots and p-value from the test, there is evidence of departure from the PH assumption in the ITT population of pembro combo vs control.

Plot of log(-log(survival)) against log(time) was generated for pembro combo vs control in the ITT population. 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 for pembro combo vs control in the ITT population. 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.





The PH assumption was also tested at the 0.1 significance level by including treatment*time as a factor in the model (see table below). Nonsignificance (p-value >0.1) of this factor would suggest proportionality.

Table 29: Assessment of proportional hazard assumption for overall survival Cox PH Model with treatment-by-time interaction

Comparison	Population	p-value[†]
Pembro combo vs. Standard treatment	ITT	0.03941
Pembro mono vs. Standard treatment	ITT	0.02066
	CPS>=1	0.04742
	CPS>=20	0.04289

[†] Two-sided p-value of Wald Chi-square test based on Cox regression model with Efron's method of tie handling with treatment and treatment-by-time interaction as covariates, stratified by factors used for randomization.
Database Cutoff Date: 13JUN2018.

To account for the non-proportional hazards effect associated with immunotherapies, two sensitivity analyses were conducted:

1) Weighted log-rank test with parameter (0,1) (which puts more weight on the late differences between the survival curves, commonly seen with immunotherapy, rather than early differences)

Table 30: Analysis of overall survival using Log-Rank and weighted Log-Rank tests

Comparison	Population	Test	p-value[†]
Pembro combo vs. Standard treatment	ITT	Log-Rank	0.00335
		FH (0,1)	0.00130
Pembro mono vs. Standard treatment	ITT	Log-Rank	0.04563
		FH (0,1)	0.00080
	CPS>=1	Log-Rank	0.00855
		FH (0,1)	0.00015
	CPS>=20	Log-Rank	0.00074
		FH (0,1)	<.00001

[†] One-sided p-values based on log-rank and weighted log-rank tests, stratified by factors used for randomization.
FH (0,1): Fleming and Harrington weighted log-rank test weighting towards late difference.
Database Cutoff Date: 13JUN2018.

2) Restricted mean survival time (RMST) method

Table 31: Summary of RMST of overall survival (Pembro combo vs control) – ITT population

	Pembrolizumab + Chemotherapy (N=281)		Cetuximab + Chemotherapy (N=278)		Difference (95% CI) vs. Control
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	37	2.78	29	2.83	-0.04 (-0.15 , 0.06)
RMST based on 6 months of follow up	68	5.26	58	5.35	-0.09 (-0.35 , 0.17)
RMST based on 9 months of follow up	99	7.37	114	7.42	-0.05 (-0.49 , 0.39)
RMST based on 12 months of follow up	132	9.12	155	8.94	0.18 (-0.45 , 0.81)
RMST based on 15 months of follow up	158	10.6	176	10.1	0.47 (-0.35 , 1.28)
RMST based on 18 months of follow up	175	11.8	201	11.0	0.73 (-0.27 , 1.73)
RMST based on 24 months of follow up	193	13.8	217	12.4	1.38 (0.05 , 2.72)

RMST:Restricted mean survival time.
(Database Cutoff Date: 13JUN2018).

Table 32: Summary of RMST of PFS based on BICR per RECIST 1.1 (Pembro combo vs control) – ITT population

	Pembrolizumab + Chemotherapy (N=281)		Cetuximab + Chemotherapy (N=278)		Difference (95% CI) vs. Control
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	80	2.61	61	2.70	-0.09 (-0.21 , 0.03)
RMST based on 6 months of follow up	152	4.30	150	4.48	-0.18 (-0.49 , 0.13)
RMST based on 9 months of follow up	200	5.31	215	5.31	-0.00 (-0.48 , 0.47)
RMST based on 12 months of follow up	226	5.94	233	5.77	0.17 (-0.45 , 0.78)
RMST based on 15 months of follow up	232	6.41	240	6.09	0.31 (-0.42 , 1.05)
RMST:Restricted mean survival time. (Database Cutoff Date: 13JUN2018).					

Subsequent anticancer therapies

Table 33: Subjects Who Received Subsequent Anti-Cancer Therapy (pembro combo vs control) – ITT population

	Pembrolizumab + Chemotherapy (N=281)	Cetuximab + Chemotherapy (N=278)
Subjects Who Received New Anti-Cancer Therapy	107 (38.1)	143 (51.4)
Subjects Who Did Not Receive New Anti-Cancer Therapy	163 (58.0)	122 (43.9)
Unknown (Withdrew Consent)	11 (3.9)	13 (4.7)
(Database Cutoff Date: 13JUN2018).		

A third or higher lines of therapy was administered to 39 (13.9%) subjects in the pembro combo arm vs 51 (18.3%) in the control arm.

The most frequently used 2L therapy was paclitaxel (or paclitaxel albumin) in 14.2% of pembrolizumab plus chemotherapy participants and in 11.9% of standard treatment participants, and the most frequently used 3L therapy also being paclitaxel in 4.6% of pembrolizumab plus chemotherapy participants, and 5.0% of standard treatment participants.

At the database cut-off of 25-FEB-2019, overall 115 (40.9%) and 145 (52.2%) patients have received a subsequent anticancer therapy in pembro combo and control arm, respectively.

Table 34: Subjects who received subsequent checkpoint immunotherapy (pembro combo vs control) ITT population

	Pembrolizumab + Chemotherapy (N=281)	Cetuximab + Chemotherapy (N=278)
Subjects Who Received Subsequent Checkpoint Immunotherapy	15 (5.3)	69 (24.8)
Subjects Who Did Not Receive Subsequent Checkpoint Immunotherapy	255 (90.7)	195 (70.1)
Unknown (Withdrew Consent)	11 (3.9)	14 (5.0)
Database Cutoff Date: 13JUN2018		

PFS2 (IA2: cutoff date 13-JUN-2018)

PFS2 was defined as the time from randomization to subsequent disease progression after initiation of an anti-cancer therapy subsequent to discontinuation of study-specified treatments, or death from any cause, whichever occurs first. If progression after next-line therapy cannot be measured, a PFS event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first. Subjects alive and for whom a PFS event has not been observed should be censored at the last time known to be alive and without second disease progression.

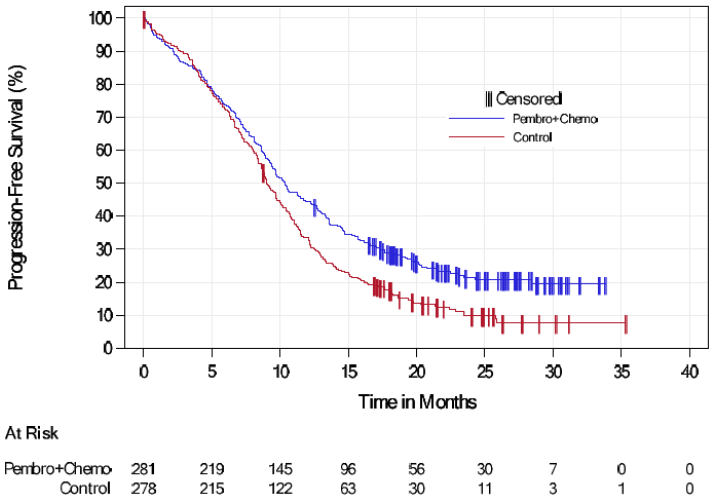


Figure 18: Kaplan-Meier estimates of PFS2 based on investigator assessment (pembro combo vs control) – ITT population

Table 35: Analysis of PFS2 based on investigator assessment (Pembro combo vs control) – ITT population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS2 † (Months) (95% CI)	PFS2 Rate at Months 6 in % † (95% CI)
Pembrolizumab + Chemotherapy	281	217 (77.2)	3484.7	6.2	10.4 (9.3, 12.3)	73.7 (68.1, 78.4)
Cetuximab + Chemotherapy	278	245 (88.1)	2902.5	8.4	9.0 (8.4, 10.0)	72.6 (66.9, 77.4)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					0.74 (0.62, 0.89)	0.00081§

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

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status. In case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

Database Cutoff Date: 13JUN2018.

Pembrolizumab vs chemotherapy (EXTREME regimen)

Interim analysis 2 (data cut-off 13-Jun-2018, DBL 29 June 2018)

A total of 13 (4.3%) of 300 participants randomized to standard treatment decided not to receive any study medication, versus 1 (0.3%) of 301 participants randomized to pembrolizumab monotherapy.

During the procedure, the MAH provided the results of the Final analysis for KEYNOTE-048 study (cut-off date 25-FEB-2019, DBL 25-MAR-2019).

A summary of all efficacy results for the comparison pembro mono vs chemotherapy at the Final analysis is presented in the table below:

Table 36: Key Efficacy Results Pembrolizumab Monotherapy vs Standard Treatment ITT, CPS ≥1 and CPS ≥20 Population Findings KEYNOTE-048 (FA)

	ITT (All Participants)		PD-L1 CPS ≥1		PD-L1 CPS ≥20	
	Pembrolizumab Monotherapy N=301	Std Treatment N=300	Pembrolizumab Monotherapy N=257	Std Treatment N=255	Pembrolizumab Monotherapy N=133	Std Treatment N=122
OS						
Number of events (%)	237 (78.7)	264 (88.0)	197 (76.7)	229 (89.8)	94 (70.7)	108 (88.5)
Median in months (95% CI)	11.5 (10.3, 13.4)	10.7 (9.3, 11.7)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)	14.8 (11.5, 20.6)	10.7 (8.8, 12.8)
HR (95% CI)	0.83 (0.70, 0.99)		0.74 (0.61, 0.90)		0.58 (0.44, 0.78)	
P-value (superiority statistic)	0.01985		0.00133		0.00010	
OS rate at 12 months (95% CI)	48.7 (42.9, 54.2)	44.4 (38.7, 49.9)	50.4 (44.1, 56.4)	43.6 (37.4, 49.6)	56.4 (47.5, 64.3)	44.9 (35.9, 53.4)
OS rate at 18 months (95% CI)	35.7 (30.3, 41.1)	27.2 (22.3, 32.4)	38.7 (32.7, 44.6)	26.6 (21.3, 32.1)	45.1 (36.5, 53.3)	26.6 (19.1, 34.7)
OS rate at 24 months (95% CI)	27.0 (22.1, 32.1)	18.8 (14.6, 23.5)	28.9 (23.5, 34.5)	17.4 (13.0, 22.4)	35.3 (27.3, 43.4)	19.1 (12.7, 26.6)
PFS (BICR per RECIST 1.1)						
Number of events (%)	272 (90.4)	277 (92.3)	228 (88.7)	237 (92.9)	115 (86.5)	114 (93.4)
Median in months (95% CI)	2.3 (2.2, 3.3)	5.2 (4.9, 6.1)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)	3.4 (3.2, 3.8)	5.3 (4.8, 6.3)
HR (95% CI)[b]	1.29 (1.09, 1.53)		1.13 (0.94, 1.36)		0.99 (0.76, 1.29)	
P-value	0.99830		0.89580		0.46791	
PFS rate at 6 months (95% CI)	26.2 (21.4, 31.3)	45.7 (39.9, 51.3)	28.7 (23.3, 34.4)	43.9 (37.6, 49.9)	33.0 (25.2, 41.0)	46.6 (37.5, 55.2)
PFS rate at 9 months (95% CI)	20.0 (15.7, 24.7)	21.4 (16.9, 26.3)	23.5 (18.5, 28.9)	19.8 (15.1, 25.0)	26.8 (19.5, 34.5)	22.0 (15.1, 29.8)
PFS rate at 12 months (95% CI)	17.6 (13.5, 22.1)	15.0 (11.2, 19.4)	20.6 (15.9, 25.8)	13.6 (9.6, 18.2)	23.5 (16.6, 31.1)	15.1 (9.3, 22.2)
ORR (BICR per RECIST 1.1, with confirmation)						
% (95% CI)	16.9 (12.9, 21.7)	36.0 (30.6, 41.7)	19.1 (14.5, 24.4)	34.9 (29.1, 41.1)	23.3 (16.4, 31.4)	36.1 (27.6, 45.3)
Complete Responses (CR)	14 (4.7%)	8 (2.7%)	14 (5.4%)	7 (2.7%)	10 (7.5%)	4 (3.3%)
Partial Responses (PR)	37 (12.3%)	100 (33.3%)	35 (13.6%)	82 (32.2%)	21 (15.8%)	40 (32.8%)
Stable Disease (SD)	82 (27.2%)	102 (34.0%)	72 (28.0%)	84 (32.9%)	40 (30.1%)	43 (35.2%)
Progressive Disease (PD)	122 (40.5%)	37 (12.3%)	100 (38.9%)	33 (12.9%)	42 (31.6%)	12 (9.8%)
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Number of responders	51	108	49	89	31	44
Median in months (range)	22.6 (1.5+ - 43.0+)	4.5 (1.2+ - 38.7+)	23.4 (1.5+ - 43.0+)	4.5 (1.2+ - 38.7+)	22.6 (2.7+ - 43.0+)	4.2 (1.2+ - 31.5+)
Median time to response (range)	2.1 (1.5 – 9.1)	2.1 (1.3 – 10.4)	2.1 (1.5 – 9.1)	2.1 (1.3 – 10.4)	2.1 (1.5 -9.1)	2.1 (1.9 - 6.0)
Number (Kaplan-Meier %) With Extended Response Duration (≥6 months)	37 (77.8)	32 (38.8)	37 (81.1)	24 (36.0)	24 (83.5)	12 (34.8)

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; 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 Tumours Version 1.1; Std=Standard. Database cutoff date: 25-FEB-2019

Primary endpoints

OS – pembro mono vs control

OS benefit in the ITT population did not reach statistically significant superiority at FA (HR 0.83 [0.70, 0.99], p=0.01985).

In the population of participants whose tumours express PD-L1 CPS ≥1 or PD-L1 CPS ≥20, comparing pembrolizumab monotherapy to standard treatment, FA OS results confirmed the statistically significant OS benefit observed at IA2.

Overall, OS HR point estimates improved compared to the IA2 in the ITT population and all CPS subgroups, with the exception of CPS<1 population (from 1.37 to 1.51).

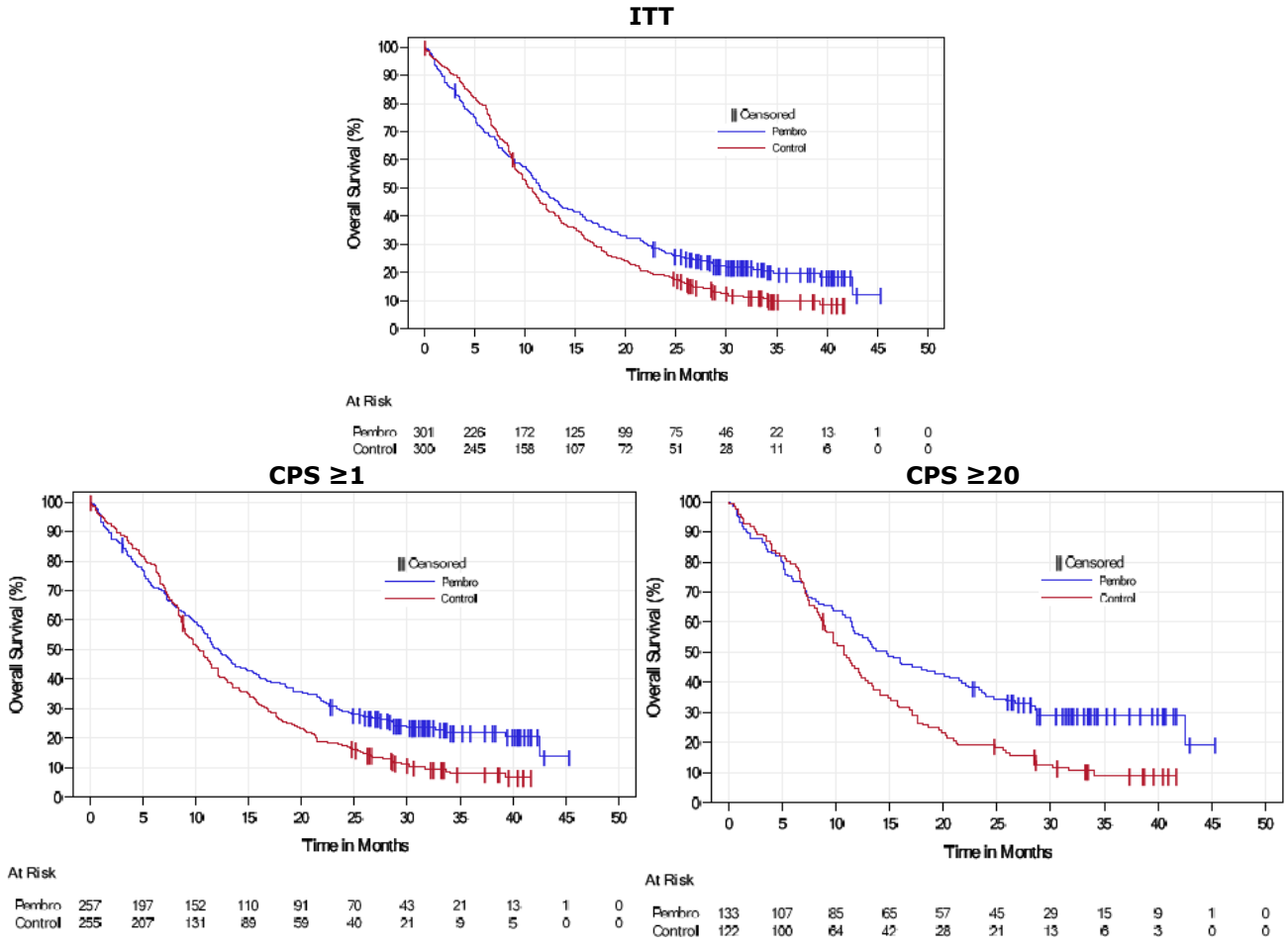


Figure 19: Kaplan-Meier Estimates of Overall Survival (Pembro Mono vs Control) – (Final Analysis – cut-off date 25 Feb 2019)

Table 37: Summary of Timing of Overall Survival Events (Pembro Mono vs Control) - ITT Population

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	301		300	
Subjects With OS Event	237	(78.7)	264	(88.0)
<30 Days Following Randomization	13	(4.3)	13	(4.3)
30-60 Days Following Randomization	19	(6.3)	7	(2.3)
>60 Days Following Randomization	205	(68.1)	244	(81.3)
Subjects Without OS Event	64	(21.3)	36	(12.0)
(Database Cutoff Date: 25FEB2019).				

PFS – pembro mono vs control

There was no statistically significant improvement in PFS in the CPS ≥20 population, therefore, PFS in the CPS ≥1 and ITT populations were not tested as per the multiplicity strategy.

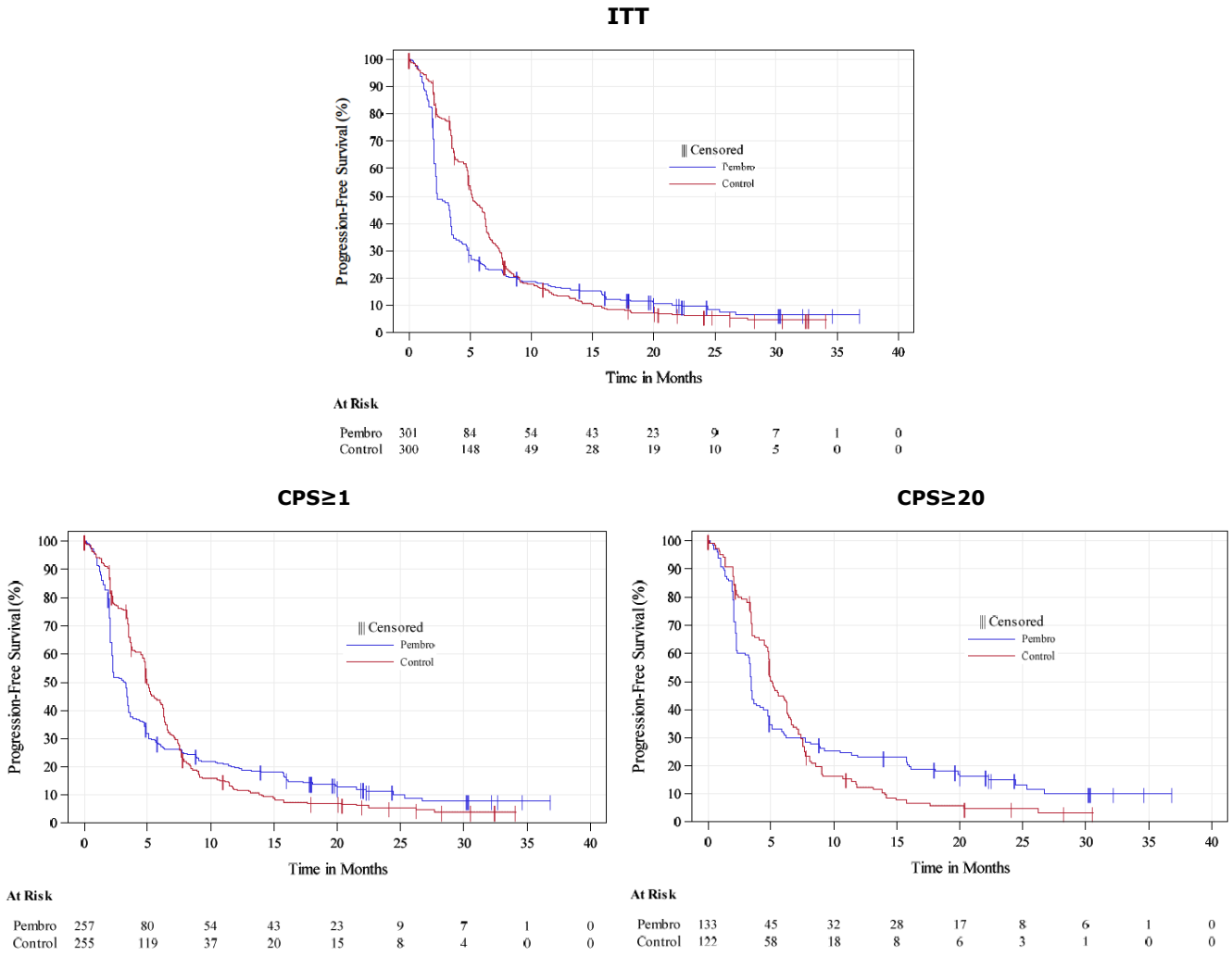


Figure 20: Kaplan-Meier plots of Progression Free Survival, based on BICR per RECIST 1.1 (ITT, CPS≥1, CPS≥20), Pembro Mono vs Control (IA2 - cut-off date 13-Jun-2018, DBL 29 June 2018)

PFS was not tested at FA, as prespecified in the protocol. PFS did not show improvement; however, PFS rates at 9 and 12 months were higher for pembro in the CPS≥1 and CPS≥20 populations.

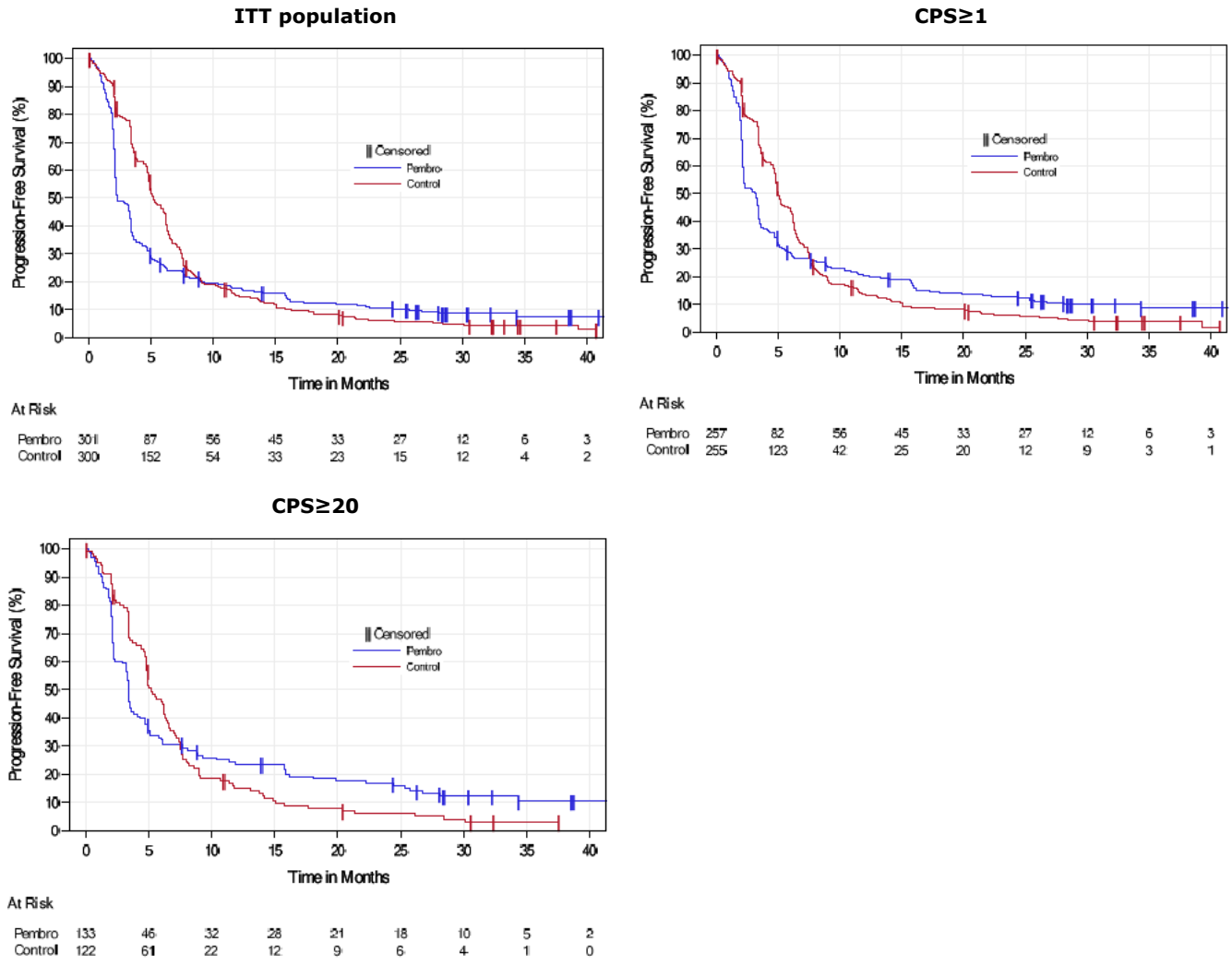


Figure 21: Kaplan-Meier estimates of PFS, based on BICR assessment per RECIST 1.1 (ITT, CPS≥1, CPS≥20), Pembro mono vs Control - (Final Analysis – cut-off date 25 Feb 2019)

Secondary endpoints

ORR – pembro mono vs control

ORR results based on BICR assessment per RECIST 1.1 for the ITT, CPS≥1 and CPS≥20 are reported in tables below. Objective responses are confirmed.

Table 38: Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (Pembro mono vs Control) - ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembrolizumab	301	51	16.9 (12.9,21.7)	-19.0 (-25.8,-12.1)	1.0000
Cetuximab + Chemotherapy	300	108	36.0 (30.6,41.7)		

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with 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); in case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is >=5; 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: 13JUN2018.

Table 39: Summary of Best Objective Response with Confirmation Based on BICR per RECIST 1.1 (Pembro mono vs Control) - ITT Population

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	301		300	
Complete Response (CR)	14	(4.7)	8	(2.7)
Partial Response (PR)	37	(12.3)	100	(33.3)
Objective Response (CR+PR)	**51**	**(16.9)**	**108**	**(36.0)**
Stable Disease (SD)	82	(27.2)	101	(33.7)
Progressive Disease (PD)	122	(40.5)	38	(12.7)
Non-CR/Non-PD (NN)	14	(4.7)	11	(3.7)
Not Evaluable (NE)	6	(2.0)	2	(0.7)
No Assessment	26	(8.6)	40	(13.3)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Table 40: Summary of Best Objective Response with Confirmation Based on BICR per RECIST 1.1 (Pembro mono vs Control) - CPS≥1

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	257		255	
Complete Response (CR)	14	(5.4)	7	(2.7)
Partial Response (PR)	35	(13.6)	82	(32.2)
Objective Response (CR+PR)	**49**	**(19.1)**	**89**	**(34.9)**
Stable Disease (SD)	72	(28.0)	83	(32.5)
Progressive Disease (PD)	100	(38.9)	34	(13.3)
Non-CR/Non-PD (NN)	11	(4.3)	11	(4.3)
Not Evaluable (NE)	5	(1.9)	2	(0.8)
No Assessment	20	(7.8)	36	(14.1)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Table 41: Summary of Best Objective Response with Confirmation Based on BICR per RECIST 1.1 (Pembro mono vs Control) - CPS≥20

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	133		122	
Complete Response (CR)	10	(7.5)	4	(3.3)
Partial Response (PR)	21	(15.8)	40	(32.8)
Objective Response (CR+PR)	**31**	**(23.3)**	**44**	**(36.1)**
Stable Disease (SD)	40	(30.1)	42	(34.4)
Progressive Disease (PD)	42	(31.6)	13	(10.7)
Non-CR/Non-PD (NN)	8	(6.0)	6	(4.9)
Not Evaluable (NE)	1	(0.8)	0	(0.0)
No Assessment	11	(8.3)	17	(13.9)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Analysis of objective response with both confirmed and unconfirmed responses yielded similar results as analysis with confirmed responses.

ORR results at the updated FA cut-off date were consistent with the results at the IA2. ORR was lower in pembrolizumab monotherapy responders; however, more responders achieved a complete response.

Patient Reported Outcome – pembro mono vs control

The PRO FAS population (i.e. all participants regardless of PD-L1 status who were randomized and treated and had at least one PRO assessment) included 294 and 280 participants in the pembrolizumab and in the control group, respectively. The compliance rates for the EORTC QLQ-30 were similar in both pembro

mono and control arm at baseline (94.9% versus 92%) and remained high at Week 15 (94.2% versus 83%). Compliance rates at baseline through Week 15 were similar for the EORTC QLQ H&N35 and EQ-5D.

Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/Quality of Life Score (secondary endpoint)

Table 42: Analysis of change from baseline of EORTC QLQ-C30 Global health status/QoI scales at Week 15 (Pembro mono vs Control) – FAS population

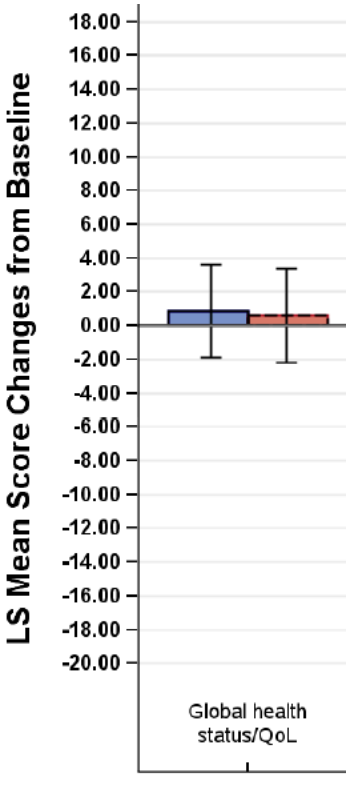
	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab	280	61.31 (21.599)	191	64.66 (20.546)	294	0.85 (-1.90, 3.59)
Cetuximab + Chemotherapy	262	59.70 (21.479)	182	62.59 (18.803)	279	0.60 (-2.19, 3.40)

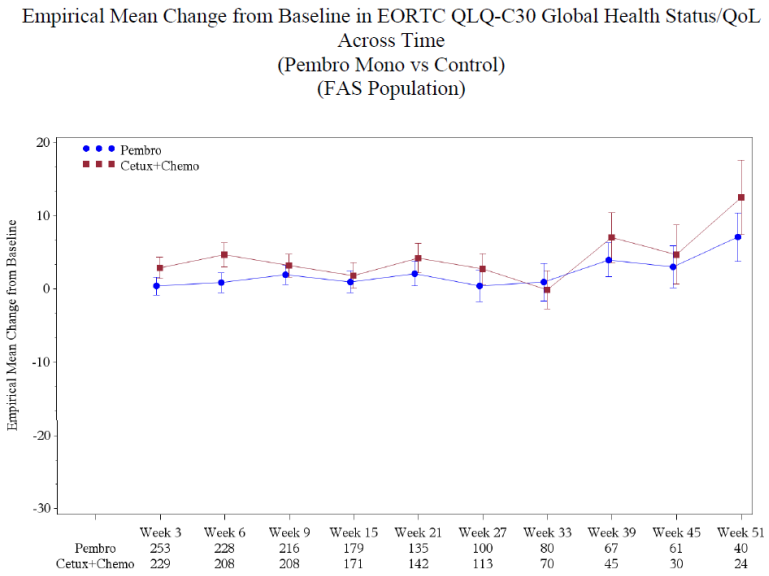
Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
Pembrolizumab vs. Cetuximab + Chemotherapy	0.24 (-3.34, 3.82)	0.893

[†] 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: 13JUN2018





Time to Deterioration in EORTC QLQ-C30 Global Health Status/Quality of Life (secondary endpoint)

In the PRO FAS population, TTD in the EORTC QLQ-C30 global health status/QoL score for pembrolizumab plus monotherapy compared to standard treatment resulted HR = 1.38 (95% CI: 0.95, 2.00) (see figure below):

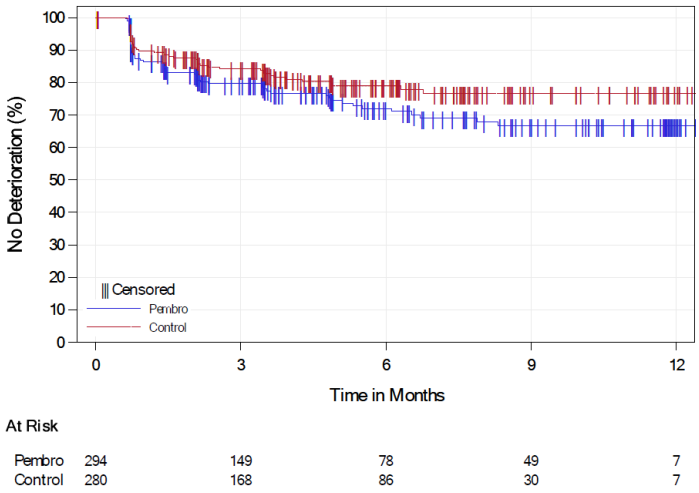
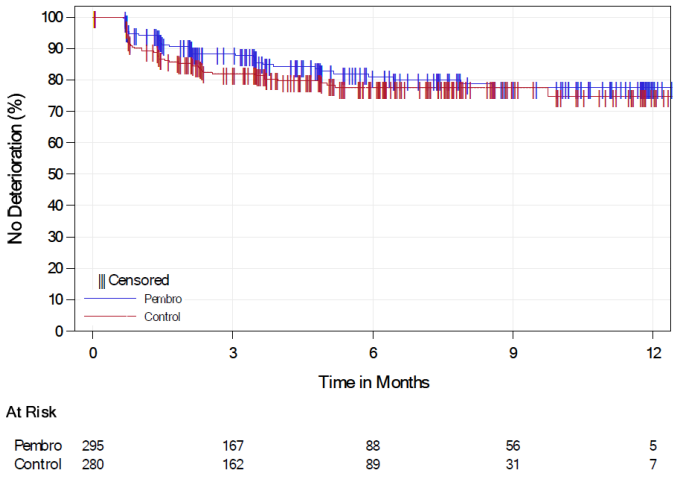


Figure 22: Kaplan-Meier plot of time to true deterioration for EORTC QLQ-C30 global health status/QoL (Pembro mono vs control) – FAS population (Cutoff date 13JUN2018)

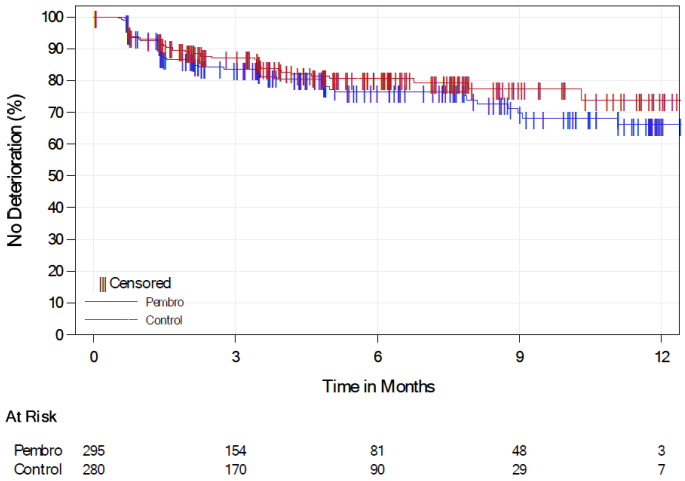
Time to Deterioration EORTC QLQ-H&N35 Pain and Swallowing Scores (secondary endpoints)

In the PRO FAS population, TTD in the EORTC QLQ-H&N35 pain score was HR = 0.80 (95% CI: 0.53, 1.21) and swallowing score was HR = 1.26 (95% CI: 0.85, 1.88) for pembrolizumab monotherapy when compared with standard treatment (see figures below):



(Database Cutoff Date: 13JUN2018)

Figure 23: Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Pain (Pembro mono vs control)



(Database Cutoff Date: 13JUN2018)

Figure 24: Kaplan-Meier plot of time to deterioration for EORTC QLQ-H&N35 Swallowing (Pembro combo vs control)

Exploratory endpoints

Duration of Response (and Time to Response) – pembro mono vs control

Table 43: Summary of TTR and DOR based on BICR per RECIST 1.1 in subjects with CR in ITT population – pembro mono vs control

	Pembrolizumab (N=301)	Cetuximab + Chemotherapy (N=300)
Number of subjects with response†	51	108
Time to Response (months)		
Mean (SD)	3.0 (1.8)	2.5 (0.8)
Median (Range)	2.1 (1.5-9.1)	2.1 (1.3-6.2)
Response Duration‡ (months)		
Median (Range)	20.9 (1.5+ - 34.8+)	4.5 (1.2+ - 30.6+)
Number (%‡) of Subjects with Extended Response Duration:		
≥6 months	36 (75.7)	32 (38.8)

† Includes subjects with 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: 13JUN2018.

Source: [P048V01MK3475: adam-adsl; adrs; adtte]

Table 44: Summary of response outcome in subjects with CR based on BICR per RECIST 1.1 (ITT population) – pembro mono vs control

	Pembrolizumab (N=301)	Cetuximab + Chemotherapy (N=300)
Number of Subjects with Response†	51	108
Subjects Who Progressed or Died‡ (%)	**25 (49.0)**	**77 (71.3)**
Range of DOR (months)	2.2 to 23.4	2.0 to 15.5
Censored Subjects (%)	**26 (51.0)**	**31 (28.7)**
Subjects who missed 2 or more consecutive disease assessments	1 (2.0)	12 (11.1)
Subjects who started new anti-cancer treatment	2 (3.9)	6 (5.6)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	0 (0.0)	2 (1.9)
Ongoing response§	23 (45.1)	11 (10.2)
≥6 months	23 (45.1)	11 (10.2)
Range of DOR (months)	13.6+ to 34.8+	16.0+ to 30.6+

† Includes subjects with a confirmed complete response or partial response.
‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.
'+' indicates there was no progressive disease by the time of last disease assessment.
Database Cutoff Date: 13JUN2018

Source: [P048V01MK3475: adam-adsl; adtte]

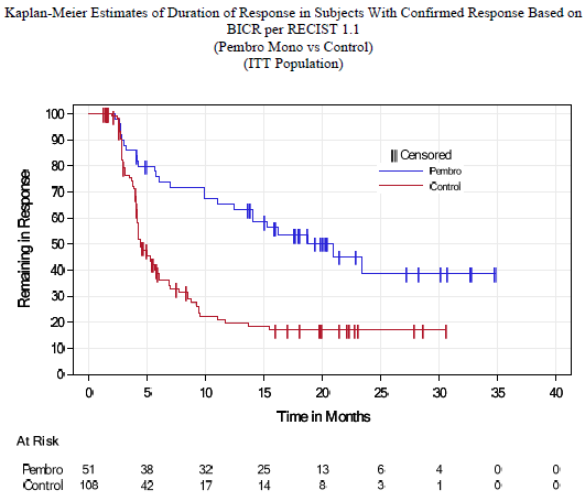


Figure 25: Kaplan-Meier estimates of DoR in subjects with CR based on BICR per RECIST 1.1 (ITT population) – pembro mono vs control

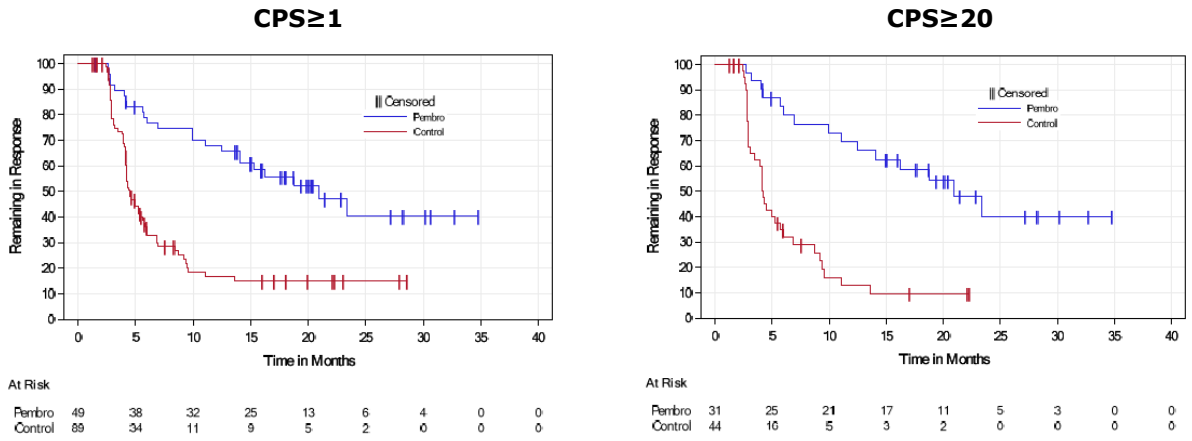


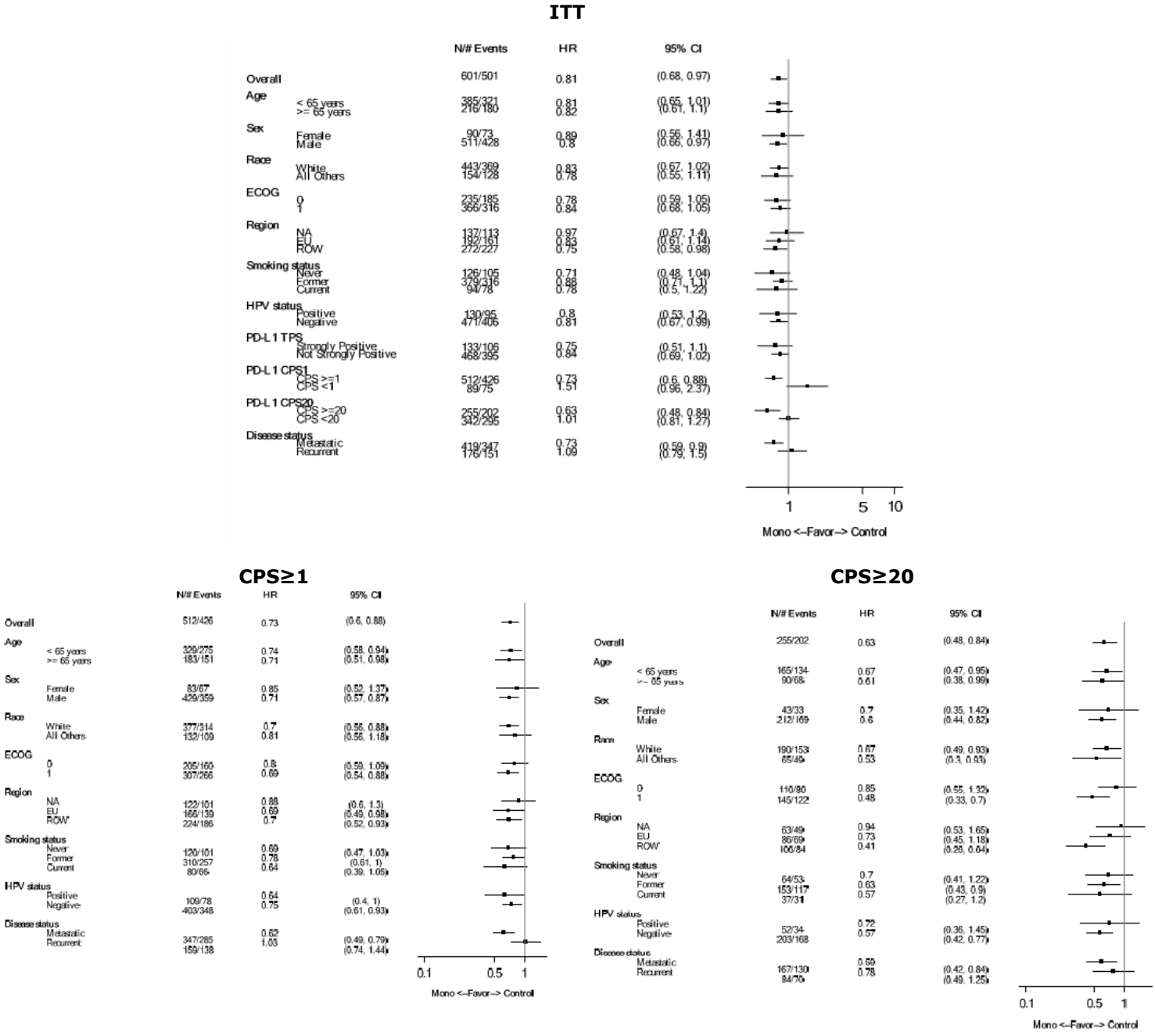
Figure 26: Kaplan-Meier estimates of DOR in subjects with confirmed response based on BICR per RECIST 1.1 in CPS≥1 and CPS≥20 – pembro mono vs control

DOR and TTR results at the FA were consistent with prior data at IA2. Median TTR was similar, median DOR was longer and more participants had a response duration ≥6 months in the pembro mono arm compared to control.

Ancillary analyses – pembro mono vs control

Subgroup analyses – Pembro mono vs Control

Forest Plots of OS, PFS and ORR by subgroup factors are reported in the figures below:



(database cut-off 25 Feb 2019)

Figure 27: Forest plots of OS Hazard Ratio in the ITT, CPS≥1 and CPS≥20 populations – pembro mono vs control

PFS

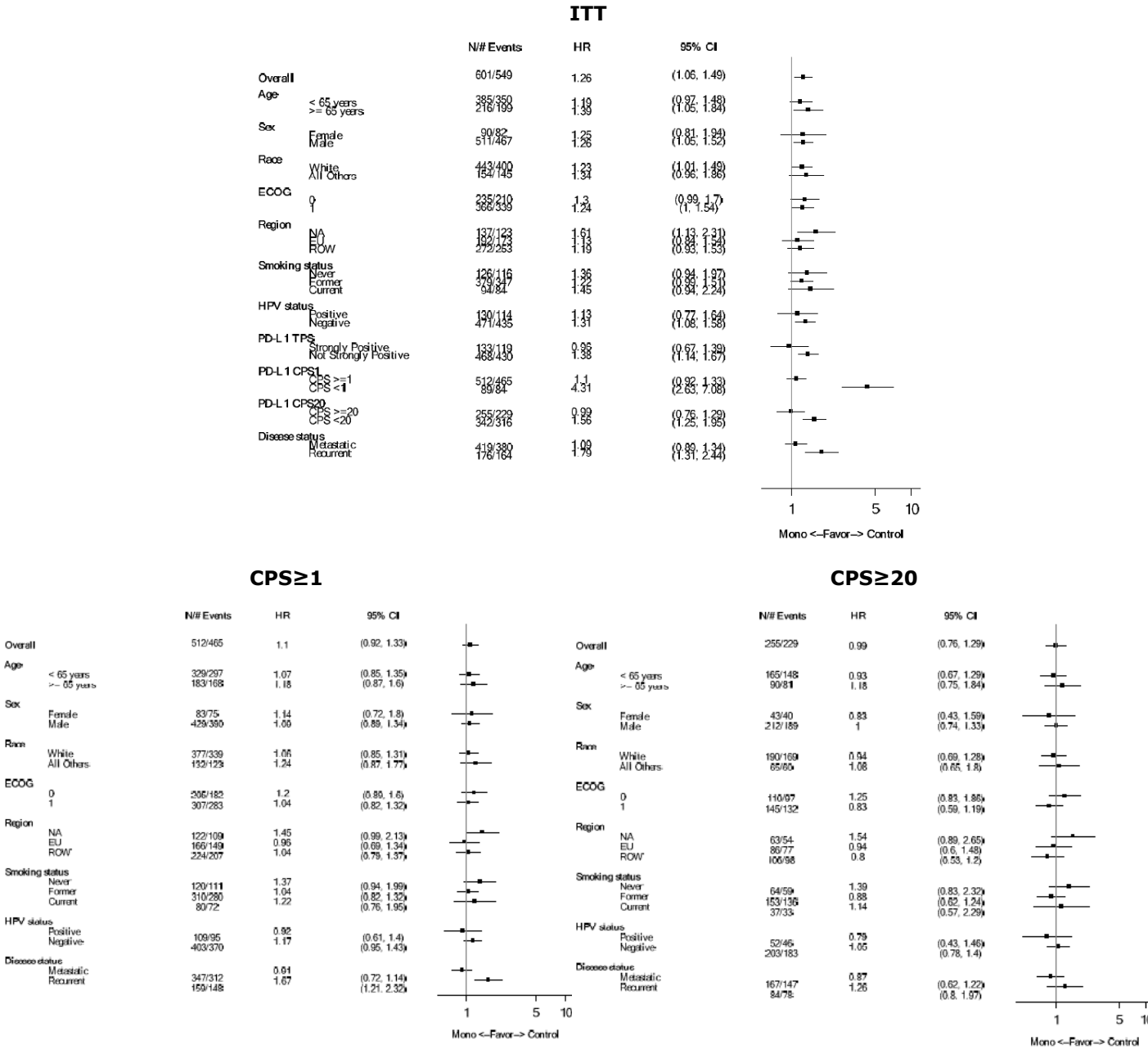


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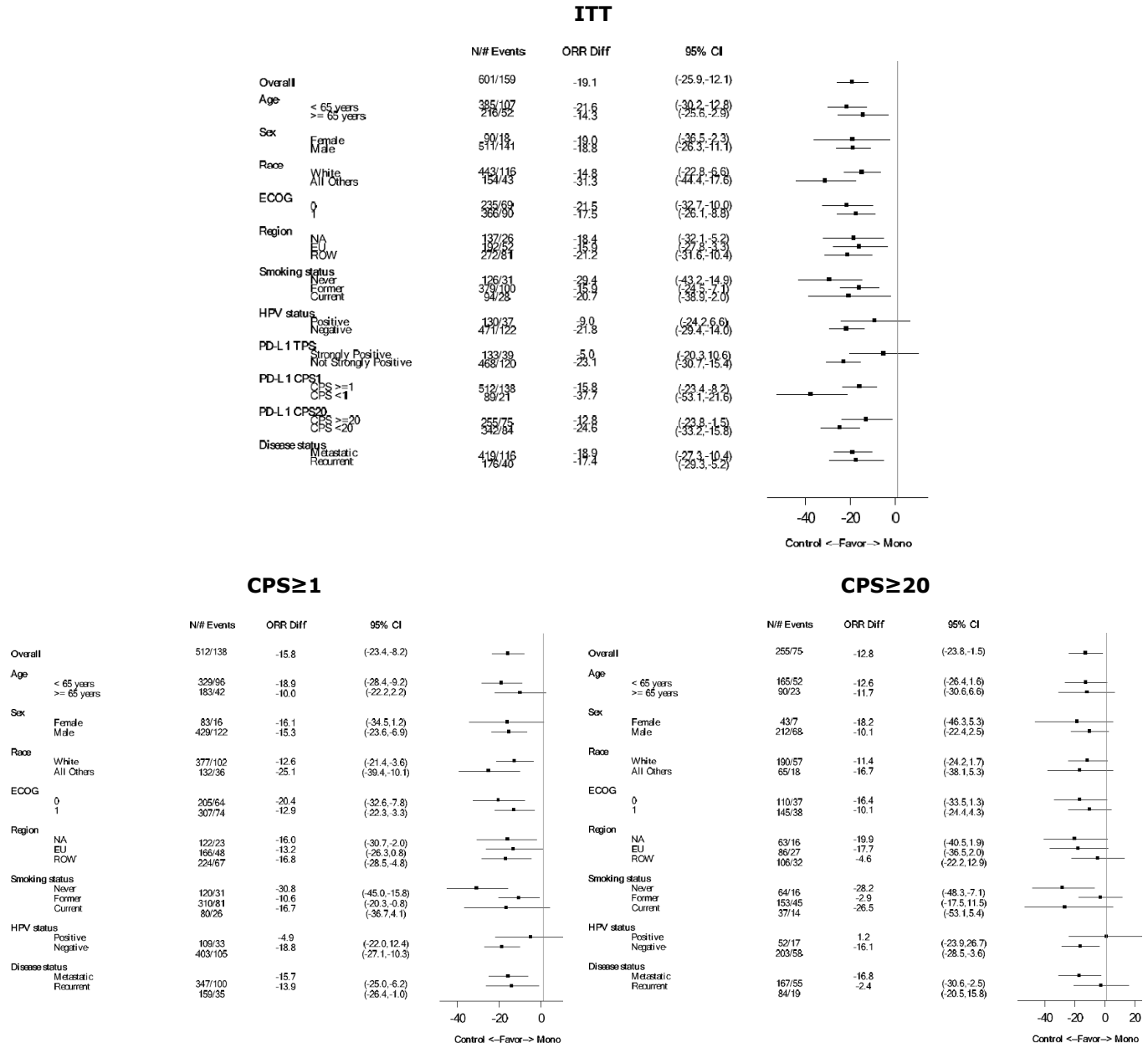
Figure 28: Forest plots of PFS Hazard Ratio based on BICR per RECIST 1.1 in the ITT, CPS≥1 and CPS≥20 populations – pembro mono vs control

ORR



(database cut-off 25 Feb 2019)

Figure 29: Forest plots of Best objective response (confirmed) rate based on BICR per RECIST 1.1 in the ITT, CPS≥1 and CPS≥20 populations – pembro mono vs control

Analyses in CPS <1, CPS <20, and CPS ≥1 to <20 Populations – pembro mono vs control

The subset analyses described in the three populations CPS <1, CPS <20, and CPS ≥1 to <20 were requested by the CHMP, are exploratory analyses, not adequately powered to test statistical significance, and should be interpreted with caution and considered hypothesis generating.

Table 45: Key Efficacy Results Pembrolizumab Monotherapy versus Standard Treatment CPS <1, CPS <20, and CPS ≥1 to CPS <20 Population Findings KEYNOTE-048 (FA)

	PD-L1 CPS <1		PD-L1 CPS <20		PD-L1 CPS ≥1 to CPS <20	
	Pembrolizumab Monotherapy N=44	Std Treatment N=45	Pembrolizumab Monotherapy N=167	Std Treatment N=175	Pembrolizumab Monotherapy N=124	Std Treatment N=133
OS						
Number of events (%)	40 (90.9)	35 (77.8)	142 (85.0)	153 (87.4)	103 (83.1)	121 (91.0)
Median in months (95% CI)	7.9 (4.7, 13.6)	11.3 (9.1, 15.9)	10.3 (8.4, 12.1)	10.3 (9.1, 12.2)	10.8 (9.0, 12.6)	10.1 (8.7, 12.1)
HR (95% CI)	1.51 (0.96, 2.37)		1.01 (0.81, 1.27)		0.86 (0.66, 1.12)	
P-value (superiority statistic)	0.96241		0.54273		0.12827	
OS rate at 12 months (95% CI)	38.6 (24.5, 52.6)	48.9 (33.7, 62.4)	42.8 (35.2, 50.2)	44.8 (37.3, 52.0)	44.0 (35.1, 52.5)	42.4 (33.9, 50.7)
OS rate at 18 months (95% CI)	18.2 (8.5, 30.7)	31.1 (18.4, 44.7)	28.3 (21.7, 35.3)	28.2 (21.7, 35.0)	31.8 (23.7, 40.0)	26.5 (19.3, 34.2)
OS rate at 24 months (95% CI)	15.9 (7.0, 28.1)	26.7 (14.9, 40.0)	20.5 (14.7, 26.9)	19.0 (13.5, 25.1)	22.0 (15.1, 29.6)	15.9 (10.3, 22.6)
PFS (BICR per RECIST 1.1)						
Number of events (%)	44 (100.0)	40 (88.9)	156 (93.4)	160 (91.4)	113 (91.1)	123 (92.5)
Median in months (95% CI)	2.1 (1.9, 2.3)	6.2 (5.1, 7.6)	2.2 (2.1, 2.3)	5.3 (4.8, 6.2)	2.2 (2.1, 2.9)	4.9 (3.8, 6.0)
HR (95% CI)b	4.31 (2.63, 7.08)		1.56 (1.25, 1.95)		1.25 (0.96, 1.61)	
P-value	1.00000		0.99996		0.95093	
PFS rate at 6 months (95% CI)	11.4 (4.2, 22.6)	56.0 (40.0, 69.2)	21.0 (15.2, 27.4)	45.8 (38.2, 53.1)	24.2 (17.1, 32.0)	41.4 (32.8, 49.7)
ORR (BICR per RECIST 1.1)						
% (95% CI)	4.5 (0.6, 15.5)	42.2 (27.7, 57.8)	12.0 (7.5, 17.9)	36.6 (29.4, 44.2)	14.5 (8.8, 22.0)	33.8 (25.9,42.5)
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Number of responders	2	19	20	64	18	45
Median in months (range)	2.6 (2.2 – 3.0)	7.8 (2.0 – 38.6+)	15.2 (1.5+ - 38.9+)	5.0 (1.4+ - 38.7+)	NR (1.5+ - 38.9+)	5.0 (1.4+ - 38.7+)
Median time to response (range)	1.9 (1.7-2.1)	2.1 (1.9-4.9)	2.1 (1.7-7.6)	2.1 (1.3-10.4)	2.2 (2.0-7.6)	2.1 (1.3-10.4)
Number (Kaplan-Meier %) With Extended Response Duration (≥6 months)	0 (NR)	8 (52.7)	13 (68.4)	20 (41.2)	13 (76.5)	12 (36.6)

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: 25-FEB-2019

Overall survival

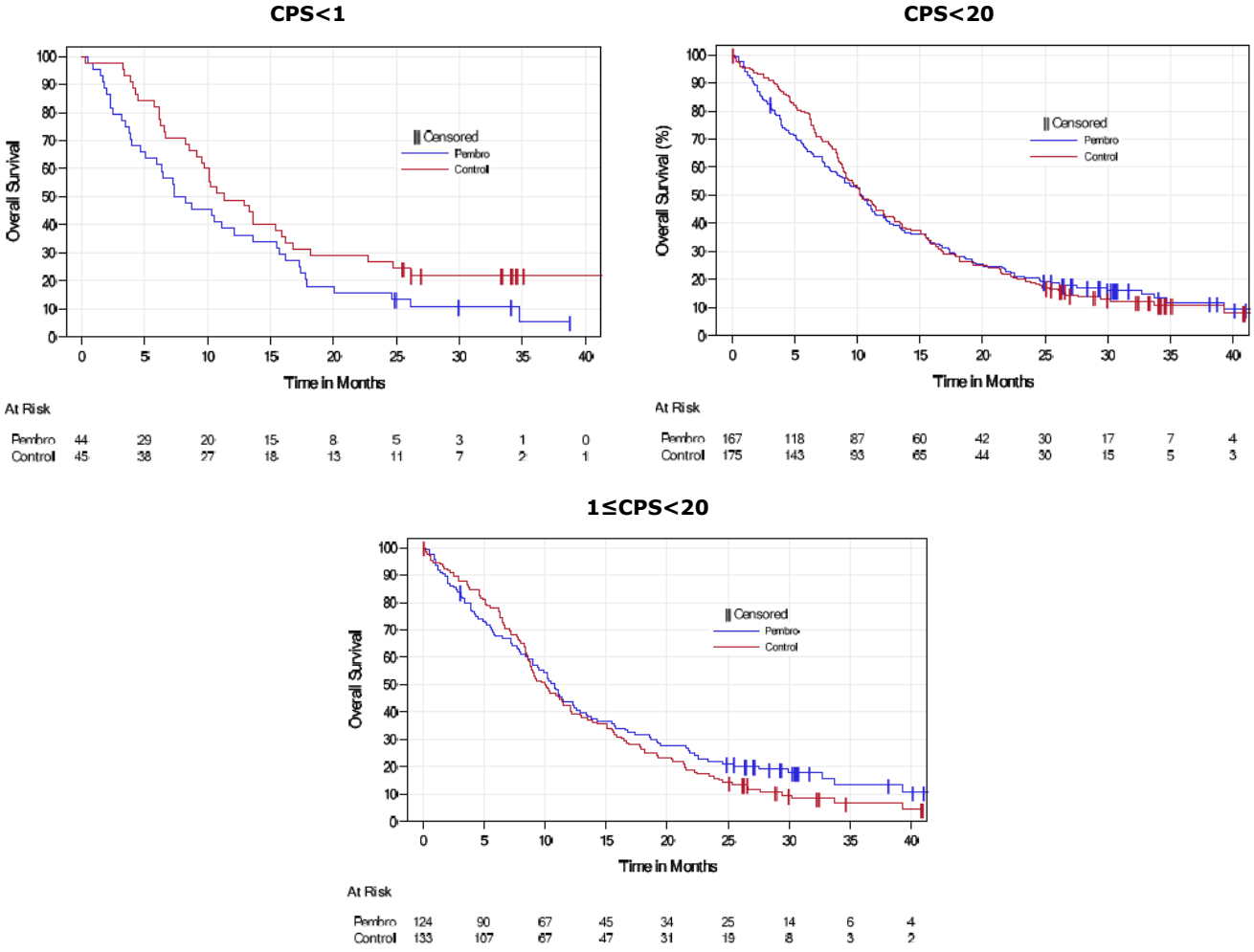
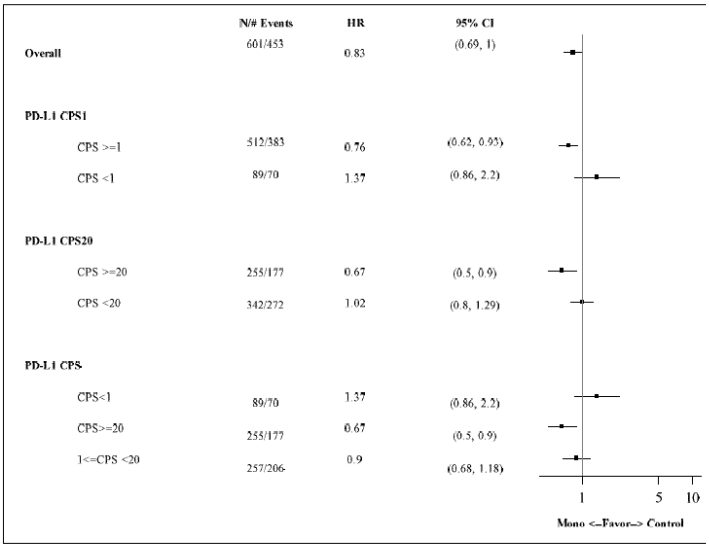


Figure 30: Kaplan-Meier of OS – Pembro mono vs control (Final analysis)



(Database Cutoff Date: 13JUN2018).

Figure 31: Forest plot of OS Hazard Ratio by PD-L1 subgroup (Pembro combo vs control) – ITT population (IA2)

Progression free survival

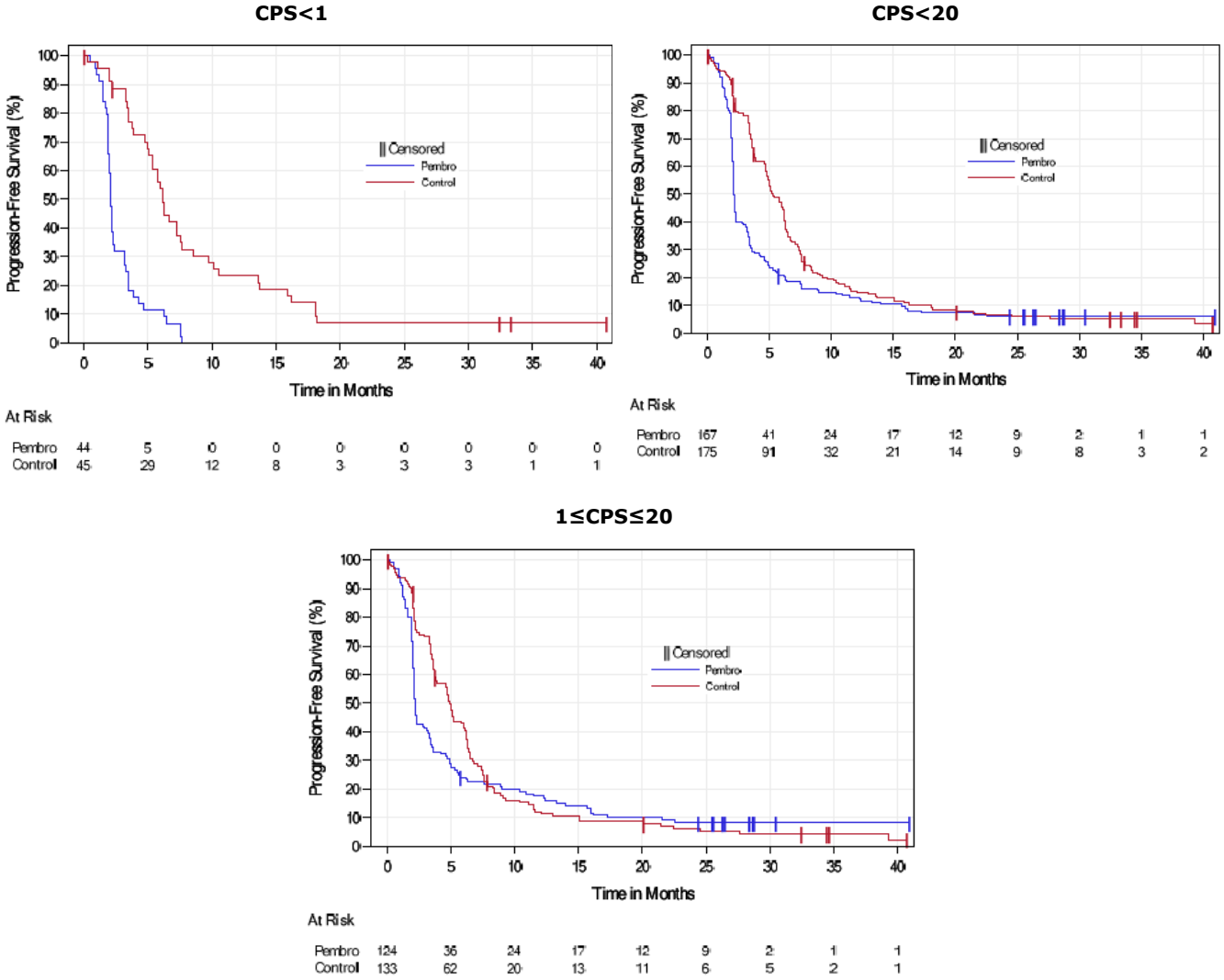


Figure 32: Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1 (primary analysis) – Pembro mono vs control

Analyses in TPS <50% and TPS ≥50% Populations – pembro mono vs control

Table 46: Key Efficacy Results Pembrolizumab Monotherapy versus Standard Treatment TPS <50%, TPS ≥50% Population Findings - KEYNOTE-048 IA2 Analysis

	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	Pembrolizumab Monotherapy N=234	Std Treatment N=234	Pembrolizumab Monotherapy N=67	Std Treatment N=66
OS				
Number of events (%)	168 (71.8)	191 (81.6)	45 (67.2)	49 (74.2)
Median in months† (95% CI)	11.6 (10.3, 13.8)	10.3 (9.1, 11.7)	11.7 (7.0, 17.1)	11.4 (8.6, 15.8)
HR (95% CI) ‡	0.84 (0.68, 1.03)		0.91 (0.60, 1.37)	
P-value (superiority statistic)	0.04863§		0.32407§	
OS rate at 12 months (95% CI)	49.8 (43.2, 56.0)	43.3 (36.9, 49.6)	47.2 (34.8, 58.6)	48.2 (35.7, 59.6)
PFS (BICR per RECIST 1.1)				
Number of events (%)	213 (91.0)	210 (89.7)	56 (83.6)	60 (90.9)
Median in months† (95% CI)	2.3 (2.2, 3.3)	5.3 (4.9, 6.2)	3.3 (2.1, 4.7)	4.9 (3.6, 6.2)
HR (95% CI) ‡	1.45 (1.19, 1.76)		0.95 (0.65, 1.38)	

	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	Pembrolizumab Monotherapy N=234	**Std Treatment N=234**	**Pembrolizumab Monotherapy N=67**	**Std Treatment N=66**
P-value	0.99990§		0.39271§	
PFS rate at 12 months† (95% CI)	15.0 (10.8, 20.0)	14.9 (10.6, 20.0)	31.3 (20.7, 42.5)	41.5 (29.3, 53.2)
ORR (BICR per RECIST 1.1)				
(%) (95% CI)	14.1 (9.9,19.2)	37.2 (31.0,43.7)	26.9 (16.8,39.1)	31.8 (20.9,44.4)
DOR (Confirmed CR or PR BICR per RECIST 1.1)				
Number of responders	33	87	18	21
Median in months (range)	15.2 (1.5+ - 30.6+)	4.5 (1.4+ - 30.6+)	23.4 (2.7 - 34.8+)	4.4 (1.2+ - 22.3+)
Median time to response (range)	2.1 (1.7-9.1)	2.1 (1.3-6.2)	2.1 (1.5-8.9)	2.2 (2.0-6.0)
Number (Kaplan-Meier %†) With Extended Response Duration (≥6 months)	22 (71.7)	26 (41.1)	14 (83.0)	6 (30.0)

Analysis of the first part of the OS curves

Table 47: Piecewise Hazard Rate for Overall Survival (Pembro Mono vs Control) (ITT Population) (CPS>=1)

Month	Pembrolizumab (N=257)		Cetuximab + Chemotherapy(N=255)		HR
	Event	Rate	Event	Rate	
2	27	0.055	19	0.039	1.42
4	23	0.053	18	0.040	1.32
6	23	0.059	17	0.041	1.44
7	5	0.028	20	0.105	0.27
8	11	0.064	14	0.081	0.79
9	7	0.043	22	0.141	0.31
10	7	0.045	12	0.089	0.51
12+	74	0.048	84	0.076	0.63
Database Cutoff Date: 13JUN2018					

Table 48: Summary of Death Reasons (ITT Population-Patients Who Died Within 6 Months) (CPS>=1)

	Pembrolizumab (N=73) n(%)	Cetuximab + Chemotherapy (N=54) n(%)
Subjects who died	73 (100.0)	54 (100.0)
Progressive Disease	**52 (71.2)**	**27 (50.0)**
Adverse Event	**18 (24.7)**	**24 (44.4)**
Not Related	14 (19.2)	16 (29.6)
Related	4 (5.5)	8 (14.8)
Unknown	**3 (4.1)**	**3 (5.6)**
Withdrawal By Subject	1 (1.4)	1 (1.9)
Other	2 (2.7)	2 (3.7)
Database Cutoff Date: 13JUN2018		

Table 49: Piecewise Hazard Rate for Overall Survival (Pembro Mono vs Control) (ITT Population) (CPS>=20)

Month	Pembrolizumab(N=133)		Cetuximab + Chemotherapy(N=122)		HR
	Event	Rate	Event	Rate	
2	14	0.056	9	0.038	1.45
4	8	0.035	8	0.037	0.95
6	11	0.052	8	0.040	1.31
7	4	0.041	10	0.107	0.38
8	5	0.054	7	0.085	0.64
9	3	0.034	9	0.119	0.28
10	2	0.023	6	0.089	0.26
12+	35	0.037	38	0.070	0.53
Database Cutoff Date: 13JUN2018					

Table 50: Summary of Death Reasons (ITT Population-Patients Who Died Within 6 Months) (CPS>=20)

	Pembrolizumab (N=33) n(%)	Cetuximab + Chemotherapy (N=25) n(%)
Subjects who died	33 (100.0)	25 (100.0)
Progressive Disease	**23 (69.7)**	**14 (56.0)**
Adverse Event	**9 (27.3)**	**9 (36.0)**
Not Related	6 (18.2)	5 (20.0)
Related	3 (9.1)	4 (16.0)
Unknown	**1 (3.0)**	**2 (8.0)**
Withdrawal By Subject	1 (3.0)	1 (4.0)
Other	0 (0.0)	1 (4.0)
Database Cutoff Date: 13JUN2018		

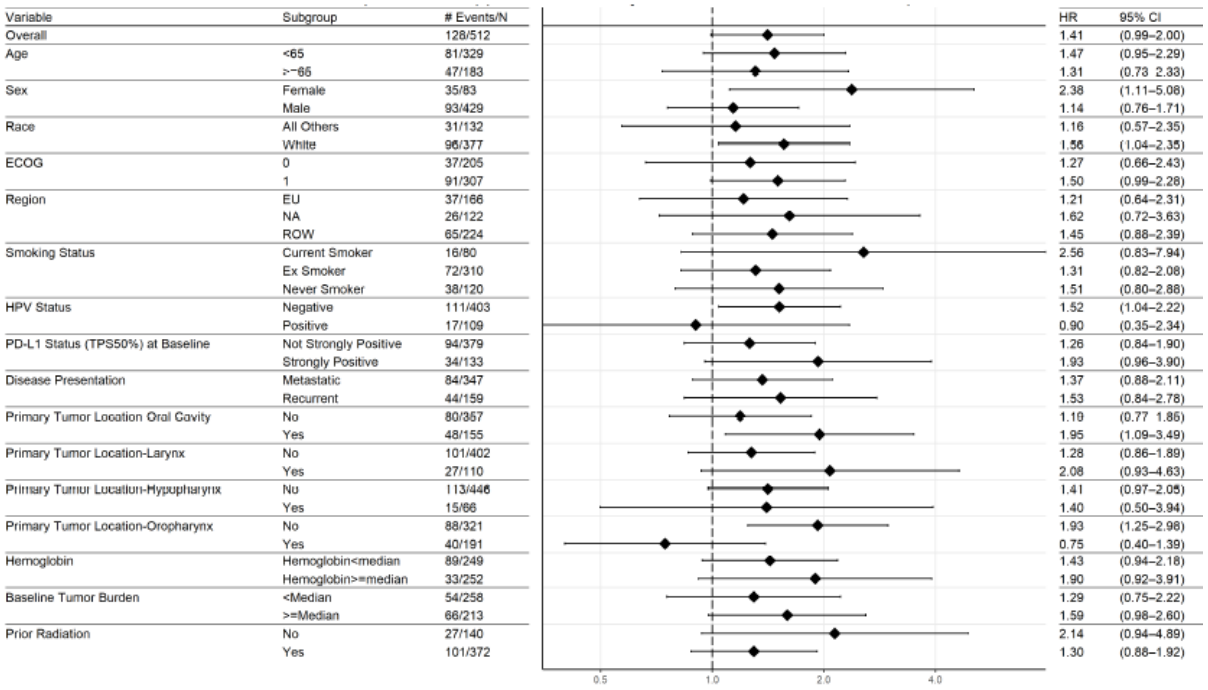


Figure 33: Forest plot of OS Hazard ratio by subgroup factors CPS≥1 population – up to month 6

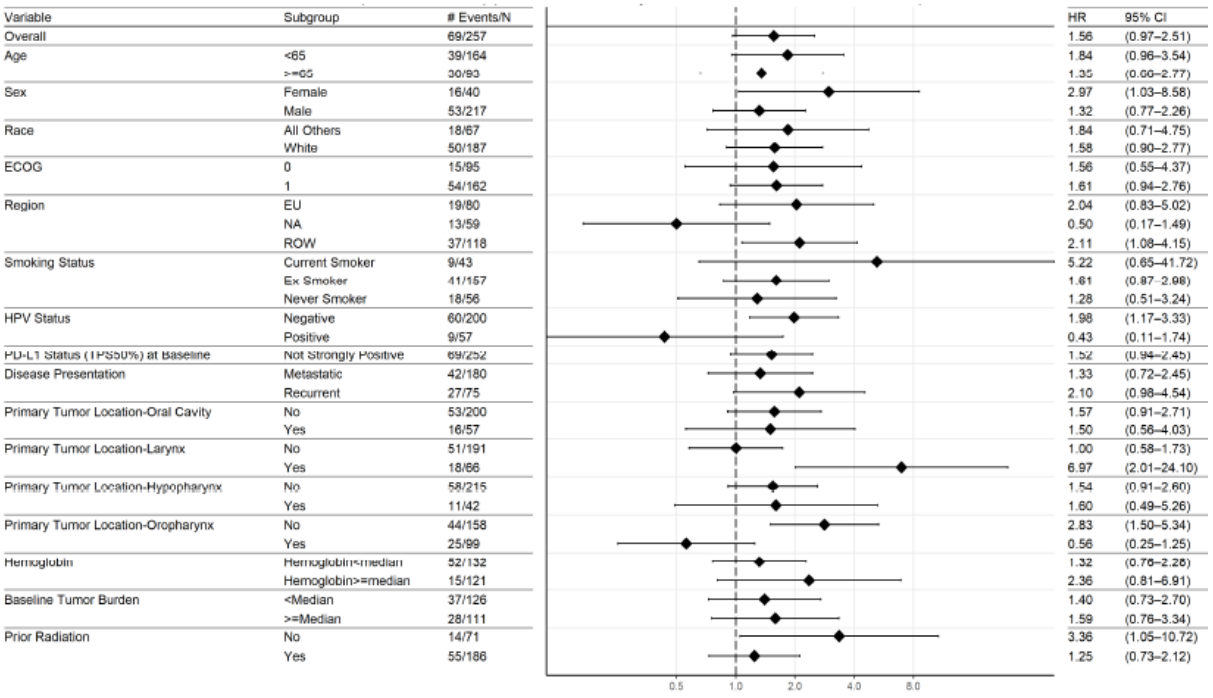


Figure 34: Forest plot of OS Hazard ratio by subgroup factors 1≤CPS<20 population – up to month 6

Proportional Hazards (PH) assumption for OS

The PH assumption for OS was examined using both graphical (not shown) and analytical methods (see above "ancillary analyses" in pembro combo comparison section). From both the plots and p-value from the test, there is evidence of departure from the PH assumption in all the three population (ITT, CPS≥1, CPS≥20) of pembro mono vs control.

To account for the non-proportional hazards effect associated with immunotherapies, two sensitivity analyses were conducted:

1) Weighted log-rank test with parameter (0,1) (see above "ancillary analyses" in pembro combo comparison section)

2) Restricted mean survival time (RMST) method

Sensitivity analyses: Restricted mean survival times (RMST) – pembro mono vs control

Table 51: Summary of RMST of overall survival (Pembro mono vs control) – ITT population

	Pembrolizumab (N=301)		Cetuximab + Chemotherapy (N=300)		Difference (95% CI) vs. Control
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	45	2.76	30	2.84	-0.07 (-0.17 , 0.02)
RMST based on 6 months of follow up	90	5.08	62	5.37	-0.29 (-0.54 , -.03)
RMST based on 9 months of follow up	120	7.03	125	7.43	-0.40 (-0.83 , 0.04)
RMST based on 12 months of follow up	152	8.69	166	8.94	-0.25 (-0.88 , 0.37)
RMST based on 15 months of follow up	172	10.0	191	10.1	-0.07 (-0.88 , 0.73)
RMST based on 18 months of follow up	189	11.2	217	11.1	0.17 (-0.81 , 1.15)
RMST based on 24 months of follow up	206	13.2	233	12.4	0.76 (-0.56 , 2.08)
RMST:Restricted mean survival time. (Database Cutoff Date: 13JUN2018).					

Table 52: Summary of RMST of overall survival (Pembro mono vs control) – CPS≥1

	Pembrolizumab (N=257)		Cetuximab + Chemotherapy (N=255)		Difference (95% CI) vs. Control
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	36	2.77	29	2.82	-0.05 (-0.16 , 0.05)
RMST based on 6 months of follow up	73	5.13	54	5.33	-0.20 (-0.48 , 0.08)
RMST based on 9 months of follow up	96	7.14	110	7.37	-0.23 (-0.71 , 0.24)
RMST based on 12 months of follow up	125	8.86	143	8.86	0.00 (-0.67 , 0.68)
RMST based on 15 months of follow up	143	10.3	164	10.0	0.26 (-0.61 , 1.14)
RMST based on 18 months of follow up	154	11.5	186	10.9	0.58 (-0.49 , 1.65)
RMST based on 24 months of follow up	171	13.6	200	12.2	1.35 (-0.08 , 2.78)
RMST:Restricted mean survival time. (Database Cutoff Date: 13JUN2018).					

Table 53: Summary of RMST of overall survival (Pembro mono vs control) – CPS≥20

	Pembrolizumab (N=133)		Cetuximab + Chemotherapy (N=122)		Difference (95% CI) vs. Control
	Number of Events	RMST	Number of Events	RMST	
RMST based on 3 months of follow up	16	2.78	13	2.83	-0.05 (-0.20 , 0.10)
RMST based on 6 months of follow up	33	5.22	25	5.35	-0.13 (-0.52 , 0.26)
RMST based on 9 months of follow up	45	7.33	51	7.41	-0.09 (-0.75 , 0.58)
RMST based on 12 months of follow up	57	9.22	67	8.95	0.27 (-0.68 , 1.22)
RMST based on 15 months of follow up	66	10.8	79	10.1	0.70 (-0.53 , 1.93)
RMST based on 18 months of follow up	71	12.2	89	11.1	1.20 (-0.31 , 2.71)
RMST based on 24 months of follow up	79	14.8	93	12.4	2.34 (0.29 , 4.39)
RMST:Restricted mean survival time. (Database Cutoff Date: 13JUN2018).					

Subsequent anticancer therapies

Table 54: Subjects Who Received Subsequent Anti-Cancer Therapy (Pembro Mono vs Control) (ITT Population)

	Pembrolizumab (N=301)	Cetuximab + Chemotherapy (N=300)
Subjects Who Received New Anti-Cancer Therapy	140 (46.5)	156 (52.0)
Subjects Who Did Not Receive New Anti-Cancer Therapy	150 (49.8)	129 (43.0)
Unknown (Withdrew Consent)	11 (3.7)	15 (5.0)

(Database Cutoff Date: 13JUN2018).

A third or higher lines of therapy was administered to a similar rate of subjects in both arms: 56 (18.6%) vs 54 (18%) in pembro mono vs control.

The most frequently used 2L therapy was carboplatin in 21.3% of pembrolizumab monotherapy participants, and paclitaxel in 13.0% of standard treatment participants, and the most frequently used 3L therapy being paclitaxel in 8.0% of pembrolizumab monotherapy participants, and nivolumab in 5.7% of standard treatment participants.

Table 55: subjects who received subsequent checkpoint immunotherapy (pembro mono vs control) ITT population

	Pembrolizumab (N=301)	Cetuximab + Chemotherapy (N=300)
Subjects Who Received Subsequent Checkpoint Immunotherapy	13 (4.3)	73 (24.3)
Subjects Who Did Not Receive Subsequent Checkpoint Immunotherapy	276 (91.7)	211 (70.3)
Unknown (Withdrew Consent)	12 (4.0)	16 (5.3)
Database Cutoff Date: 13JUN2018		

Updated data: At the database cut-off of 25-FEB-2019, overall 148 (49.2%) and 159 (53%) patients have received a subsequent anticancer therapy in pembro mono and control arm, respectively.

PFS2

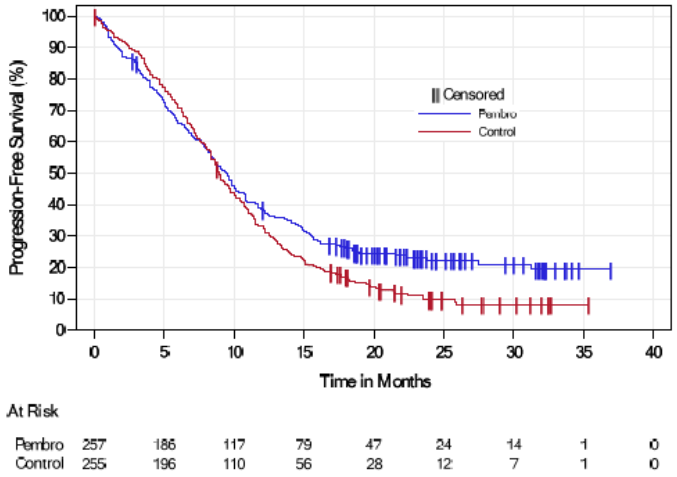


Figure 35: Kaplan-Meier estimates of PFS2 based on investigator assessment (pembro mono vs control) – CPS⩾1

Table 56: Analysis of PFS2 based on investigator assessment (Pembro mono vs control) – CPS⩾1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS2 † (Months) (95% CI)	PFS2 Rate at Months 6 in % † (95% CI)
Pembrolizumab	257	197 (76.7)	2965.0	6.6	9.4 (8.3, 10.3)	66.4 (60.2, 71.8)
Cetuximab + Chemotherapy	255	226 (88.6)	2665.6	8.5	8.9 (8.3, 9.8)	71.3 (65.3, 76.4)
Pairwise Comparisons					Hazard Ratio ‡ (95% CI) ‡	p-Value
Primary Pembrolizumab vs. Cetuximab + Chemotherapy					0.81 (0.67, 0.98)	0.01702 §

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status. In case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.
§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.
Database Cutoff Date: 13JUN2018.

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 57: Summary of Efficacy for trial KEYNOTE-048

Title: A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma			
Study identifier	P048V02MK3475 (IND: 122,325 EudraCT: 2014-003698-41)		
Design	Phase 3, randomized, multi-center, open-label, 3 arms		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		enrollment started on 1 Apr 2015; study ongoing not applicable not applicable
Hypothesis	Superiority and Non-inferiority		
Treatments groups	Pembro combo		Cisplatin 100 mg/m2 Q3W OR carboplatin AUC 5 Q3W for 6 cycles + 5-FU 1000 mg/m2/day D1-4 Q3W for 6 cycles + Pembrolizumab 200 mg Q3W until progression 301 pts randomized
	Pembro mono		Pembrolizumab 200 mg Q3W until progression 281 pts randomized
	Control		Cisplatin 100 mg/m2 Q3W OR carboplatin AUC 5 Q3W for 6 cycles + 5-FU 1000 mg/m2/day D1-4 Q3W for 6 cycles + Cetuximab 400 mg/m2 on D1 (loading dose) followed by 250 mg/m2 weekly until progression (EXTREME regimen) 300 pts randomized
Endpoints and definitions	Dual Primary	**OS** (CPS≥20, CPS≥1,ITT)	Time from randomization to death due to any cause
		PFS (CPS≥20, CPS≥1,ITT)	Time from randomization to first PD (per RECIST 1.1 based on BICR) or death due to any cause
	Secondary	**ORR** (CPS≥20, CPS≥1,ITT)	Proportion of participants who had confirmed CR or PR (per RECIST 1.1 based on BICR)
		QoL, PRO	EORTC QLQ-C30 global health status/quality of life scores at baseline and week 15. Time from baseline to first onset of patient reported outcomes (PRO) deterioration with confirmation (true deterioration).
	Exploratory	**DOR** (CPS≥20, CPS≥1,ITT)	Time from first documented evidence of CR or PR until PD (per RECIST 1.1 based on BICR) or death
Data cut-off Database lock	25 Feb 2019 (FA) 25 Mar 2019 (FA)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	**Pembrolizumab**	**Pembrolizumab + Chemo**	**SOC (vs. Mono) (vs. Combo)**
	ITT - Number of subject	301	281	300 (vs. Mono) 287 (vs. Combo)
	OS number of events (%)	237 (78.7%)	213 (75.8%)	264 (88%) 247 (88.8%)
	OS (Median (months))	11.5	13	10.7
	95%-CI	(10.3, 13.4)	(10.9, 14.7)	(9.3, 11.7)
	PFS (Median (months))	2.3	4.9	5.1
	95%-CI	(2.2, 3.3)	(4.7, 6.1)	(4.9, 6.1)
	PD-L1 CPS ≥ 1	257	242	255 (vs. Mono) 235 (vs. Combo)

	OS number of events (%)	197 (76.7%)	177 (73.1%)	229 (89.8%) 213 (90.6%)
	OS (Median (months))	12.3	13.6	10.3 10.4
	95%-CI	(10.8, 14.3)	(10.7, 15.5)	(9.0, 11.5) (9.1, 11.7)
	PFS (Median (months))	3.2	5.1	5.0
	95%-CI	(2.2, 3.4)	(4.7, 6.2)	(4.8, 6.0)
	PD-L1 CPS ≥ 20	133	126	122 (vs. Mono) 110 (vs. Combo)
	OS number of events (%)	94 (70.7%)	84 (66.7%)	108 (88.5%) 98 (89.1%)
	OS (Median (months))	14.8	14.7	10.7 11.0
	95%-CI	(11.5, 20.6)	(10.3, 19.3)	(8.8, 12.8) (9.2, 13.0)
	PFS (Median (months))	3.4	5.8	5.3
	95%-CI	(3.2, 3.8)	(4.7, 7.6)	(4.8, 6.3)
Effect estimate per comparison	*OS all subjects*	Comparison groups	**Pembrolizumab vs. SOC**	**Pembrolizumab + Chemo vs. SOC**
		HR	0.83	0.72
		95%-CI	(0.70, 0.99)	(0.60, 0.87)
		P-value (superiority)	0.01985* (one-sided, H10)	0.00025 (H14)
	OS PD-L1 CPS ≥ 1	HR	0.74	0.65
		95%-CI	(0.61, 0.90)	(0.53, 0.80)
		P-value	0.00133 (H8)	0.00002 (H2)
	OS PD-L1 CPS ≥ 20	HR	0.58	0.60
		95%-CI	(0.44, 0.78)	(0.45, 0.82)
		P-value	0.00010 (H7)	0.00044 (H11)
	PFS all subjects	HR	1.29	0.93
		95%-CI	(1.09, 1.53)	(0.78, 1.11)
		P-value	0.99830	0.21211
	PFS PD-L1 CPS ≥ 1	HR	1.13	0.84
		95%-CI	(0.94, 1.36)	(0.69, 1.02)
		P-value	0.89580	0.03697
	PFS PD-L1 CPS ≥ 20	HR	0.99	0.76
		95%-CI	(0.76, 1.29)	(0.58, 1.01)
		P-value	0.46791	0.02951
Notes	* Hypothesis rejected			
Analysis description	**Secondary Analyses**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	**Pembrolizumab**	**Pembrolizumab + Chemo**	**SOC (vs. Mono) (vs. Combo)**
	Number of subject	301	281	300 (vs. Mono) 278 (vs. Combo)
	ORR	16.9	35.6	36.3
	95%-CI	(12.9, 21.7)	(30.0, 41.5)	(30.7, 41.7)
	PD-L1 CPS ≥ 1	257	242	255 (vs. Mono) 235 (vs. Combo)
	ORR	19.1	36.4	34.9 35.7
	95%-CI	(14.5, 24.4)	(30.3, 42.8)	(29.1, 41.1) (29.6, 42.2)
	PD-L1 CPS ≥ 20	133	126	122 (vs. Mono) 110 (vs. Combo)
	ORR	23.3	42.9	36.1 38.2
	95%-CI	(16.4, 31.4)	(34.1, 52.0)	(27.6, 45.3) (29.1, 47.9)
Effect estimate per comparison	ORR	Comparison groups	**Pembrolizumab vs. SOC**	**Pembrolizumab + Chemo vs. SOC**
		Difference	-19.0	-0.8
		95%-CI	(-25.8, -12.1)	(-8.7, 7.2)

		P-value	1.0000	0.5740
	ORR, PD-L1 CPS ≥ 1	Difference	-15.9	0.5
		95%-CI	(-23.4, -8.3)	(-8.2, 9.1)
		P-value	1.0000	0.4586
	ORR, PD-L1 CPS ≥ 20	Difference	-12.8	5.0
		95%-CI	(23.8, -1.5)	(-7.5, 17.4)
		P-value	0.9869	0.2161
Notes	The study was designed to compare pembro combo to standard treatment, and to compare pembro mono to standard treatment. No comparison was conducted between pembro mono and pembro combo groups. 22 subjects enrolled in the control arm during an enrollment pause in the pembro combo arm were excluded for the comparison between the pembro combo vs control, according to ITT principle.			

Clinical studies in special populations

Age

Table 58: efficacy results according to age (ITT population) KN-048 – Final analysis (data cut-off 25-FEB-2019)

Age	<65 y	65-74 y	75-84 y
Pembro combo vs control			
Nb patients (inv,cont)	180, 181	86, 71	14, 26
OS (HR) (months)	0.84 mOS 11.7 vs 10.7	0.53 mOS 14.6 vs 9.3	0.52 mOS 14.3 vs 10.7
PFS (HR)	1.00	0.65	1.03
ORR	34.4% vs 39.2%	40.7% vs 32.4%	21.4% vs 26.9%
Pembro mono vs control			
Nb patients (inv,cont)	190, 195	95, 77	15, 28
OS (HR) (months)	0.81 mOS 11.8 vs 10.7	0.76 mOS 11.3 vs 10.1	1.30 mOS 10.8 vs 12.1
PFS (HR)	1.19	1.34	2.45
ORR	16.8% vs 38.5%	17.9% vs 32.5%	13.3% vs 28.6%

Inv = investigational arm. Cont = control arm. (table made by assessor)

Gender

Table 59: Key Efficacy Results Males Versus Females OS Findings for Pembrolizumab - Pembrolizumab Monotherapy Versus Standard Treatment - ITT, CPS ≥1, and CPS ≥20 Population Findings - KEYNOTE-048 IA2 Analysis

	ITT (All Participants)		PD-L1 CPS ≥1		PD-L1 CPS ≥20	
	Pembrolizumab Plus Chemotherapy N=281	Std Treatment N=278	Pembrolizumab Plus Chemotherapy N=242	Std Treatment N=235	Pembrolizumab Plus Chemotherapy N=126	Std Treatment N=110
OS Results in Females Pembrolizumab Monotherapy versus Standard Treatment Primary Analysis Versus MVA Analyses						
HR (95% CI) Primary analysis	0.93 (0.58, 1.49)		0.89 (0.54, 1.46)		0.80 (0.38, 1.70)	
HR (95% CI) Multivariable analysis	0.71 (0.41, 1.22)		0.66 (0.37, 1.17)		0.35 (0.13, 0.94)	
OS Results in Males Pembrolizumab Monotherapy versus Standard Treatment Primary Analysis Versus MVA Analyses						
HR (95% CI) Primary analysis	0.81 (0.67, 1.00)		0.74 (0.59, 0.92)		0.63 (0.46, 0.88)	
HR (95% CI) Multivariable analysis	0.82 (0.67, 1.01)		0.73 (0.58, 0.92)		0.55 (0.39, 0.79)	

Abbreviations: CI=Confidence interval; CPS=Combined positive score; HR=Hazard ratio; IA2=Interim analysis 2; ITT=Intention to treat; MVA=Multivariate analyses; OS=Overall survival; PD-L1=Programmed cell death ligand 1; Std=Standard. Database cutoff date: 13-JUN-2018

Recurrent disease

Table 60: Key Efficacy Results OS Findings for Pembrolizumab Plus Chemotherapy versus Standard Treatment in Recurrent Disease in ITT, CPS ≥1, and CPS ≥20 Populations - KEYNOTE-048 Final Analysis

Population	N (Combo/ SOC)	Number of Events		Median in months (95% CI)		HR (95% CI)	P-value	OS rate at 12 months (95% CI)		OS rate at 24 months (95% CI)	
		Pembro Plus Chemo	Std Treatment	Pembro Plus Chemo	Std Treatment			Pembro Plus Chemo	Std Treatment	Pembro Plus Chemo	Std Treatment
ITT	76/88	64 (84.2)	78 (88.6)	13.0 (8.5, 14.4)	11.1 (9.2, 13.4)	0.90 (0.65, 1.25)	0.26311	51.3 (39.6, 61.8)	48.9 (38.1, 58.8)	21.1 (12.7, 30.8)	17.0 (10.1, 25.6)
CPS≥1	65/78	54 (83.1)	71 (91.0)	13.4 (8.5, 15.3)	11.0 (8.8, 13.0)	0.80 (0.56, 1.14)	0.10913	53.8 (41.0, 65.0)	47.4 (36.1, 58.0)	21.5 (12.5, 32.1	15.4 (8.4, 24.2)
CPS ≥20	38/40	28 (73.7)	36 (90.0)	14.5 (7.9, 21.0)	11.1 (8.8, 13.6)	0.66 (0.40, 1.09)	0.05168	60.5 (43.3, 74.0)	47.5 (31.6, 61.8)	28.9 (15.7, 43.6)	15.0 (6.1, 27.6)

Abbreviations: CI=Confidence interval; COMBO=combination therapy; CPS=Combined positive score; HR=Hazard ratio; ITT=Intention to treat; N=number of participants; OS=Overall survival; SOC=standard of care. Database cutoff date: 25-FEB-2019

Table 61: Key Efficacy Results OS Findings for Pembrolizumab Monotherapy versus Standard Treatment for Recurrent Disease in ITT, CPS≥1, CPS≥20 Populations - KEYNOTE-048 Final Analysis

Population	N (Mono/ SOC)	Number of Events		Median in months (95% CI)		HR (95% CI)	P-value	OS rate at 12 months (95% CI)		OS rate at 24 months (95% CI)	
		Pembro Mono	Std Treatment	Pembro Mono	Std Treatment			Pembro Mono	Std Treatment	Pembro Mono	Std Treatment
ITT	82/94	70 (85.4)	81 (86.2)	11.5 (7.8, 13.3)	12.1 (9.8, 14.1)	1.09 (0.79, 1.50)	0.69191	46.3 (35.3, 56.7)	52.1 (41.6, 61.6)	18.3 (10.8, 27.3)	20.2 (12.8, 28.8)
CPS≥1	75/84	64 (85.3)	74 (88.1)	11.5 (7.8, 13.0)	12.1 (9.2, 13.9)	1.03 (0.74, 1.44)	0.57175	45.3 (33.9, 56.1)	51.2 (40.1, 61.2)	18.7 (10.8, 28.2)	19.0 (11.5, 28.1)
CPS ≥20	42/42	33 (78.6)	37 (88.1)	12.6 (8.8, 16.0)	11.7 (8.8, 14.1)	0.78 (0.49, 1.25)	0.14718	52.4 (36.4, 66.1)	50.0 (34.2, 63.9)	26.2 (14.1, 40.0)	16.7 (7.3, 29.3)

Abbreviations: CI=Confidence interval; MONO= monotherapy; CPS=Combined positive score; HR=Hazard ratio; ITT=Intention to treat; N=number of participants; OS=Overall survival; SOC=standard of care. Database cutoff date: 25-FEB-2019

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

KEYNOTE-048 is an ongoing, Phase 3, randomized, multicenter, active-controlled, 3 arms, open-label clinical study in first line patients with R/M HNSCC considered incurable by local therapies.

The eligibility criteria of the study are considered acceptable, and the enrolled population appears overall representative of real life, although data are restricted to patients with good performance status (ECOG 0-1).

Patients were randomized 1:1:1 to three arms: pembro combo (pembrolizumab + cisplatin/carboplatin + 5FU), pembro mono (pembrolizumab) or standard treatment (cetuximab + cisplatin/carboplatin + 5FU, known as EXTREME regimen). The EXTREME regimen is considered an appropriate comparator in accordance with current treatment guidelines, and overall, the control arm performed as expected based on the EXTREME pivotal study (Vermorken, 2008).

The use of cisplatin or carboplatin based on investigator's decision (taken before randomization) is considered clinically appropriate. The use of platinum compounds appeared balanced in the ASaT population (approximately 40% received cisplatin and 60% carboplatin in both chemo-containing arms). While the use of platinum compound was quite balanced in the two arms of CPS≥1 population, in CPS<1 ~10% more subjects started with cisplatin in the control group, on the contrary more patients (~8%) received cisplatin at first dose in the pembro combo arm of CPS≥20 population. During the study, 33.6% (40 of 119 participants) and 30.3% (36 of 119 participants) switched from cisplatin to carboplatin in the pembrolizumab plus chemotherapy and standard treatment groups, respectively, with no overall imbalances in exposure to each platinum compound in those subjects.

The study was designed to compare pembro combo to standard treatment, and to compare pembro mono to standard treatment. No comparison was conducted between the pembrolizumab monotherapy and pembrolizumab plus chemotherapy groups.

Participants were stratified according to PD-L1 (TPS≥50% vs not ≥50%), HPV (positive vs negative) and ECOG (0 vs 1). Stratification factors appear appropriate.

OS and PFS (by BICR per RECIST 1.1) were the primary efficacy endpoints in KEYNOTE-048. They were tested for superiority of pembrolizumab monotherapy and pembrolizumab plus chemotherapy over standard treatment, respectively, in 3 populations: 1) PD-L1 CPS ≥20, 2) PD-L1 CPS≥1, and 3) ITT. The choice of OS and PFS as primary endpoints are considered of relevance for the evaluation of clinical efficacy.

KEYNOTE-048 is an event and time driven trial. The sample size was chosen to achieve the required number of PFS and OS events at the time of the 1st planned analysis, followed by time driven analysis at a 2nd interim and final timepoints.

Most common reason for non-eligibility was ECOG ≥2 (20.8%). A total of 882 patients were recruited and randomized in 228 centers worldwide from 1-APR-2015 to 17-JAN-2017.

Overall, the important protocol deviations occurred in a similar rate in each of the 3 treatment arms, thus not raising concern on relevant impact on study results.

Several changes to the sample size and to the follow-up have been made with respect to the original protocol. Likely due to these changes regarding the extension of the sample size and of the follow-up time, more PFS/OS events than planned have been observed in all populations (except for the CPS ≥20 population), inflating the power and affecting minimal detectable HRs that slightly shift toward the null hypothesis. Expected timing of the analyses was updated to reflect changes in follow-up time, and efficacy boundaries used to control the type I error were adjusted according to the alpha level spent at the actual time of IA2 (following the predefined spending function) and to the number of PFS/OS events actually observed at the cut-off date.

As occurred in study KEYNOTE-040, leading to the approval of pembrolizumab in the 2LR/M HNSCC (see Keytruda EPAR var II/42), the PD-L1 scoring method was changed from TPS (tumor proportion score, i.e. PD-L1 expression on tumor cells only), used as stratification factor, to CPS (combined positive score, considering PD-L1 expression on tumour and immune cells infiltrating the tumour stroma), applied for the analysis of efficacy. In both KEYNOTE-040 and KEYNOTE-048, the choice of the new scoring system was based on external data from the single arm study KEYNOTE-012, showing that CPS with cut-off 1 was able to discriminate patients with worse and better outcome compared to TPS. The biomarker cut point for efficacy analyses was also changed from strongly positive (TPS≥50%) to CPS≥20, CPS≥10, and CPS ≥1, although subsequently the cut-point of 10 was removed with protocol amendment n.7 (dated 17/03/2017). The final analyses were therefore conducted according to the new CPS score with cut-offs ≥20 and ≥1.

The evaluation of the proportional hazards assumption indicates that there is evidence of departure from the PH assumption, commonly seen with immunotherapy.

Overall, approximately half of the subjects in the control arm received a subsequent anticancer therapy after being treated within the trial (18% at least 2 further lines). Subsequent checkpoint inhibitors were used by participants in the KEYNOTE-048 study (no crossover was pre-specified). In the ITT population, a much larger number of participants crossed over to checkpoint inhibitors in the standard treatment group (about 25%) compared with the number of participants who crossed over to checkpoint inhibitors in the pembrolizumab plus chemotherapy group (5.3%) or in the pembrolizumab monotherapy group (4.3%). Sensitivity analyses performed to analyse the phenomenon of switching showed OS results in the

ITT as well as in subgroups according to PD-L1 score for both comparisons similar to the respective primary analyses (with the exception of the method that censors patients crossing over, suggesting a different timing of switching occurring in the two treatment arms).

Efficacy data and additional analyses

The results originally submitted by the MAH were based on the pre-planned IA2 (i.e. final for PFS and interim for OS) with a data cut-off date 13-JUN-2018. During the procedure, the MAH provided the results relative to the Final Analysis with a data cut-off date 25-FEB-2019.

The two comparisons are reported separately below.

1) PEMBRO COMBO vs CONTROL

Baseline characteristics in the ITT population appeared overall well balanced. Median age was 61, with about 35% of patients over 65 in both arms. About 40% of subjects had ECOG 0 and 60% ECOG 1. A higher proportion of female (20.3% vs 12.9%) and current smoker (19.9% vs 12.9%) was however observed in the pembro combo compared to the control arm. Approximately 33% of patients were enrolled in EU region. Overall, 70% of patients had metastatic disease and 30% recurrent. Baseline tumor size appeared slightly higher in the pembro combo compared to control (median 67.3 vs 58.7 mm, tumor≥ITT median 52% vs 44.6%). A shorter time from the latest platinum therapy/prior systemic therapy in the pembro combo compared to control is also observed. Overall, approximately half of the subjects in both arms had received a prior systemic therapy for primary/locally advanced/with curative intent. When analysing PD-L1 expression, 23% of patients overall had TPS≥50% (stratification factor). The distribution according to CPS appeared also quite well balanced for CPS≥1 (~85% in both arms), while there was 5% more patients of CPS≥20 tumors in the pembro combo compared to the control arm (44.8% vs 39.6%). For comparison, a similar rate of TPS≥50% (25%) and CPS≥1 (80%) tumors was seen in the 2L study KEYNOTE-040.

The distribution of patients with CPS scores (≥1 and ≥20) were overall balanced between the treatment arms. However, when considering the CPS≥1 and CPS≥20 populations, some imbalances (>5% difference) in baseline characteristics among the two treatment arms are noted (e.g. in both populations: more female, more metastatic disease, higher disease tumour burden and shorter time from latest platinum/prior systemic therapy in pembro combo vs control; in CPS≥1 population: more current smoker in pembro combo vs control; in CPS≥20 population: older and more ECOG 1 subjects in pembro combo vs control). Overall, additional analyses to explore the potential impact of factors with relevant imbalance between treatment arms in the two populations CPS≥1 and CPS≥20 show that the imbalances observed have not had a relevant impact on the treatment HR estimates.

Overall, at the IA2, an OS event occurred in about 76% of the overall population. In the comparison pembro combo vs control, OS reached statistical significance in the ITT population only (HR 0.77, 95%CI 0.63, 0.93, p=0.00335), although this result was of borderline statistical significance (p-value boundary 0.0041). Gain in median OS was 2.3 months in the ITT population. The OS result in the higher PD-L1 expression population of CPS≥20 resulted to be not statistically significant, although the HR estimate (HR 0.69, 95%CI 0.51, 0.94) as well as the appearance of the KM curve seems to suggest a clinical benefit in this population. As per the multiplicity analysis strategy, because the OS hypothesis for CPS≥20 was not statistically significant, the CPS≥1 hypothesis could not be tested (OS HR was 0.71 (95%CI 0.57, 0.88) p=0.00072 in CPS≥1). At visual inspection, in all three populations analysed (ITT, CPS≥1 and CPS≥20) the survival KM curves of the two arms appear to overlap up to month 8, then divide and remain separated in favour of pembro combo, with a difference in OS rate at 15 months of ≥10%. Extensive censoring in the OS curves is seen from month 16 onward.

Compared to the IA2, OS at the final analysis resulted to be statistically significant superior for pembro combo compared to control in the CPS≥1 and CPS≥20, while at the IA2 statistical significance superiority was demonstrated in the ITT only. OS HRs point estimates tend to improve from the IA2 to the FA in the ITT as well as in all subpopulation according to PD-L1 expression (with the exception of worsening result in CPS<1, see below).

The RMST sensitivity analyses showed that the benefit of pembrolizumab over standard treatment seems to increase over time in term of OS, according which, based on the confidence intervals, there is an indication of a difference in terms of RMST based on 24 months of follow up in the ITT and CPS≥1 populations in pembrolizumab plus chemotherapy vs standard treatment comparison.

No PFS advantage with the experimental treatment is observed (not statistically significant in the ITT and in the CPS≥20, while not tested in the CPS≥1 per multiplicity strategy). PFS curves are mostly overlapping, although a separation in the PFS curve is seen after month 6, particularly in the CPS≥20 subgroup.

There was no observed ORR advantage for pembro combo over the EXTREME regimen. ORR (according to BICR per RECIST 1.1, with confirmation) was around 35% in each treatment arm, although in pembro combo a higher rate of complete responses is seen (3% in chemotherapy vs 6% in pembro combo, rising to 9% in CPS≥20). On the contrary, there was about 5% more PD as best response in the pembro combo arm. While ORR and median time to response were similar, median DOR was longer (6.7 vs 4.3 months) in the pembro combo arm, with a higher rate of responses that last ≥6 months (53% vs 37%). The advantage in duration of response does not appear however remarkable, and lower than what observed when pembrolizumab is used a single agent (see below). This lower duration of response in pembro in association with chemotherapy compared to pembro monotherapy has also been observed in indirect comparison in the NSCLC setting (see Keytruda II/60), likely due to some responses with pembro combo being (solely) attributable to the chemotherapy component.

The MAH was requested to provide exploratory statistics in the populations according to PD-L1 expression CPS<1, CPS 1-19 and CPS<20. Based on the data provided, the main concern pertains to the negative PD-L1 subgroup (i.e. CPS<1), representing 15% of the ITT population (39 vs 43 pts in pembro combo vs control, respectively). In this subgroup, no advantage in OS is seen (HR=1.07) with KM curves totally overlapping; PFS appears clearly negative (HR=1.49). Response rate is lower with pembro combo compared to standard treatment (ORR 30.8% vs 39.5%) and no advantage in duration of response is evident either (median DOR 5.7 vs 4.3 months, responses ≥6 months duration 47% vs 49%). At the final analysis the longer follow-up indicated a trend for worse OS results in the CPS<1 population [HR=1.21 (95% CI 0.76, 1.94)], which is of concern. As pointed out by the MAH, some patients with CPS<1 disease could benefit from the use of immunotherapy in combination with chemo upfront, such as ECOG 0 or HPV positive patients. However, on the other hand, the standard treatment could be a better option in subjects with ECOG 1 or HPV negative. Numbers are however too limited to draw conclusion in this regard. It is acknowledged that the CPS<1 is a small and exploratory subgroup for which the study was not powered for, and that OS was statistically significant superior in the CPS≥1 subgroup and in the ITT population. However, it is considered that the lack of biological plausibility in using pembrolizumab in CPS<1 disease, together with the overall similar/slightly inferior results in CPS<1 population for pembrolizumab combination over EXTREME, do not satisfactorily support the substitution of cetuximab with pembrolizumab in combination with platinum/5-FU chemotherapy, which represents a potentially less active combination, with no clear advantage in terms of tolerability for patients with PD-L1 CPS<1. Thus, the indication of pembrolizumab combination is restricted to patients whose disease expresses PD-L1 with CPS score ≥1.

Baseline global health status/QoL scores were similar between the pembrolizumab and standard treatment groups in the PRO FAS population. Over 15 weeks of follow-up, participants showed overall

stable global health status/QoL in both arms. The K-M curves of time to deterioration for global health status and pain indicate a detrimental effect of the pembrolizumab combination compared to the standard treatment. K-M curves for swallowing are instead overlapping. The open-label design hampers the interpretation of data. No proposal for inclusion of PRO data in the SmPC has been made, which is agreed.

Relevant differences in efficacy according to age (<65, 65-74, 75-84 years) are not seen in the ITT or in the CPS≥1 and CPS≥20 populations. However, results in the older age subgroup (75-84 years) should be interpreted with caution because of the small sample size (14 and 26 in the pembro combo and control arm, respectively). The limited amount of data available in over 75 subjects has been reflected in the SmPC.

Subgroup analyses according to disease status suggest an apparent very limited benefit of pembro combo over standard treatment in recurrent disease in the ITT population as well as in the CPS≥1 subjects (but not in the CPS≥20 population).

In the HPV positive subgroup a pembro combo benefit is observed in OS, PFS and ORR. For the HPV negative subgroup the median OS was only slightly higher, PFS results were similar and ORR was slightly less compared to the control arm.

2) PEMBRO MONO vs CONTROL

For the comparison pembro mono vs control, the ITT population included 301 and 300 patients randomized to pembrolizumab and to chemotherapy arm, respectively. 89.3% vs 96.5% had discontinued trial medications in the two arms at the cut-off date, main reason being radiological disease progression (62% vs 64.8%). Clinical progressions were however more common in the pembrolizumab arm: so, when considering discontinuation due to radiological and clinical progression and death, this is slightly higher in the pembro arm (216/301=72%, 204/300=68%). Discontinuations due to adverse events were more commonly observed in the chemotherapy arm (11% vs 15.3%) as expected. Overall, patient disposition appears similar in the CPS≥1 and CPS ≥20 populations.

Baseline characteristics in the ITT population appeared overall well balanced. In the pembro monotherapy arm, a shorter median time from the latest platinum therapy/prior systemic therapy compared to the control arm is observed, similarly to pembro combo. Overall, approximately half of the subjects in both arms had received a prior systemic therapy for primary/locally advanced/with curative intent. When analysing PD-L1 expression, 22% of patients overall had TPS≥50% (stratification factor). The distribution according to CPS appeared also quite well balanced for CPS≥1 (~85% in both arms). CPS≥20 subjects were 44.2% and 40.7% in the pembro mono and the control arm, respectively.

However, when considering the CPS≥1 and CPS≥20 populations, some imbalances (>5% difference) in baseline characteristics among the two treatment arms are noted, particularly in the higher PD-L1 expression subgroup (in CPS≥1 population: less EU subjects, shorter time from latest platinum therapy/prior systemic therapy in pembro mono vs control; in CPS≥20 population more female, higher median age, more HPV negative, shorter time from prior systemic therapy in the pembro mono vs control). Overall, additional analyses to explore the potential impact of factors with relevant imbalance between treatment arms in the two populations CPS≥1 and CPS≥20 show that the imbalances observed have not had a relevant impact on the treatment HR estimates.

Overall, at the IA2 approximately 75% of the total population has experienced an OS event. In the ITT population, OS in the pembrolizumab monotherapy arm resulted non-inferior, but not statistically significantly superior, compared to the control arm (OS HR=0.85, 95% CI 0.71, 1.03, median OS 11.6 vs 10.7 months). Statistically significant OS superiority was instead demonstrated in both positive PD-L1 subgroups (CPS≥1: HR 0.78 [0.64, 0.96], p = 0.00855, gain in median OS of 2 months; CPS≥20: HR 0.61 [0.45, 0.83], p=0.00074, gain in median OS of 4.2 months). While the H7 hypothesis (i.e. OS in CPS≥20) is most compelling from a statistical perspective, the H8 hypothesis (CPS≥1 superiority in mono vs. SOC

comparison) resulted to be statistically significant due to the α-shift from H14 hypothesis (OS combo) to H7 hypothesis (OS mono). At the final analysis, OS superiority for mono vs SOC in the ITT population was again not demonstrated.

As repeatedly observed with anti-PD1/PDL1 agents, a worse early performance of pembro mono compared to the standard treatment is seen, with KM curves crossing around month 8. While this crossing is evident in the ITT and in the CPS≥1 populations, this appears less definite in the CPS≥20 group. After the crossing of the KM curves, the pembrolizumab monotherapy curve lies above the control arm one, with long-term advantage for some patients more pronounced the higher PD-L1 expression is (difference in OS rate at 12 months: 5% in the ITT, 7% in CPS≥1, 12% in CPS≥20). Instantaneous hazard rates between 0 and 6 months generally favour the chemotherapy arm in the CPS≥1 and CPS≥20 populations. This issue is of particular concern for CPS≥1 patients. Indeed patients who died over the first 6 months were 73 in pembro mono arm and 54 in EXTREME arm; of those, 52 vs 27 died due to PD (i.e. 20% vs 10% of the overall population in each arm). In the 1≤CPS<20 population, subjects dying due to PD during the first 6 month of treatment have more than doubled in pembro mono vs standard treatment (29 vs 13). The data provided confirmed an early detrimental effect with pembro mono vs chemotherapy. Considering the results obtained from specific analyses performed to explore the issue of the early detrimental effect of immunotherapy compared with chemotherapy, it is believed that at the moment no specific recommendation can be included in the SmPC, since consistency of results obtained from different studies is needed to make the results strong and convincing.

The OS RMST sensitivity analyses underline that the benefit of pembrolizumab over standard treatment increases over time and based on the confidence intervals, for the pembro mono comparison, there is an indication of a difference in terms of RMST based on 24 months of follow up in the CPS≥20 population only.

PFS did not show statistically significant improvement (HR 1.34, 95%IC 1.13, 1.59). It is observed that the KM curves of PFS2 in the ITT population are crossing as well, with a very late separation after month 10.

Although slightly improving with higher PD-L1 expression, the ORR to pembrolizumab monotherapy remains steadily below the response rate achieved with chemotherapy (ORR in the ITT population: 17% vs 36%). Rate of stable disease is lower for pembro mono than for standard treatment as well. Few more complete responses are however observed with pembrolizumab monotherapy compared to chemo. On the contrary, as known with immunotherapy, the median DOR was substantially longer (21 vs 4.5 months), and patients who achieve tumour response with pembro mono have high chance to respond for a long time (response duration ≥6 months 75% vs 39% in the ITT population). Median time to response was similar in both arms (2.1 months).

Exploratory analyses of the complementary PD-L1 populations CPS<1, 1≤CPS<20 and CPS<20 have been provided, showing no benefit from the use of pembrolizumab over standard treatment in all the subgroups, and clearly negative results for pembrolizumab monotherapy in the CPS<1 population.

Therefore, the demonstration of a non-inferiority (and lack of superiority) in the ITT population is not considered supporting the clinical benefit of pembro mono in this 1L HNSCC setting (moreover based on NI margin which has not been justified), in light also of a (not so early) crossing of OS curve (at month 8). This is further corroborated by negative PFS and ORR data. An indication in the overall population was therefore not agreed by the CHMP. The MAH subsequently decided to restrict the sought indication for pembrolizumab monotherapy to CPS≥1 population only.

For the 1≤CPS<20 population, representing about 40% of the overall population, the OS HR for pembro mono is 0.86 (95% CI 0.66, 1.12), OS KM curves cross at about 8 months, then overlap and clearly separate only at around month 15 in favour of pembrolizumab; the separation of the curves is rather

small; however a small proportion of patients appear to derive a long-term benefit compared to SOC also in this subgroup. The early inferior OS of pembrolizumab is also reflected by a 10% lower OS rate at month 6 (68% vs. 78%). In the 1≤CPS<20 population, an indication for pembrolizumab monotherapy could be acceptable as a treatment alternative, if taking the considerable better safety profile compared to the SOC into account.

Quality of life evaluation showed similar baseline global health status/QoL scores between the pembrolizumab and standard treatment groups in the PRO FAS population, with overall stable global health status/QoL over 15 weeks of follow-up. The K-M curves of time to deterioration for global health status and pain indicate a detrimental effect of the pembrolizumab combination compared to the standard treatment. An opposite tendency is seen for swallowing.

The apparent trend towards decreasing effect of pembrolizumab monotherapy compared to standard treatment is observed with increasing age in the ITT and in the CPS≥1 populations (not evident in the CPS≥20 subgroup, where however 75-84 years patients are only 12 overall). Data in patients over 75 are limited, based on a small sample size.

According to subgroup analysis, there is no clear benefit of pembro mono over standard treatment in the recurrent setting in CPS≥1 population.

The OS result appears less convincing in female patients compared to male in subgroup analyses, however definitive conclusions are hampered by the small sample size of female subjects, which is by the way expected based on the epidemiology of the disease. Among subjects who died within the first 6 months from randomization a higher rate of female is seen in pembro mono compared to control in CPS≥1 and ≥20 populations.

A small benefit in median OS in favour of pembro mono is observed in HPV negative patients. KM curves cross around month 9 indicating an early favourable effect for standard treatment. For HPV positive patients the KM curves are similar between the treatment arms. No PFS advantage is observed compared to standard treatment regardless of HPV status. Higher response rates were observed in the standard arm compared to Pembro Mono. The ORR difference between the treatment arms is smaller in the HPV positive subgroup.

KEYNOTE-048 study was not statistically powered to compare the two pembrolizumab-containing arms. This is acknowledged. However, the MAH was requested to provide a descriptive comparison between pembrolizumab monotherapy and pembrolizumab plus chemotherapy. OS in pembro mono and pembro combo arms appear overall quite similar. However, while KM OS curve of the pembro mono lies slightly below the one of pembro combo in the ITT population, curves appear closer in CPS≥1 up to completely overlapping in the CPS≥20 subgroup. Across all 3 populations (ITT, CPS≥1, CPS≥20), PFS and ORR were clearly in favour of the pembro combo. Conversely, mDOR and the number of durable (i.e. ≥6 months) responses were higher in the pembrolizumab monotherapy group. Median time to response was similar.

When taking the data for the pembro combo into account in the 1≤CPS<20 population, a higher risk of early death is observed with pembro mono vs SOC but not with pembro combo vs SOC, reflected by similar 6 months OS rates for both treatment arms; the OS HR improves to 0.71 and the curves separate earlier and slightly more pronounced in the later parts compared to observations for monotherapy. Thus lastly, the considerably improved safety profile of the monotherapy has to be weighed against the better efficacy outcome for the pembro combination therapy. Regarding long-term efficacy, the difference is not so prominent anymore (OS rates at 18 months 34.5% vs. 31.8% and OS rates at 24 months 25.9% vs. 22% for pembro combo vs. pembro mono, respectively). From a regulatory point of view, it is acceptable to allow individual treatment decisions based on patients preferences if a clear presentation of efficacy data in the SmPC in a comparative way is included in section 5.1 of the SmPC for the subgroups 1<CPS<20 and CPS≥20.

In patients with CPS≥20, the relevance for the addition of chemotherapy to pembrolizumab monotherapy appears questionable in view of the added toxicity of the chemotherapy. However, individual patients might benefit from combination therapy especially when a response with tumour shrinkage is needed, due to the higher ORR of pembro combo. Information regarding the B/R evaluation being dependent on CPS status has been included in section 4.4, as well as efficacy data for the CPS ≥20 subgroup in section 5.1 of the SmPC.

2.4.4. Conclusions on the clinical efficacy

Pembrolizumab combination demonstrated statistically significant superiority compared to EXTREME regimen in all the 3 pre-specified populations (ITT, CPS≥1 and CPS≥20). As opposed to the ITT and the other biomarker subpopulations, the longer follow-up indicated a trend for worse OS results in the CPS<1 population, together with inferior results for PFS and ORR, and the lack of DOR benefit. Acknowledging that the CPS<1 is a small and exploratory subgroup for which the study was not powered, the lack of biological plausibility in using pembrolizumab in CPS<1 disease, together with the overall similar/slightly inferior results in CPS<1 population for pembrolizumab combination over EXTREME, do not satisfactorily support the substitution of cetuximab with pembrolizumab in combination with platinum/5-FU chemotherapy. Thus, the indication of pembrolizumab combination is restricted to patients whose disease expresses PD-L1 with CPS≥1 score.

For pembrolizumab monotherapy, an indication restricted to the CPS≥1 population is considered acceptable.

2.5. Clinical safety

Introduction

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 safety profile to support the claimed indications for use of pembrolizumab in combination with chemotherapy based on platinum (cisplatin or carboplatin) and 5-FU, and as monotherapy for 1L treatment of patients with R/M HNSCC is based on the second interim analysis (IA2) in all subjects as treated (ASaT) of the KEYNOTE-048 study.

The IA2 was a time-driven analysis with data cut-off date 13-JUN-2018 (database lock date 29-JUN-2018), when all the participants had the opportunity to be followed for at least 17 months. Out of the 882 randomized subjects, 863 participants were included in all safety comparisons (the ASaT population).

Supportive data is provided by the pooled safety databases of HNSCC Safety DS for pembrolizumab and Pembrolizumab monotherapy RSD.

The pooled HNSCC Safety DS for pembrolizumab is used to reflect existing safety information of pembrolizumab monotherapy for HNSCC in the 2L+ treatment setting (N=609).

The pooled safety data from the Pembrolizumab monotherapy RSD enable comparison of safety of Pembrolizumab + Chemotherapy and of Pembrolizumab monotherapy for HNSCC with the established safety profile of pembrolizumab monotherapy across all the other indications (N=3830).

The table below summarizes the 5 datasets upon which safety results are based:

Table 62: Safety datasets

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-048 pembrolizumab plus chemotherapy	(N=276): Safety data from participants with R/M HNSCC who received pembrolizumab in combination with chemotherapy in KEYNOTE-048	KN048 Data for MK-3475 + Chemotherapy	Pembrolizumab plus chemotherapy*
KEYNOTE-048 pembrolizumab	(N=300): Safety data from participants with R/M HNSCC who received pembrolizumab as monotherapy in KEYNOTE-048	KN048 Data for MK-3475	Pembrolizumab monotherapy*
KEYNOTE-048 standard treatment	(N=287): Safety data from participants with R/M HNSCC who received cetuximab in combination with chemotherapy in KEYNOTE-048	KN048 Data for SOC	Standard treatment*
HNSCC pembrolizumab safety	(N=609): Pooled safety data from participants with R/M HNSCC who received pembrolizumab as monotherapy in KEYNOTE-040, KEYNOTE-012, and KEYNOTE-055	HNSCC Safety Dataset for MK-3475	HNSCC pembrolizumab monotherapy
Pembrolizumab monotherapy reference safety	(N=3830): Pooled safety data from participants who received at least 1 dose of pembrolizumab in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3 (NSCLC, melanoma), KEYNOTE-002 (original phase, melanoma), KEYNOTE-006 (melanoma), KEYNOTE-010 (NSCLC), KEYNOTE-013 Cohort 3 (Hodgkin's lymphoma), KEYNOTE-024 (NSCLC), KEYNOTE-045 and KEYNOTE-052 (urothelial cancer), and KEYNOTE-087 (classical Hodgkin's lymphoma).	Reference Safety Dataset for MK-3475	Pembrolizumab monotherapy RSD

Abbreviations: HNSCC=head and neck squamous cell carcinoma; N=number; NSCLC=nonsmall cell lung cancer; R/M=recurrent/metastatic; RSD=reference safety dataset.

* For the 3 KEYNOTE-048 study datasets, the term "dataset" and "group" may be used interchangeably throughout the document.

Note: The MAH and the Rapporteurs had agreed in advance not to include a "Pembrolizumab Monotherapy Cumulative running Dataset" in the submission of this type II variation.

Patient exposure

Table 63: Summary of drug exposure (ASaT population)

	KN048 Data for MK-3475 (N=300)	KN048 Data for MK-3475 + Chemotherapy (N=276)	KN048 Data for SOC (N=287)	HNSCC Safety Dataset for MK3475[‡‡] (N=609)	Reference Safety Dataset for MK-3475[‡‡‡] (N=3830)
Study Days On-Therapy (Months)					
Mean	6.4	7.4	6.1	4.9	6.7
Median	3.50	5.78	4.86	2.83	4.71
SD	7.04	6.64	5.84	5.42	6.05
Range	0.03 to 47.90	0.10 to 28.72	0.03 to 35.25	0.03 to 25.56	0.03 to 30.39
Number of Administrations					
Mean	9.7	10.7	8.7	8.1	11.1
Median	6.00	8.00	7.00	5.00	8.00
SD	9.39	9.11	8.10	8.50	9.56
Range	1.00 to 40.00	1.00 to 35.00	1.00 to 48.00	1.00 to 52.00	1.00 to 59.00

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 KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)

MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adexsum]

Table 64: Clinical trial exposure to drug by duration (ASaT population)

	KN048 Data for MK-3475 (N=300)			KN048 Data for MK-3475 + Chemotherapy (N=276)			KN048 Data for SOC (N=287)			HNSCC Safety Dataset for MK3475[‡‡] (N=609)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	300	(100.0)	(158.9)	276	(100.0)	(171.2)	287	(100.0)	(145.0)	609	(100.0)	(249.4)
>=1 m	256	(85.3)	(157.2)	239	(86.6)	(170.2)	260	(90.6)	(144.2)	478	(78.5)	(245.4)
>=3 m	165	(55.0)	(141.7)	198	(71.7)	(163.0)	207	(72.1)	(135.3)	294	(48.3)	(215.6)
>=6m	105	(35.0)	(120.5)	129	(46.7)	(136.5)	106	(36.9)	(97.7)	176	(28.9)	(173.1)
>=12m	52	(17.3)	(86.0)	52	(18.8)	(83.2)	23	(8.0)	(43.1)	66	(10.8)	(97.8)

Adverse events

AEs were coded using MedDRA (Version 21.0). All safety analyses were conducted using data from the ASaT population (i.e. all randomized participants who received at least 1 dose of study treatment) for each study or cohort as of the data cut-off dates.

The analysis of safety results followed a tiered approach. No Tier 1 safety parameters were pre-specified in the protocol.

Table 65: Safety analyses

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
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 Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
Tier 3	Specific AEs, SOCs			X
	Change from Baseline Results (Labs)			X

KEYNOTE-048 updated safety data – final analysis (cut-off date 25 Feb 2019)

A summary of AE at the updated cut-off date of the Final Analysis (25 Feb 2019) for KEYNOTE-048 study submitted during the procedure is presented below for the two comparisons.

Table 66: Adverse event summary, Pembro combo vs Control (ASaT population)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	276		287		563	
with one or more adverse events	271	(98.2)	286	(99.7)	557	(98.9)
with no adverse event	5	(1.8)	1	(0.3)	6	(1.1)
with drug-related[1] adverse events	264	(95.7)	278	(96.9)	542	(96.3)
with toxicity grade 3-5 adverse events	235	(85.1)	239	(83.3)	474	(84.2)
with toxicity grade 3-5 drug-related adverse events	198	(71.7)	199	(69.3)	397	(70.5)
with serious adverse events	165	(59.8)	141	(49.1)	306	(54.4)
with serious drug-related adverse events	103	(37.3)	72	(25.1)	175	(31.1)
with any dose modification[†] due to an adverse event	233	(84.4)	240	(83.6)	473	(84.0)
Pembrolizumab/Cetuximab dose modification	159	(57.6)	190	(66.2)	349	(62.0)
Any Chemotherapy dose modification	220	(79.7)	206	(71.8)	426	(75.7)
All components dose modification	123	(44.6)	105	(36.6)	228	(40.5)
who died	32	(11.6)	28	(9.8)	60	(10.7)
who died due to a drug-related adverse event	11	(4.0)	8	(2.8)	19	(3.4)
discontinued any drug due to an adverse event	90	(32.6)	79	(27.5)	169	(30.0)
discontinued Pembrolizumab/Cetuximab	47	(17.0)	51	(17.8)	98	(17.4)
discontinued Any Chemotherapy	74	(26.8)	60	(20.9)	134	(23.8)
discontinued All components	23	(8.3)	26	(9.1)	49	(8.7)
discontinued any drug due to a drug-related adverse event	69	(25.0)	59	(20.6)	128	(22.7)
discontinued Pembrolizumab/Cetuximab	25	(9.1)	30	(10.5)	55	(9.8)
discontinued Any Chemotherapy	61	(22.1)	44	(15.3)	105	(18.7)
discontinued All components	12	(4.3)	11	(3.8)	23	(4.1)
discontinued any drug due to a serious adverse event	58	(21.0)	48	(16.7)	106	(18.8)
discontinued Pembrolizumab/Cetuximab	39	(14.1)	36	(12.5)	75	(13.3)
discontinued Any Chemotherapy	43	(15.6)	38	(13.2)	81	(14.4)
discontinued All components	20	(7.2)	21	(7.3)	41	(7.3)
discontinued any drug due to a serious drug-related adverse event	35	(12.7)	28	(9.8)	63	(11.2)
discontinued Pembrolizumab/Cetuximab	18	(6.5)	16	(5.6)	34	(6.0)
discontinued Any Chemotherapy	29	(10.5)	22	(7.7)	51	(9.1)
discontinued All components	9	(3.3)	7	(2.4)	16	(2.8)

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

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

ALL : all study drug(s) on respective treatment arm

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

Grades are based on NCI CTCAE version 4.03.

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.

Discontinuation/dose modification in study drugs listed in the nested sub-rows are not mutually exclusive. A subject can be counted in different rows as applicable. But a subject can be counted in each row and column only once.

CHEMO THERAPY: Cisplatin/Carboplatin +5-FU. A subject will be counted in the chemotherapy group if one or more of the components are discontinued/dose modified due to an adverse event.

Database Cutoff Date: 25FEB2019.

Table 67: Adverse event summary, Pembro mono vs Control (ASaT population)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	300		287		587	
with one or more adverse events	290	(96.7)	286	(99.7)	576	(98.1)
with no adverse event	10	(3.3)	1	(0.3)	11	(1.9)
with drug-related[1] adverse events	175	(58.3)	278	(96.9)	453	(77.2)
with toxicity grade 3-5 adverse events	164	(54.7)	239	(83.3)	403	(68.7)
with toxicity grade 3-5 drug-related adverse events	51	(17.0)	199	(69.3)	250	(42.6)
with serious adverse events	123	(41.0)	141	(49.1)	264	(45.0)
with serious drug-related adverse events	28	(9.3)	72	(25.1)	100	(17.0)
with dose modification[†] due to an adverse event	116	(38.7)	240	(83.6)	356	(60.6)
who died	25	(8.3)	28	(9.8)	53	(9.0)
who died due to a drug-related adverse event	3	(1.0)	8	(2.8)	11	(1.9)
discontinued drug due to an adverse event	36	(12.0)	79	(27.5)	115	(19.6)
discontinued drug due to a drug-related adverse event	15	(5.0)	59	(20.6)	74	(12.6)
discontinued drug due to a serious adverse event	29	(9.7)	48	(16.7)	77	(13.1)
discontinued drug due to a serious drug-related adverse event	9	(3.0)	28	(9.8)	37	(6.3)

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

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

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

Grades are based on NCI CTCAE version 4.03.

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: 25FEB2019.

Overall and exposure-adjusted Adverse Events

Table 68: Exposure-adjusted adverse event summary (including multiple occurrence of events (ASaT population)) - cut-off date 13-JUN-2018

	Event Count and Rate (Events/100 person-years)[†]				
	KN048 Data for MK-3475	KN048 Data for MK-3475 + Chemotherapy	KN048 Data for SOC	HNSCC Safety Dataset for MK3475[‡‡]	Reference Safety Dataset for MK-3475[‡‡‡]
Number of subjects exposed	300	276	287	609	3830
Total exposure[‡] in person-years	180.61	190.63	167.83	295.92	2385.46
Total events (rate)					
adverse events	2619 (1450.11)	5002 (2623.92)	6111 (3641.08)	5801 (1960.31)	41960 (1758.99)
drug-related[§] adverse events	667 (369.31)	2795 (1466.18)	3691 (2199.19)	1290 (435.92)	13236 (554.86)
toxicity grade 3-5 adverse events	365 (202.10)	884 (463.72)	859 (511.81)	861 (290.95)	3912 (163.99)
toxicity grade 3-5 drug-related adverse events	73 (40.42)	568 (297.96)	566 (337.24)	126 (42.58)	853 (35.76)
serious adverse events	224 (124.03)	342 (179.40)	266 (158.49)	536 (181.13)	2624 (110.00)
serious drug-related adverse events	37 (20.49)	165 (86.55)	117 (69.71)	76 (25.68)	548 (22.97)
adverse events resulting in dose modification[‖]	214 (118.49)	697 (365.63)	716 (426.61)	356 (120.30)	2099 (87.99)
adverse events leading to death	25 (13.84)	32 (16.79)	28 (16.68)	56 (18.92)	162 (6.79)
drug-related adverse events leading to death	3 (1.66)	10 (5.25)	8 (4.77)	5 (1.69)	17 (0.71)
adverse events resulting in drug discontinuation	37 (20.49)	105 (55.08)	111 (66.14)	91 (30.75)	490 (20.54)
drug-related adverse events resulting in drug discontinuation	15 (8.31)	80 (41.97)	85 (50.65)	41 (13.85)	239 (10.02)
serious adverse events resulting in drug discontinuation	29 (16.06)	61 (32.00)	55 (32.77)	69 (23.32)	361 (15.13)
serious drug-related adverse events resulting in drug discontinuation	9 (4.98)	37 (19.41)	34 (20.26)	24 (8.11)	157 (6.58)

[†] Event rate per 100 person-years of exposure=event count *100/person-years of exposure.
[‡] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[§] Determined by the investigator to be related to the drug.
[‖] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

All Adverse Events (AEs)

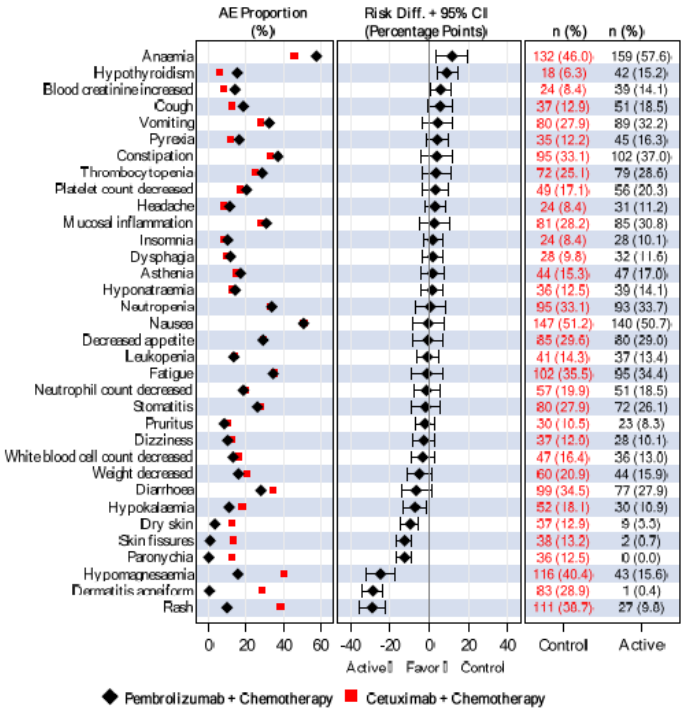
Table 69: Subjects with adverse events (incidence ≥10% in one or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population) - cut-off date 13-JUN-2018

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	290	(96.7)	271	(98.2)	286	(99.7)	592	(97.2)	3,720	(97.1)
with no adverse events	10	(3.3)	5	(1.8)	1	(0.3)	17	(2.8)	110	(2.9)
Anaemia	63	(21.0)	159	(57.6)	132	(46.0)	142	(23.3)	508	(13.3)
Nausea	50	(16.7)	140	(50.7)	147	(51.2)	102	(16.7)	884	(23.1)
Constipation	59	(19.7)	102	(37.0)	95	(33.1)	118	(19.4)	695	(18.1)
Fatigue	83	(27.7)	95	(34.4)	102	(35.5)	198	(32.5)	1,320	(34.5)
Neutropenia	6	(2.0)	93	(33.7)	95	(33.1)	3	(0.5)	32	(0.8)
Vomiting	33	(11.0)	89	(32.2)	80	(27.9)	63	(10.3)	533	(13.9)
Mucosal inflammation	13	(4.3)	85	(30.8)	81	(28.2)	25	(4.1)	52	(1.4)
Decreased appetite	44	(14.7)	80	(29.0)	85	(29.6)	105	(17.2)	822	(21.5)
Thrombocytopenia	6	(2.0)	79	(28.6)	72	(25.1)	2	(0.3)	72	(1.9)
Diarrhoea	46	(15.3)	77	(27.9)	99	(34.5)	87	(14.3)	838	(21.9)
Stomatitis	9	(3.0)	72	(26.1)	80	(27.9)	20	(3.3)	90	(2.3)
Platelet count decreased	3	(1.0)	56	(20.3)	49	(17.1)	11	(1.8)	48	(1.3)
Cough	40	(13.3)	51	(18.5)	37	(12.9)	105	(17.2)	804	(21.0)
Neutrophil count decreased	1	(0.3)	51	(18.5)	57	(19.9)	5	(0.8)	24	(0.6)
Asthenia	17	(5.7)	47	(17.0)	44	(15.3)	47	(7.7)	470	(12.3)
Pyrexia	38	(12.7)	45	(16.3)	35	(12.2)	70	(11.5)	531	(13.9)
Weight decreased	44	(14.7)	44	(15.9)	60	(20.9)	84	(13.8)	308	(8.0)
Hypomagnesaemia	12	(4.0)	43	(15.6)	116	(40.4)	35	(5.7)	98	(2.6)
Hypothyroidism	54	(18.0)	42	(15.2)	18	(6.3)	92	(15.1)	346	(9.0)
Blood creatinine increased	12	(4.0)	39	(14.1)	24	(8.4)	16	(2.6)	192	(5.0)
Hyponatraemia	25	(8.3)	39	(14.1)	36	(12.5)	66	(10.8)	219	(5.7)
Leukopenia	4	(1.3)	37	(13.4)	41	(14.3)	3	(0.5)	28	(0.7)
White blood cell count decreased	4	(1.3)	36	(13.0)	47	(16.4)	10	(1.6)	35	(0.9)
Dysphagia	24	(8.0)	32	(11.6)	28	(9.8)	67	(11.0)	69	(1.8)
Headache	36	(12.0)	31	(11.2)	24	(8.4)	59	(9.7)	468	(12.2)
Hypokalaemia	23	(7.7)	30	(10.9)	52	(18.1)	55	(9.0)	166	(4.3)
Dizziness	14	(4.7)	28	(10.1)	37	(12.9)	41	(6.7)	320	(8.4)
Insomnia	21	(7.0)	28	(10.1)	24	(8.4)	51	(8.4)	295	(7.7)
Rash	30	(10.0)	27	(9.8)	111	(38.7)	69	(11.3)	642	(16.8)
Pruritus	33	(11.0)	23	(8.3)	30	(10.5)	53	(8.7)	764	(19.9)
Dyspnoea	39	(13.0)	21	(7.6)	20	(7.0)	98	(16.1)	688	(18.0)
Oedema peripheral	12	(4.0)	17	(6.2)	17	(5.9)	33	(5.4)	401	(10.5)
Arthralgia	16	(5.3)	15	(5.4)	7	(2.4)	60	(9.9)	628	(16.4)
Back pain	21	(7.0)	12	(4.3)	11	(3.8)	52	(8.5)	477	(12.5)
Abdominal pain	3	(1.0)	10	(3.6)	20	(7.0)	29	(4.8)	382	(10.0)
Dry skin	13	(4.3)	9	(3.3)	37	(12.9)	21	(3.4)	225	(5.9)
Skin fissures	0	(0.0)	2	(0.7)	38	(13.2)	2	(0.3)	5	(0.1)
Dermatitis acneiform	8	(2.7)	1	(0.4)	83	(28.9)	6	(1.0)	42	(1.1)
Paronychia	1	(0.3)	0	(0.0)	36	(12.5)	3	(0.5)	5	(0.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

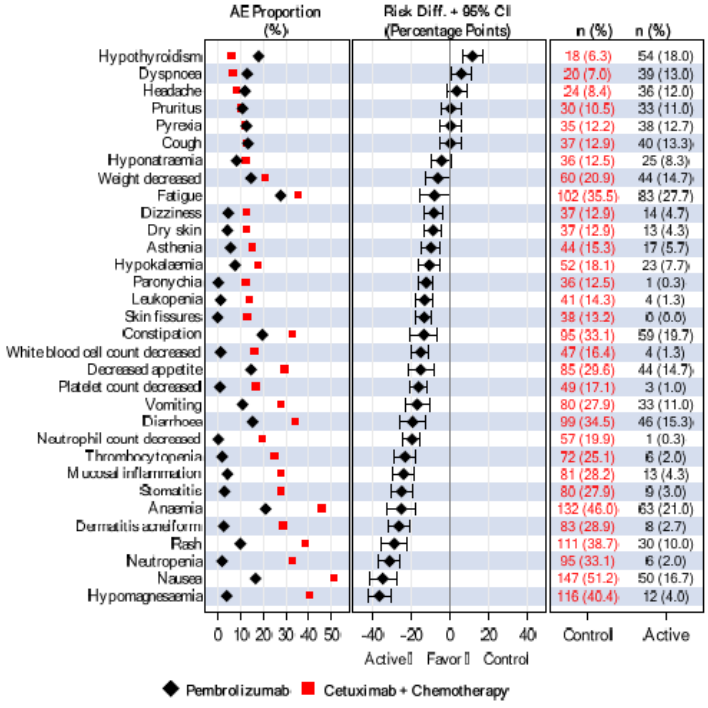
Source: [ISS: adam-adsl; adae]

Between-treatment comparisons in AEs for selected AE (≥10% incidence rate) proportions are shown below:



Database Cutoff Date: 13JUN2018.
Source: [P048V01MK3475: analysis-adsl; adae]

Figure 36: Between-treatment comparison in adverse events – selected AEs (≥10% incidence) and sorted by risk difference (ASaT) population) – Pembro + Chemotherapy (N=276) vs. Cetuximab + Chemotherapy (N=287)



Database Cutoff Date: 13JUN2018.
Source: [P048V01MK3475: analysis-adsl; adae]

Figure 37: Between-treatment comparison in adverse events – selected AEs (≥10% incidence) and sorted by risk difference (ASaT) population) – Pembro mono (N=300) vs. Cetuximab + Chemotherapy (N=287)

Table 70: Subjects with Adverse Events by Maximum Toxicity Grade (Excerpt)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	290	(96.7)	271	(98.2)	286	(99.7)	592	(97.2)	3,720	(97.1)
Grade 1	30	(10.0)	4	(1.4)	1	(0.3)	59	(9.7)	546	(14.3)
Grade 2	98	(32.7)	33	(12.0)	45	(15.7)	185	(30.4)	1,372	(35.8)
Grade 3	111	(37.0)	136	(49.3)	146	(50.9)	240	(39.4)	1,439	(37.6)
Grade 4	26	(8.7)	66	(23.9)	67	(23.3)	55	(9.0)	206	(5.4)
Grade 5	25	(8.3)	32	(11.6)	27	(9.4)	53	(8.7)	157	(4.1)
with no adverse events	10	(3.3)	5	(1.8)	1	(0.3)	17	(2.8)	110	(2.9)

Grade 3 to 5 AEs

Table 71: Subjects with Grade 3-5 adverse events (incidence ≥1% in one or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population) - cut-off date 13-JUN-2018

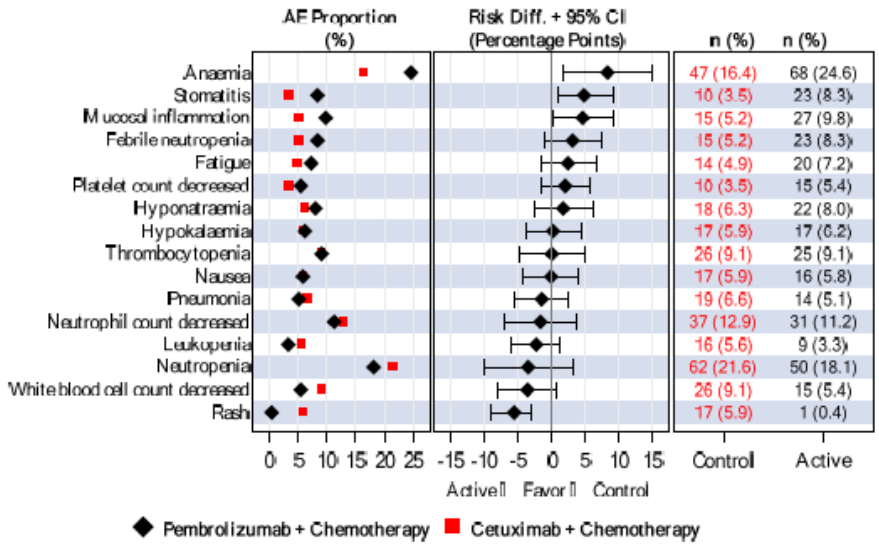
	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	162	(54.0)	234	(84.8)	240	(83.6)	348	(57.1)	1,802	(47.0)
with no adverse events	138	(46.0)	42	(15.2)	47	(16.4)	261	(42.9)	2,028	(53.0)
Anaemia	14	(4.7)	68	(24.6)	47	(16.4)	44	(7.2)	159	(4.2)
Neutropenia	1	(0.3)	50	(18.1)	62	(21.6)	2	(0.3)	11	(0.3)
Neutrophil count decreased	0	(0.0)	31	(11.2)	37	(12.9)	1	(0.2)	5	(0.1)
Mucosal inflammation	4	(1.3)	27	(9.8)	15	(5.2)	2	(0.3)	2	(0.1)
Thrombocytopenia	1	(0.3)	25	(9.1)	26	(9.1)	0	(0.0)	15	(0.4)
Febrile neutropenia	0	(0.0)	23	(8.3)	15	(5.2)	0	(0.0)	4	(0.1)
Stomatitis	0	(0.0)	23	(8.3)	10	(3.5)	2	(0.3)	5	(0.1)
Hyponatraemia	17	(5.7)	22	(8.0)	18	(6.3)	26	(4.3)	91	(2.4)
Fatigue	9	(3.0)	20	(7.2)	14	(4.9)	15	(2.5)	103	(2.7)
Hypokalaemia	6	(2.0)	17	(6.2)	17	(5.9)	16	(2.6)	33	(0.9)
Nausea	0	(0.0)	16	(5.8)	17	(5.9)	5	(0.8)	40	(1.0)
Platelet count decreased	0	(0.0)	15	(5.4)	10	(3.5)	0	(0.0)	6	(0.2)
White blood cell count decreased	0	(0.0)	15	(5.4)	26	(9.1)	0	(0.0)	3	(0.1)
Pneumonia	16	(5.3)	14	(5.1)	19	(6.6)	43	(7.1)	102	(2.7)
Decreased appetite	3	(1.0)	13	(4.7)	10	(3.5)	12	(2.0)	45	(1.2)
Lymphocyte count decreased	2	(0.7)	11	(4.0)	9	(3.1)	11	(1.8)	16	(0.4)
Asthenia	3	(1.0)	10	(3.6)	9	(3.1)	1	(0.2)	45	(1.2)
Hypercalcaemia	6	(2.0)	10	(3.6)	2	(0.7)	21	(3.4)	19	(0.5)
Vomiting	1	(0.3)	10	(3.6)	8	(2.8)	5	(0.8)	33	(0.9)
Leukopenia	0	(0.0)	9	(3.3)	16	(5.6)	0	(0.0)	7	(0.2)
Pneumonia aspiration	5	(1.7)	9	(3.3)	3	(1.0)	21	(3.4)	4	(0.1)
Dysphagia	7	(2.3)	8	(2.9)	6	(2.1)	16	(2.6)	7	(0.2)
Lung infection	3	(1.0)	8	(2.9)	1	(0.3)	3	(0.5)	15	(0.4)
Weight decreased	6	(2.0)	8	(2.9)	4	(1.4)	5	(0.8)	12	(0.3)
Dehydration	2	(0.7)	7	(2.5)	8	(2.8)	15	(2.5)	42	(1.1)
Diarrhoea	2	(0.7)	7	(2.5)	8	(2.8)	10	(1.6)	55	(1.4)
Hyperglycaemia	4	(1.3)	7	(2.5)	3	(1.0)	7	(1.1)	45	(1.2)
Hypertension	4	(1.3)	7	(2.5)	4	(1.4)	5	(0.8)	50	(1.3)
Dyspnoea	6	(2.0)	6	(2.2)	3	(1.0)	15	(2.5)	95	(2.5)
Hypomagnesaemia	0	(0.0)	6	(2.2)	14	(4.9)	0	(0.0)	0	(0.0)
Hypotension	5	(1.7)	6	(2.2)	6	(2.1)	9	(1.5)	15	(0.4)
Pulmonary embolism	4	(1.3)	6	(2.2)	8	(2.8)	8	(1.3)	58	(1.5)
Septic shock	1	(0.3)	6	(2.2)	2	(0.7)	1	(0.2)	8	(0.2)
Syncope	2	(0.7)	6	(2.2)	10	(3.5)	9	(1.5)	19	(0.5)
Acute kidney injury	4	(1.3)	5	(1.8)	2	(0.7)	1	(0.2)	41	(1.1)

Sepsis	6	(2.0)	5	(1.8)	3	(1.0)	10	(1.6)	21	(0.5)
Tumour haemorrhage	9	(3.0)	5	(1.8)	5	(1.7)	11	(1.8)	2	(0.1)
Alanine aminotransferase increased	1	(0.3)	4	(1.4)	4	(1.4)	3	(0.5)	38	(1.0)
Hypocalcaemia	0	(0.0)	4	(1.4)	4	(1.4)	3	(0.5)	4	(0.1)
Aspartate aminotransferase increased	2	(0.7)	3	(1.1)	5	(1.7)	11	(1.8)	41	(1.1)
Bronchitis	2	(0.7)	3	(1.1)	1	(0.3)	2	(0.3)	12	(0.3)
Cellulitis	2	(0.7)	3	(1.1)	2	(0.7)	8	(1.3)	17	(0.4)
Hypophosphataemia	0	(0.0)	3	(1.1)	9	(3.1)	15	(2.5)	19	(0.5)
Laryngeal oedema	1	(0.3)	3	(1.1)	0	(0.0)	2	(0.3)	1	(0.0)
Lymphopenia	1	(0.3)	3	(1.1)	5	(1.7)	3	(0.5)	9	(0.2)
Myocardial infarction	3	(1.0)	3	(1.1)	3	(1.0)	4	(0.7)	7	(0.2)
Neck pain	2	(0.7)	3	(1.1)	2	(0.7)	2	(0.3)	3	(0.1)
Oral pain	0	(0.0)	3	(1.1)	3	(1.0)	0	(0.0)	2	(0.1)
Peripheral sensory neuropathy	0	(0.0)	3	(1.1)	2	(0.7)	0	(0.0)	0	(0.0)
Pleural effusion	0	(0.0)	3	(1.1)	0	(0.0)	6	(1.0)	48	(1.3)
Respiratory tract infection	1	(0.3)	3	(1.1)	2	(0.7)	1	(0.2)	12	(0.3)
Urinary tract infection	0	(0.0)	3	(1.1)	3	(1.0)	2	(0.3)	67	(1.7)
Abdominal pain	1	(0.3)	2	(0.7)	5	(1.7)	6	(1.0)	35	(0.9)
Cancer pain	3	(1.0)	2	(0.7)	1	(0.3)	3	(0.5)	20	(0.5)
Death	2	(0.7)	2	(0.7)	2	(0.7)	11	(1.8)	19	(0.5)
Gamma-glutamyltransferase increased	4	(1.3)	2	(0.7)	1	(0.3)	1	(0.2)	23	(0.6)
Pancytopenia	0	(0.0)	2	(0.7)	3	(1.0)	0	(0.0)	1	(0.0)
Pneumonitis	4	(1.3)	2	(0.7)	2	(0.7)	7	(1.1)	49	(1.3)
Respiratory failure	1	(0.3)	2	(0.7)	1	(0.3)	9	(1.5)	18	(0.5)
Blood alkaline phosphatase increased	2	(0.7)	1	(0.4)	0	(0.0)	8	(1.3)	30	(0.8)
Colitis	0	(0.0)	1	(0.4)	2	(0.7)	1	(0.2)	47	(1.2)
Device related infection	4	(1.3)	1	(0.4)	4	(1.4)	2	(0.3)	5	(0.1)
Hyperkalaemia	1	(0.3)	1	(0.4)	3	(1.0)	2	(0.3)	17	(0.4)
Hypoxia	2	(0.7)	1	(0.4)	1	(0.3)	6	(1.0)	17	(0.4)
Infected neoplasm	3	(1.0)	1	(0.4)	1	(0.3)	3	(0.5)	2	(0.1)
Infusion related reaction	0	(0.0)	1	(0.4)	3	(1.0)	0	(0.0)	0	(0.0)
Mouth haemorrhage	0	(0.0)	1	(0.4)	0	(0.0)	7	(1.1)	0	(0.0)
Rash	2	(0.7)	1	(0.4)	17	(5.9)	2	(0.3)	16	(0.4)
Aphthous ulcer	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)
Back pain	3	(1.0)	0	(0.0)	1	(0.3)	6	(1.0)	53	(1.4)
Constipation	1	(0.3)	0	(0.0)	4	(1.4)	2	(0.3)	20	(0.5)
Dermatitis acneiform	0	(0.0)	0	(0.0)	6	(2.1)	0	(0.0)	0	(0.0)
Face oedema	1	(0.3)	0	(0.0)	0	(0.0)	6	(1.0)	0	(0.0)
General physical health deterioration	0	(0.0)	0	(0.0)	3	(1.0)	2	(0.3)	29	(0.8)
Malnutrition	4	(1.3)	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.1)
Osteomyelitis	0	(0.0)	0	(0.0)	4	(1.4)	1	(0.2)	3	(0.1)
Soft tissue infection	3	(1.0)	0	(0.0)	1	(0.3)	1	(0.2)	2	(0.1)
Tumour pain	1	(0.3)	0	(0.0)	4	(1.4)	8	(1.3)	21	(0.5)
Upper gastrointestinal haemorrhage	1	(0.3)	0	(0.0)	3	(1.0)	0	(0.0)	3	(0.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: ISS: adam-adsl: adae1

In the next figures, rainfall plots show between-treatment comparisons of Pembrolizumab+Chemotherapy and Pembrolizumab monotherapy each versus Standard Treatment:

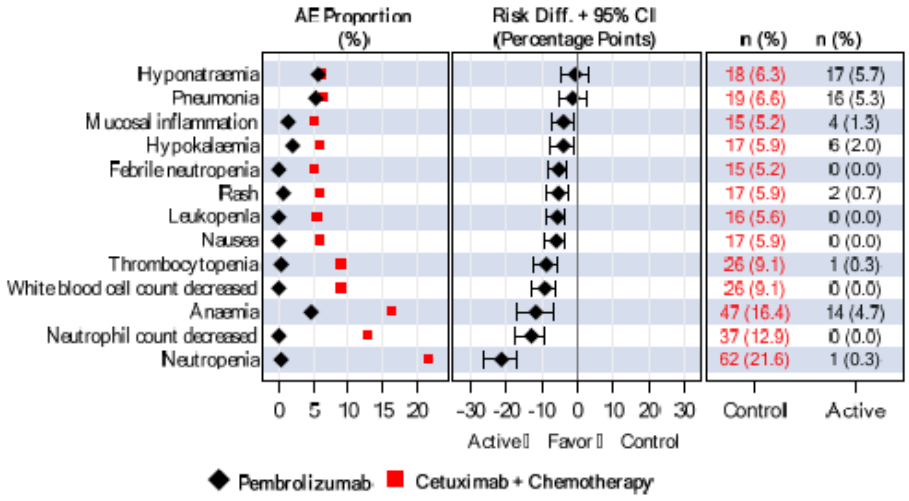


Database Cutoff Date: 13JUN2018.
Source: [P048V01MK3475: analysis-adsl; adae]

Figure 38: Between-treatment comparison in Grade 3-5 AEs – selected AEs (≥5% incidence) and sorted by risk difference (ASaT population) – Pembro combo (N=276) vs. Control (N=287)

Table 72: Exposure-adjusted Grade 3-5 AEs (including multiple occurrence of events) - incidence ≥5% in one or more treatment groups – Pembro combo vs. control (ASaT population) - cut-off date 13-JUN-2018

	Event Count and Rate (Events/100 person-years)[†]	
	Pembrolizumab + Chemotherapy	Cetuximab + Chemotherapy
Number of subjects exposed	276	287
Total exposure[‡] person-years	190.63	167.83
Total events (rate)	453 (237.64)	485 (288.98)



Database Cutoff Date: 13JUN2018.

Figure 39: Between-treatment comparison in Grade 3-5 AEs – selected AEs (≥5% incidence) and sorted by risk difference (ASaT population) – Pembro mono (N=300) vs. Cetuximab + Chemotherapy (N=287)

Table 73: Exposure-adjusted Grade 3-5 AEs (including multiple occurrence of events) - incidence ≥5% in one or more treatment groups – Pembro mono vs. control (ASaT population) - cut-off date 13-JUN-2018

	Event Count and Rate (Events/100 person-years)[†]	
	Pembrolizumab	Cetuximab + Chemotherapy
Number of subjects exposed	300	287
Total exposure[‡] person-years	180.60	167.83
Total events (rate)	62 (34.33)	446 (265.74)

Drug-related Adverse Events

Table 74: Subjects with drug-related adverse events (incidence ≥5% in one or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population) - cut-off date 13-JUN-2018

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	175	(58.3)	263	(95.3)	278	(96.9)	387	(63.5)	2,751	(71.8)
with no adverse events	125	(41.7)	13	(4.7)	9	(3.1)	222	(36.5)	1,079	(28.2)
Anaemia	12	(4.0)	133	(48.2)	118	(41.1)	31	(5.1)	122	(3.2)
Nausea	12	(4.0)	124	(44.9)	131	(45.6)	34	(5.6)	395	(10.3)
Neutropenia	3	(1.0)	91	(33.0)	90	(31.4)	0	(0.0)	20	(0.5)
Fatigue	43	(14.3)	84	(30.4)	83	(28.9)	103	(16.9)	826	(21.6)
Mucosal inflammation	8	(2.7)	77	(27.9)	76	(26.5)	11	(1.8)	28	(0.7)
Thrombocytopenia	4	(1.3)	75	(27.2)	63	(22.0)	1	(0.2)	29	(0.8)
Vomiting	7	(2.3)	75	(27.2)	64	(22.3)	11	(1.8)	146	(3.8)
Stomatitis	2	(0.7)	67	(24.3)	69	(24.0)	10	(1.6)	48	(1.3)
Decreased appetite	16	(5.3)	62	(22.5)	62	(21.6)	39	(6.4)	337	(8.8)
Platelet count decreased	1	(0.3)	51	(18.5)	46	(16.0)	4	(0.7)	23	(0.6)
Diarrhoea	16	(5.3)	49	(17.8)	75	(26.1)	35	(5.7)	445	(11.6)
Neutrophil count decreased	1	(0.3)	46	(16.7)	54	(18.8)	4	(0.7)	17	(0.4)
White blood cell count decreased	2	(0.7)	36	(13.0)	43	(15.0)	4	(0.7)	19	(0.5)
Hypothyroidism	39	(13.0)	35	(12.7)	1	(0.3)	68	(11.2)	309	(8.1)
Leukopenia	2	(0.7)	34	(12.3)	38	(13.2)	1	(0.2)	17	(0.4)
Asthenia	7	(2.3)	33	(12.0)	30	(10.5)	19	(3.1)	260	(6.8)
Blood creatinine increased	2	(0.7)	30	(10.9)	15	(5.2)	1	(0.2)	51	(1.3)
Hypomagnesaemia	3	(1.0)	29	(10.5)	95	(33.1)	3	(0.5)	23	(0.6)
Constipation	9	(3.0)	28	(10.1)	31	(10.8)	6	(1.0)	121	(3.2)
Hyponatraemia	9	(3.0)	23	(8.3)	20	(7.0)	9	(1.5)	32	(0.8)
Rash	25	(8.3)	22	(8.0)	101	(35.2)	46	(7.6)	485	(12.7)
Febrile neutropenia	0	(0.0)	21	(7.6)	12	(4.2)	0	(0.0)	0	(0.0)
Weight decreased	9	(3.0)	21	(7.6)	30	(10.5)	16	(2.6)	84	(2.2)
Malaise	4	(1.3)	18	(6.5)	9	(3.1)	3	(0.5)	33	(0.9)
Dysgeusia	6	(2.0)	16	(5.8)	15	(5.2)	4	(0.7)	62	(1.6)
Pyrexia	10	(3.3)	16	(5.8)	12	(4.2)	19	(3.1)	197	(5.1)
Acute kidney injury	4	(1.3)	15	(5.4)	6	(2.1)	1	(0.2)	11	(0.3)
Hypokalaemia	4	(1.3)	15	(5.4)	36	(12.5)	6	(1.0)	23	(0.6)
Peripheral sensory neuropathy	1	(0.3)	15	(5.4)	6	(2.1)	3	(0.5)	17	(0.4)
Tinnitus	0	(0.0)	15	(5.4)	16	(5.6)	1	(0.2)	2	(0.1)
Pruritus	21	(7.0)	14	(5.1)	24	(8.4)	36	(5.9)	608	(15.9)
Alanine aminotransferase increased	7	(2.3)	10	(3.6)	15	(5.2)	17	(2.8)	132	(3.4)
Arthralgia	6	(2.0)	9	(3.3)	3	(1.0)	24	(3.9)	324	(8.5)
Hypophosphataemia	1	(0.3)	6	(2.2)	19	(6.6)	4	(0.7)	27	(0.7)
Dry skin	6	(2.0)	5	(1.8)	27	(9.4)	13	(2.1)	119	(3.1)
Palmar-plantar erythrodysaesthesia syndrome	1	(0.3)	4	(1.4)	20	(7.0)	0	(0.0)	10	(0.3)
Infusion related reaction	1	(0.3)	2	(0.7)	16	(5.6)	4	(0.7)	41	(1.1)
Skin fissures	0	(0.0)	2	(0.7)	36	(12.5)	1	(0.2)	1	(0.0)
Dermatitis acneiform	6	(2.0)	1	(0.4)	82	(28.6)	4	(0.7)	36	(0.9)
Paronychia	0	(0.0)	0	(0.0)	33	(11.5)	0	(0.0)	0	(0.0)

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

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

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

‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)

MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Table 75: Subjects with drug-related AEs by maximum toxicity Grade (Incidence>0% in one or more treatment groups) - Excerpt

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[‡‡]		Reference Safety Dataset for MK-3475[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	175	(58.3)	263	(95.3)	278	(96.9)	387	(63.5)	2,751	(71.8)
Grade 1	64	(21.3)	13	(4.7)	11	(3.8)	139	(22.8)	1,069	(27.9)
Grade 2	61	(20.3)	54	(19.6)	69	(24.0)	165	(27.1)	1,105	(28.9)
Grade 3	42	(14.0)	133	(48.2)	135	(47.0)	67	(11.0)	500	(13.1)
Grade 4	5	(1.7)	53	(19.2)	55	(19.2)	11	(1.8)	60	(1.6)
Grade 5	3	(1.0)	10	(3.6)	8	(2.8)	5	(0.8)	17	(0.4)
with no adverse events	125	(41.7)	13	(4.7)	9	(3.1)	222	(36.5)	1,079	(28.2)

Grade 3-5 Drug-related AEs

Table 76: Subjects with Grade 3-5 drug-related adverse events (incidence ≥1% in one or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population) - cut-off date 13-JUN-2018

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[‡‡]		Reference Safety Dataset for MK-3475[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	50	(16.7)	196	(71.0)	198	(69.0)	83	(13.6)	577	(15.1)
with no adverse events	250	(83.3)	80	(29.0)	89	(31.0)	526	(86.4)	3,253	(84.9)
Anaemia	2	(0.7)	52	(18.8)	42	(14.6)	5	(0.8)	18	(0.5)
Neutropenia	0	(0.0)	50	(18.1)	59	(20.6)	0	(0.0)	8	(0.2)
Neutrophil count decreased	0	(0.0)	28	(10.1)	35	(12.2)	1	(0.2)	3	(0.1)
Mucosal inflammation	2	(0.7)	26	(9.4)	14	(4.9)	1	(0.2)	2	(0.1)
Thrombocytopenia	1	(0.3)	24	(8.7)	24	(8.4)	0	(0.0)	4	(0.1)
Stomatitis	0	(0.0)	22	(8.0)	10	(3.5)	2	(0.3)	3	(0.1)
Febrile neutropenia	0	(0.0)	21	(7.6)	12	(4.2)	0	(0.0)	0	(0.0)
Fatigue	3	(1.0)	19	(6.9)	11	(3.8)	7	(1.1)	45	(1.2)
Nausea	0	(0.0)	15	(5.4)	16	(5.6)	1	(0.2)	12	(0.3)
White blood cell count decreased	0	(0.0)	15	(5.4)	22	(7.7)	0	(0.0)	1	(0.0)
Platelet count decreased	0	(0.0)	14	(5.1)	9	(3.1)	0	(0.0)	2	(0.1)
Decreased appetite	1	(0.3)	12	(4.3)	8	(2.8)	3	(0.5)	11	(0.3)
Hyponatraemia	6	(2.0)	10	(3.6)	9	(3.1)	3	(0.5)	16	(0.4)
Lymphocyte count decreased	1	(0.3)	9	(3.3)	6	(2.1)	1	(0.2)	5	(0.1)
Asthenia	1	(0.3)	8	(2.9)	6	(2.1)	1	(0.2)	17	(0.4)
Hypokalaemia	1	(0.3)	8	(2.9)	11	(3.8)	1	(0.2)	7	(0.2)
Leukopenia	0	(0.0)	8	(2.9)	16	(5.6)	0	(0.0)	3	(0.1)
Vomiting	0	(0.0)	7	(2.5)	5	(1.7)	0	(0.0)	10	(0.3)
Septic shock	0	(0.0)	6	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(0.3)	5	(1.8)	6	(2.1)	1	(0.2)	9	(0.2)
Acute kidney injury	1	(0.3)	4	(1.4)	1	(0.3)	1	(0.2)	4	(0.1)
Hypomagnesaemia	0	(0.0)	4	(1.4)	11	(3.8)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	4	(1.4)	2	(0.7)	1	(0.2)	0	(0.0)
Diarrhoea	1	(0.3)	3	(1.1)	5	(1.7)	5	(0.8)	40	(1.0)
Hyperglycaemia	2	(0.7)	3	(1.1)	0	(0.0)	1	(0.2)	9	(0.2)
Hypotension	0	(0.0)	3	(1.1)	0	(0.0)	0	(0.0)	1	(0.0)
Lung infection	0	(0.0)	3	(1.1)	0	(0.0)	0	(0.0)	1	(0.0)
Peripheral sensory neuropathy	0	(0.0)	3	(1.1)	2	(0.7)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(0.3)	2	(0.7)	3	(1.0)	8	(1.3)	21	(0.5)
Hypophosphataemia	0	(0.0)	2	(0.7)	5	(1.7)	1	(0.2)	8	(0.2)
Pancytopenia	0	(0.0)	2	(0.7)	3	(1.0)	0	(0.0)	1	(0.0)
Pneumonitis	4	(1.3)	2	(0.7)	1	(0.3)	6	(1.0)	45	(1.2)
Abdominal pain	0	(0.0)	1	(0.4)	4	(1.4)	1	(0.2)	1	(0.0)
Colitis	0	(0.0)	1	(0.4)	2	(0.7)	1	(0.2)	41	(1.1)

Dehydration	1	(0.3)	1	(0.4)	4	(1.4)	1	(0.2)	6	(0.2)
Lymphopenia	1	(0.3)	1	(0.4)	4	(1.4)	1	(0.2)	2	(0.1)
Rash	2	(0.7)	1	(0.4)	17	(5.9)	2	(0.3)	12	(0.3)
Sepsis	0	(0.0)	1	(0.4)	3	(1.0)	0	(0.0)	0	(0.0)
Dermatitis acneiform	0	(0.0)	0	(0.0)	6	(2.1)	0	(0.0)	0	(0.0)
Hyperkalaemia	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	1	(0.0)
Infusion related reaction	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

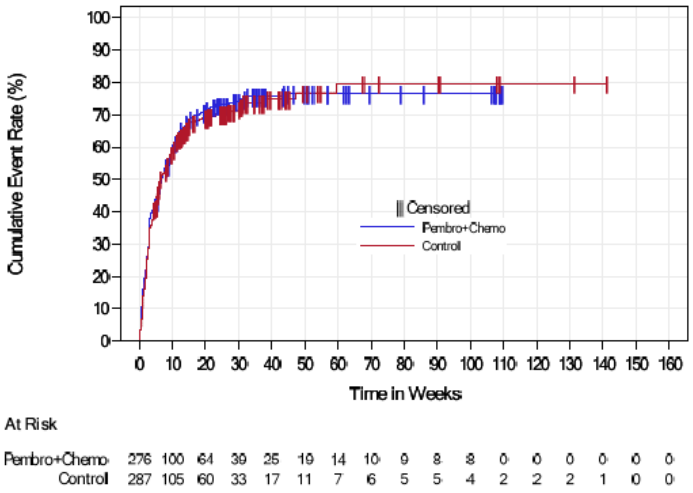


Figure 40: Kaplan-Meier estimates of time to first drug-related Grade 3-5 AE (ASaT population) – Pembro combo vs control

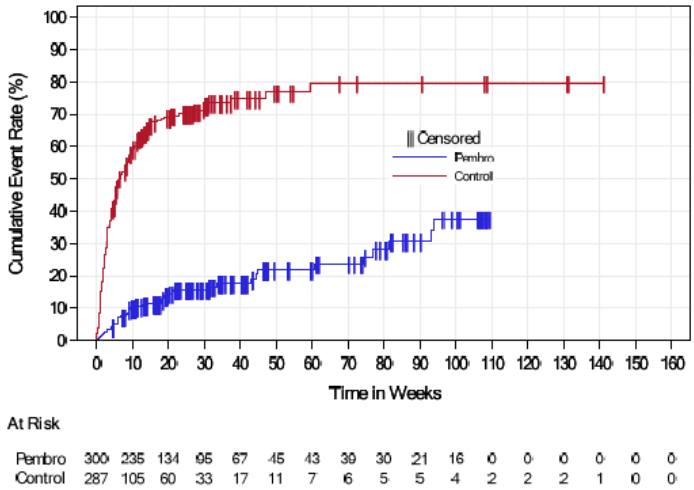


Figure 41: Kaplan-Meier estimates of time to first drug-related Grade 3-5 AE (ASaT population) – Pembro mono vs control

Adverse drug reactions (ADRs)

For pembrolizumab monotherapy, the following studies have been included in the pooled dataset: KEYNOTE-048, KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase), KEYNOTE-006, KEYNOTE-010, KEYNOTE-012 HNSCC, KEYNOTE-013 Cohort 3, KEYNOTE-024, KEYNOTE-040, KEYNOTE-042, KEYNOTE-045, KEYNOTE-052, KEYNOTE-054, KEYNOTE-055, and KEYNOTE-087.

Table 77: Adverse Reactions in Patients Treated with Pembrolizumab Monotherapy

		Monotherapy (N=5884)	
		All % (n)	Gr 3-5 n
Infections and infestations			
Common	pneumonia	5.8% (343)	209
Blood and lymphatic system disorders			
Very common	anaemia	13.9% (819)	234
Common	thrombocytopenia	1.5% (89)	17
Common	lymphopenia	1.1% (65)	16
Uncommon	neutropenia	0.8% (48)	15
Uncommon	leukopenia	0.8% (45)	7
Uncommon	eosinophilia	0.7% (39)	0
Rare	immune thrombocytopenic purpura	0.05% (3)	3
Rare	haemolytic anaemia	0.02% (1)	1

Rare	pure red cell aplasia[#]	(0)	0
Immune system disorders			
Common	infusion reactions[a]	2.3% (134)	13
Uncommon	sarcoidosis	0.2% (10)	0
Not known	solid organ transplant rejection*	(0)	0
Endocrine disorders			
Very common	hypothyroidism[b]	11.0% (645)	8
Common	hyperthyroidism	4.1% (244)	7
Uncommon	hypophysitis[c]	0.6% (36)	20
Uncommon	thyroiditis[d]	0.95% (56)	1
Uncommon	adrenal insufficiency	0.7% (41)	18
Metabolism and nutrition disorders			
Very common	decreased appetite	19.0% (1117)	72
Common	hyponatraemia	5.8% (339)	151
Common	hypokalaemia	4.6% (271)	59
Common	hypocalcaemia	1.9% (112)	10
Uncommon	type 1 diabetes mellitus[e]	0.3% (20)	19
Psychiatric disorders			
Common	insomnia	7.1% (417)	7
Nervous system disorders			
Very common	headache	11.9% (703)	18
Common	dizziness	7.2% (424)	11
Common	neuropathy peripheral	1.9% (112)	2
Common	lethargy	1.2% (71)	2
Common	dysgeusia	2.5% (149)	1
Uncommon	epilepsy	0.2% (11)	7
Rare	guillain-barre syndrome[f]	0.07% (4)	2
Rare	myasthenic syndrome[g]	0.05% (3)	1
Rare	meningitis (aseptic)[h]	0.05% (3)	3
Rare	encephalitis	0.03% (2)	2
Eye disorders			
Common	dry eye	1.6% (94)	0
Uncommon	uveitis[i]	0.3% (20)	2
Rare	Vogt-Koyanagi-Harada syndrome[#]	(0)	0
Cardiac disorders			
Uncommon	pericardial effusion	0.9% (51)	25
Uncommon	pericarditis	0.1% (8)	4
Rare	myocarditis[j]	0.08% (5)	5
Vascular disorders			
Common	hypertension	4.9% (288)	99
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	16.6% (976)	130
Very common	cough	19.0% (1118)	9
Common	pneumonitis[k]	4.3% (253)	91
Gastrointestinal disorders			
Very common	diarrhoea	20.2% (1186)	78
Very common	abdominal pain[l]	12.3% (726)	55
Very common	nausea	20.4% (1198)	49
Very common	vomiting	12.3% (721)	42
Very common	constipation	16.7% (983)	24
Common	colitism	1.8% (107)	65
Common	dry mouth	4.8% (280)	1
Uncommon	pancreatitis[n]	0.3% (16)	9
Rare	small intestinal perforation	0.03% (2)	1
Hepatobiliary disorders			
Uncommon	hepatitis[o]	0.8% (50)	39
Skin and subcutaneous tissue disorders			
Very common	rash[p]	19.5% (1149)	2
Very common	pruritus[q]	18.3% (1075)	1
Common	severe skin reactions[r]	1.5% (89)	66
Common	erythema	2.8% (165)	2
Common	dry skin	5.1% (299)	1
Common	vitiligos	4.2% (245)	0
Common	eczema	1.5% (91)	0
Common	alopecia	1.4% (84)	0
Common	dermatitis acneiform	1.2% (72)	0
Uncommon	lichenoid keratosis[t]	0.4% (25)	9
Uncommon	psoriasis	0.6% (34)	4
Uncommon	dermatitis	0.9% (55)	1
Uncommon	papule	0.5% (27)	1

Uncommon	hair colour changes	0.3% (20)	0
Rare	stevens-johnson syndrome	0.05% (3)	2
Rare	erythema nodosum	0.05% (3)	0
Rare	toxic epidermal necrolysis[#]	(0)	0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[u]	18.7% (1102)	96
Very common	arthralgia	14.3% (839)	38
Common	pain in extremity	6.6% (386)	18
Common	myositis[v]	7.5% (443)	16
Common	arthritis[w]	2.2% (132)	9
Uncommon	tenosynovitis[x]	0.5% (30)	1
Renal and urinary disorders			
Uncommon	nephritis[y]	0.4% (22)	15
General disorders and administration site conditions			
Very common	fatigue	31.8% (1870)	143
Very common	asthenia	11.2% (657)	58
Very common	oedema[z]	11.5% (678)	42
Very common	pyrexia	12.4% (729)	28
Common	influenza like illness	3.7% (219)	1
Common	chills	4.1% (244)	0
Investigations			
Common	aspartate aminotransferase increased	6.5% (380)	64
Common	alanine aminotransferase increased	6.5% (384)	59
Common	hypercalcaemia	3.1% (184)	52
Common	blood alkaline phosphatase increased	4.0% (237)	47
Common	blood bilirubin increased	2.1% (126)	23
Common	blood creatinine increased	4.2% (250)	11
Uncommon	amylase increased	0.3% (17)	8

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

[*] Adverse reaction frequencies presented may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

[#] The "rule of 3" has been applied in calculation.

a. infusion reactions (anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, infusion related reaction)
b. hypothyroidism (hypothyroidism, myxoedema, primary hypothyroidism)
c. hypophysitis (hypophysitis, hypopituitarism)
d. thyroiditis (autoimmune thyroiditis, thyroid disorder, thyroiditis)
e. type 1 diabetes mellitus (diabetic ketoacidosis, type 1 diabetes mellitus)
f. guillain-barre syndrome (axonal neuropathy, demyelinating polyneuropathy, guillain-barre syndrome)
g. myasthenic syndrome (myasthenia gravis, myasthenic syndrome)
h. meningitis (aseptic) (meningitis, meningitis noninfective)
i. uveitis (iridocyclitis, iritis, uveitis)
j. myocarditis (autoimmune myocarditis, myocarditis)
k. pneumonitis (interstitial lung disease, organising pneumonia, pneumonitis)
l. abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper)
m. colitis (autoimmune colitis, colitis, colitis microscopic, enterocolitis)
n. pancreatitis (autoimmune pancreatitis, pancreatitis, pancreatitis acute)
o. hepatitis (autoimmune hepatitis, drug-induced liver injury, hepatitis, hepatitis acute, immune-mediated hepatitis)
p. rash (genital rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular)
q. pruritus (pruritus, pruritus generalised, pruritus genital, urticaria, urticaria papular)
r. severe skin reactions (dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, pemphigus, pruritus, pruritus generalised, pruritus genital, rash, rash erythematous, rash generalised, rash maculo-papular, rash pruritic, rash pustular, skin necrosis, stevens-johnson syndrome, toxic skin eruption)
s. vitiligo (hypopigmentation of eyelid, skin depigmentation, skin hypopigmentation, vitiligo)
t. lichenoid keratosis (lichen planus, lichen sclerosus, lichenoid keratosis)
u. musculoskeletal pain (back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, torticollis)
v. myositis (myalgia, myopathy, myositis, polymyalgia rheumatica, rhabdomyolysis)
w. arthritis (arthritis, joint effusion, joint swelling, polyarthritis)
x. tenosynovitis (synovitis, tendon pain, tendonitis, tenosynovitis)
y. nephritis (acute kidney injury, autoimmune nephritis, glomerulonephritis membranous, nephritis, nephrotic syndrome, renal failure, tubulointerstitial nephritis)
z. oedema (eyelid oedema, face oedema, fluid overload, fluid retention, generalised oedema, lip oedema, localised oedema, oedema, oedema peripheral, periorbital oedema)

For pembrolizumab + chemotherapy, the following studies have been included in the pooled dataset: KEYNOTE-048, KEYNOTE-189, KEYNOTE-021 (Cohorts A, C and G) and KEYNOTE-407.

Table 78: Adverse Reactions in Patients Treated with Pembrolizumab combination therapy

	Combotherapy (N=1067)	
	All % (n)	Gr 3-5 n
Infections and infestations		

Common	pneumonia	9.1% (97)	64
Blood and lymphatic system disorders			
Very common	anaemia	50.2% (536)	192
Very common	neutropenia	29.9% (319)	181
Very common	thrombocytopenia	23.0% (245)	78
Common	febrile neutropenia	6.6% (70)	68
Common	leukopenia	8.2% (88)	32
Common	lymphopenia	1.9% (20)	5
Rare	eosinophilia	0.09% (1)	1
Immune system disorders			
Common	infusion reactions[a]	2.6% (28)	8
Endocrine disorders			
Common	hypothyroidism[b]	9.8% (105)	3
Common	hyperthyroidism	5.1% (54)	1
Uncommon	hypophysitis[c]	0.7% (7)	3
Uncommon	thyroiditis[d]	0.5% (5)	1
Uncommon	adrenal insufficiency	0.2% (2)	1
Metabolism and nutrition disorders			
Very common	hypokalaemia	10.0% (107)	35
Very common	decreased appetite	28.5% (304)	27
Common	hyponatraemia	7.0% (75)	42
Common	hypocalcaemia	4.3% (46)	10
Rare	type 1 diabetes mellitus[e]	0.09% (1)	1
Psychiatric disorders			
Common	insomnia	9.3% (99)	1
Nervous system disorders			
Very common	dizziness	11.2% (120)	4
Very common	headache	11.9% (127)	3
Very common	neuropathy	10.5% (112)	3
Very common	peripheral dysgeusia	10.3% (110)	1
Common	lethargy	1.9% (20)	0
Uncommon	epilepsy	0.2% (2)	1
Eye disorders			
Common	dry eye	3.3% (35)	0
Cardiac disorders			
Uncommon	pericardial effusion	0.3% (3)	2
Rare	myocarditis[j]	0.09% (1)	1
Rare	pericarditis	0.09% (1)	1
Vascular disorders			
Common	hypertension	5.8% (62)	24
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	16.8% (179)	31
Very common	cough	19.7% (210)	2
Common	pneumonitis[k]	5.2% (56)	23
Gastrointestinal disorders			
Very common	diarrhoea	30.5% (325)	41
Very common	nausea	49.8% (531)	35
Very common	vomiting	24.7% (264)	28
Very common	constipation	34.6% (369)	6
Very common	abdominal pain[l]	12.1% (129)	6
Common	colitism	2.8% (30)	13
Common	dry mouth	4.4% (47)	1
Uncommon	pancreatitis[n]	0.4% (4)	3
Hepatobiliary disorders			
Uncommon	hepatitis[o]	0.9% (10)	9
Skin and subcutaneous tissue disorders			
Very common	rash[p]	21.5% (229)	2
Very common	alopecia	18.0% (192)	1
Very common	pruritus[q]	13.3% (142)	1
Common	severe skin reactions[r]	1.6% (17)	15
Common	erythema	3.7% (39)	1
Common	dry skin	4.6% (49)	0
Uncommon	psoriasis	0.6% (6)	3
Uncommon	dermatitis acneiform	0.8% (9)	0
Uncommon	dermatitis	0.7% (8)	0
Uncommon	vitiligos	0.7% (7)	0
Uncommon	eczema	0.5% (5)	0
Rare	hair colour changes	0.09% (1)	0
Rare	lichenoid keratosis[t]	0.09% (1)	0
Rare	papule	0.09% (1)	0

Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[u]	17.8% (190)	9
Very common	arthralgia	12.9% (138)	8
Common	myositis[v]	6.5% (69)	4
Common	pain in extremity	7.7% (82)	2
Common	arthritis[w]	2.2% (24)	0
Uncommon	tenosynovitis[x]	0.4% (4)	1
Renal and urinary disorders			
Common	nephritis[y]	1.0% (11)	8
Common	acute kidney injury	5.6% (60)	23
General disorders and administration site conditions			
Very common	fatigue	37.4% (399)	58
Very common	asthenia	18.1% (193)	42
Very common	pyrexia	16.1% (172)	7
Very common	oedema[z]	17.3% (185)	6
Common	chills	2.3% (25)	0
Common	influenza like illness	2.3% (25)	0
Investigations			
Very common	blood creatinine increased	12.0% (128)	5
Common	hypercalcaemia	3.1% (33)	12
Common	alanine aminotransferase increased	9.5% (101)	11
Common	aspartate aminotransferase increased	9.0% (96)	9
Common	blood alkaline phosphatase increased	3.5% (37)	2
Uncommon	blood bilirubin increased	0.8% (9)	1
Uncommon	amylase increased	0.3% (3)	1

Every subject is counted a single time for each applicable row.
a. infusion reactions (anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, infusion related reaction)
b. hypothyroidism (hypothyroidism, myxoedema, primary hypothyroidism)
c. hypophysitis (hypophysitis, hypopituitarism)
d. thyroiditis (autoimmune thyroiditis, thyroid disorder, thyroiditis)
e. type 1 diabetes mellitus (diabetic ketoacidosis, type 1 diabetes mellitus)
j. myocarditis (autoimmune myocarditis, myocarditis)
k. pneumonitis (interstitial lung disease, organising pneumonia, pneumonitis)
l. abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper)
m. colitis (autoimmune colitis, colitis, colitis microscopic, enterocolitis)
n. pancreatitis (autoimmune pancreatitis, pancreatitis, pancreatitis acute)
o. hepatitis (autoimmune hepatitis, drug-induced liver injury, hepatitis, hepatitis acute, immune-mediated hepatitis)
p. rash (genital rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular)
q. pruritus (pruritus, pruritus generalised, pruritus genital, urticaria, urticaria papular)
r. severe skin reactions (dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, pemphigus, pruritus, pruritus generalised, pruritus genital, rash, rash erythematous, rash generalised, rash maculo-papular, rash pruritic, rash pustular, skin necrosis, stevens-johnson syndrome, toxic skin eruption)
s. vitiligo (hypopigmentation of eyelid, skin depigmentation, skin hypopigmentation, vitiligo)
t. lichenoid keratosis (lichen planus, lichen sclerosus, lichenoid keratosis)
u. musculoskeletal pain (back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, torticollis)
v. myositis (myalgia, myopathy, myositis, polymyalgia rheumatica, rhabdomyolysis)
w. arthritis (arthritis, joint effusion, joint swelling, polyarthritis)
x. tenosynovitis (synovitis, tendon pain, tendonitis, tenosynovitis)
y. nephritis (acute kidney injury, autoimmune nephritis, glomerulonephritis membranous, nephritis, nephrotic syndrome, renal failure, tubulointerstitial nephritis)
z. oedema (eyelid oedema, face oedema, fluid overload, fluid retention, generalised oedema, lip oedema, localised oedema, oedema, oedema peripheral, periorbital oedema)

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 79: Subjects with serious adverse events up to 90 days of last dose (incidence ≥1% in or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[‡‡]		Reference Safety Dataset for MK-3475[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	121	(40.3)	162	(58.7)	141	(49.1)	281	(46.1)	1,450	(37.9)
with no adverse events	179	(59.7)	114	(41.3)	146	(50.9)	328	(53.9)	2,380	(62.1)
Febrile neutropenia	0	(0.0)	16	(5.8)	14	(4.9)	0	(0.0)	2	(0.1)
Pneumonia	17	(5.7)	15	(5.4)	18	(6.3)	38	(6.2)	114	(3.0)
Anaemia	1	(0.3)	14	(5.1)	9	(3.1)	8	(1.3)	48	(1.3)
Lung infection	3	(1.0)	9	(3.3)	2	(0.7)	4	(0.7)	13	(0.3)
Pneumonia aspiration	5	(1.7)	8	(2.9)	3	(1.0)	15	(2.5)	4	(0.1)
Stomatitis	0	(0.0)	8	(2.9)	4	(1.4)	2	(0.3)	1	(0.0)
Hyponatraemia	1	(0.3)	7	(2.5)	3	(1.0)	6	(1.0)	28	(0.7)
Neutropenia	0	(0.0)	7	(2.5)	5	(1.7)	2	(0.3)	1	(0.0)
Pyrexia	2	(0.7)	7	(2.5)	1	(0.3)	5	(0.8)	51	(1.3)
Dehydration	1	(0.3)	6	(2.2)	4	(1.4)	8	(1.3)	31	(0.8)
Mucosal inflammation	1	(0.3)	6	(2.2)	1	(0.3)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	6	(2.2)	8	(2.8)	4	(0.7)	20	(0.5)
Septic shock	1	(0.3)	6	(2.2)	2	(0.7)	1	(0.2)	6	(0.2)
Thrombocytopenia	0	(0.0)	6	(2.2)	0	(0.0)	0	(0.0)	6	(0.2)
Tumour haemorrhage	9	(3.0)	6	(2.2)	5	(1.7)	12	(2.0)	4	(0.1)
Acute kidney injury	5	(1.7)	5	(1.8)	1	(0.3)	1	(0.2)	41	(1.1)
Decreased appetite	1	(0.3)	5	(1.8)	4	(1.4)	6	(1.0)	5	(0.1)
Sepsis	6	(2.0)	5	(1.8)	3	(1.0)	8	(1.3)	21	(0.5)
Vomiting	0	(0.0)	5	(1.8)	5	(1.7)	5	(0.8)	20	(0.5)
Hypokalaemia	1	(0.3)	4	(1.4)	1	(0.3)	1	(0.2)	6	(0.2)
Hypotension	2	(0.7)	4	(1.4)	5	(1.7)	3	(0.5)	7	(0.2)
Pulmonary embolism	2	(0.7)	4	(1.4)	6	(2.1)	6	(1.0)	48	(1.3)
Respiratory tract infection	1	(0.3)	4	(1.4)	1	(0.3)	0	(0.0)	12	(0.3)
Blood creatinine increased	0	(0.0)	3	(1.1)	0	(0.0)	1	(0.2)	3	(0.1)
Bronchitis	2	(0.7)	3	(1.1)	2	(0.7)	2	(0.3)	13	(0.3)
Dyspnoea	6	(2.0)	3	(1.1)	2	(0.7)	13	(2.1)	57	(1.5)
Hypercalcaemia	5	(1.7)	3	(1.1)	2	(0.7)	14	(2.3)	16	(0.4)
Interstitial lung disease	1	(0.3)	3	(1.1)	1	(0.3)	1	(0.2)	5	(0.1)
Laryngeal oedema	1	(0.3)	3	(1.1)	1	(0.3)	1	(0.2)	1	(0.0)
Myocardial infarction	3	(1.0)	3	(1.1)	3	(1.0)	4	(0.7)	8	(0.2)
Platelet count decreased	0	(0.0)	3	(1.1)	1	(0.3)	0	(0.0)	0	(0.0)
Pleural effusion	2	(0.7)	3	(1.1)	0	(0.0)	10	(1.6)	56	(1.5)
Renal failure	0	(0.0)	3	(1.1)	2	(0.7)	0	(0.0)	22	(0.6)
Cellulitis	2	(0.7)	2	(0.7)	1	(0.3)	8	(1.3)	17	(0.4)
Death	2	(0.7)	2	(0.7)	2	(0.7)	11	(1.8)	19	(0.5)
Dysphagia	4	(1.3)	2	(0.7)	1	(0.3)	7	(1.1)	5	(0.1)
Pneumonitis	3	(1.0)	2	(0.7)	1	(0.3)	11	(1.8)	69	(1.8)
Syncope	0	(0.0)	2	(0.7)	5	(1.7)	8	(1.3)	11	(0.3)
Colitis	0	(0.0)	1	(0.4)	2	(0.7)	4	(0.7)	41	(1.1)
Device related infection	4	(1.3)	1	(0.4)	3	(1.0)	1	(0.2)	4	(0.1)
Diarrhoea	2	(0.7)	1	(0.4)	4	(1.4)	9	(1.5)	37	(1.0)
Fatigue	3	(1.0)	1	(0.4)	4	(1.4)	1	(0.2)	17	(0.4)
Infected neoplasm	3	(1.0)	1	(0.4)	2	(0.7)	3	(0.5)	1	(0.0)
Infusion related reaction	0	(0.0)	1	(0.4)	3	(1.0)	0	(0.0)	2	(0.1)
Mouth haemorrhage	0	(0.0)	1	(0.4)	0	(0.0)	6	(1.0)	0	(0.0)
Respiratory failure	1	(0.3)	1	(0.4)	1	(0.3)	8	(1.3)	16	(0.4)
Urinary tract infection	0	(0.0)	1	(0.4)	3	(1.0)	3	(0.5)	53	(1.4)
Confusional state	0	(0.0)	0	(0.0)	0	(0.0)	6	(1.0)	15	(0.4)
Neutrophil count decreased	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	1	(0.0)
Soft tissue infection	3	(1.0)	0	(0.0)	1	(0.3)	1	(0.2)	2	(0.1)
Upper gastrointestinal haemorrhage	1	(0.3)	0	(0.0)	3	(1.0)	1	(0.2)	2	(0.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Table 80: Exposure-Adjusted Serious Adverse Events by Observation Period (Including Multiple Occurrences of Events) (Incidence > 0% in One or More Treatment Groups) (Pembro Combo vs Control)

Observation period of drug exposure	Event Count and Rate (Events/100 person-years)[†]							
	Pembrolizumab + Chemotherapy				Cetuximab + Chemotherapy			
	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[‡]	276	219	158	60	287	230	139	27
Total exposure[§] person-years	62.33	46.72	47.85	33.73	66.47	46.49	33.06	21.81
Total events (rate)	210 (336.93)	75 (160.53)	47 (98.23)	10 (29.65)	174 (261.77)	64 (137.65)	27 (81.67)	1 (4.59)

Drug-related Serious Adverse Events

Table 81: Subjects with drug-related SAEs up to 90 days of last dose (incidence ≥1% in or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[‡‡]		Reference Safety Dataset for MK-3475[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	27	(9.0)	102	(37.0)	73	(25.4)	60	(9.9)	403	(10.5)
with no adverse events	273	(91.0)	174	(63.0)	214	(74.6)	549	(90.1)	3,427	(89.5)
Febrile neutropenia	0	(0.0)	14	(5.1)	10	(3.5)	0	(0.0)	0	(0.0)
Anaemia	1	(0.3)	11	(4.0)	8	(2.8)	0	(0.0)	4	(0.1)
Stomatitis	0	(0.0)	8	(2.9)	4	(1.4)	2	(0.3)	1	(0.0)
Neutropenia	0	(0.0)	7	(2.5)	5	(1.7)	0	(0.0)	1	(0.0)
Mucosal inflammation	1	(0.3)	6	(2.2)	1	(0.3)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	6	(2.2)	7	(2.4)	1	(0.2)	6	(0.2)
Septic shock	0	(0.0)	6	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombocytopenia	0	(0.0)	6	(2.2)	0	(0.0)	0	(0.0)	2	(0.1)
Acute kidney injury	2	(0.7)	5	(1.8)	1	(0.3)	1	(0.2)	6	(0.2)
Decreased appetite	0	(0.0)	5	(1.8)	2	(0.7)	1	(0.2)	1	(0.0)
Pneumonia	1	(0.3)	5	(1.8)	7	(2.4)	1	(0.2)	10	(0.3)
Hyponatraemia	1	(0.3)	4	(1.4)	1	(0.3)	0	(0.0)	8	(0.2)
Interstitial lung disease	1	(0.3)	3	(1.1)	1	(0.3)	1	(0.2)	5	(0.1)
Lung infection	0	(0.0)	3	(1.1)	0	(0.0)	0	(0.0)	1	(0.0)
Platelet count decreased	0	(0.0)	3	(1.1)	1	(0.3)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	3	(1.1)	3	(1.0)	2	(0.3)	6	(0.2)
Pneumonitis	3	(1.0)	2	(0.7)	1	(0.3)	9	(1.5)	65	(1.7)
Dehydration	0	(0.0)	1	(0.4)	3	(1.0)	0	(0.0)	4	(0.1)
Fatigue	1	(0.3)	1	(0.4)	4	(1.4)	0	(0.0)	5	(0.1)
Sepsis	0	(0.0)	1	(0.4)	3	(1.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(0.3)	0	(0.0)	4	(1.4)	6	(1.0)	24	(0.6)
Infusion related reaction	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	2	(0.1)
Neutrophil count decreased	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[‡‡] Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Deaths due to Adverse Events

All deaths

The number of deaths in the ITT population as per study status is displayed in tables below:

Table 82: Disposition of Subjects (Pembro Combo versus Control)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	281		278		559	
Status for Trial						
Discontinued	200	(71.2)	228	(82.0)	428	(76.6)
Death	188	(66.9)	212	(76.3)	400	(71.6)
Lost To Follow-Up	1	(0.4)	1	(0.4)	2	(0.4)
Withdrawal By Subject	11	(3.9)	15	(5.4)	26	(4.7)
Subjects Ongoing	81	(28.8)	50	(18.0)	131	(23.4)

Table 83: Disposition of Subjects (Pembro Mono versus Control)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	301		300		601	
Status for Trial						
Discontinued	216	(71.8)	245	(81.7)	461	(76.7)
Death	203	(67.4)	227	(75.7)	430	(71.5)
Lost To Follow-Up	1	(0.3)	1	(0.3)	2	(0.3)
Withdrawal By Subject	12	(4.0)	17	(5.7)	29	(4.8)
Subjects Ongoing	85	(28.2)	55	(18.3)	140	(23.3)

Total numbers (%) of Overall Survival events in the ITT population are higher than the numbers of death given in the Tables "Disposition of Subjects" above:

- 197 of 281 (70.1%) in the pembrolizumab plus chemotherapy group versus
- 223 of 278 (80.2%) in the standard treatment group, and
- 213 of 301 (70.8%) in the pembrolizumab monotherapy group versus
- 240 of 300 (80.0%) in the standard treatment group (see respective Tables in section 4.4.2 above)

If withdrawal by subject occurs first and death thereafter, the subject is included with "Withdrawal By Subject" as reason for discontinuation in the Table Disposition of Subjects.

Table 84: Subjects with AEs resulting in death up to 90 days of last dose (incidence ≥0% in or more treatment groups) by decreasing frequency of preferred term from KN048 combo (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[‡‡]		Reference Safety Dataset for MK-3475[‡‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	25	(8.3)	32	(11.6)	27	(9.4)	54	(8.9)	157	(4.1)
with no adverse events	275	(91.7)	244	(88.4)	260	(90.6)	555	(91.1)	3,673	(95.9)

When adjusted for exposure, event rates were slightly lower in the pembrolizumab monotherapy dataset compared to the pembrolizumab plus chemotherapy and standard treatment datasets (13.84 versus 16.79 and 16.68 events per 100 person-years).

Table 85: Summary of Death Reasons (All Randomized Subjects)

	Pembrolizumab (N=301) n (%)	Pembrolizumab + Chemotherapy (N=281) n (%)	Cetuximab + Chemotherapy (N=300) n (%)	Total (N=882) n (%)
Subjects who died	213 (70.8)	197 (70.1)	240 (80.0)	650 (73.7)
Progressive Disease	**154 (51.2)**	**152 (54.1)**	**173 (57.7)**	**479 (54.3)**
Adverse Event	**34 (11.3)**	**33 (11.7)**	**42 (14.0)**	**109 (12.4)**
Not Related	21 (7.0)	16 (5.7)	18 (6.0)	55 (6.2)
Related	13 (4.3)	17 (6.0)	24 (8.0)	54 (6.1)
Unknown	**25 (8.3)**	**12 (4.3)**	**25 (8.3)**	**62 (7.0)**
Withdrawal by Subject	3 (1.0)	2 (0.7)	8 (2.7)	13 (1.5)
Other	22 (7.3)	10 (3.6)	17 (5.7)	49 (5.6)
Database Cutoff Date: 13JUN2018				

Table 86: Subjects with AEs resulting in death up to 90 days of last dose (incidence ≥0% in or more treatment groups) Pembro combo vs control (ASaT population)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	276		287	
with one or more adverse events resulting in death	32	(11.6)	27	(9.4)
with no adverse events resulting in death	244	(88.4)	260	(90.6)
Cardiac disorders	**4**	**(1.4)**	**3**	**(1.0)**
Cardiac arrest	2	(0.7)	0	(0.0)
Myocardial infarction	2	(0.7)	2	(0.7)
Acute myocardial infarction	0	(0.0)	1	(0.3)
General disorders and administration site conditions	**5**	**(1.8)**	**2**	**(0.7)**
Death	2	(0.7)	2	(0.7)
Multiple organ dysfunction syndrome	2	(0.7)	0	(0.0)
Sudden death	1	(0.4)	0	(0.0)
Infections and infestations	**12**	**(4.3)**	**13**	**(4.5)**
Septic shock	5	(1.8)	2	(0.7)
Pneumonia	2	(0.7)	6	(2.1)
Sepsis	2	(0.7)	2	(0.7)
Bronchitis	1	(0.4)	0	(0.0)
Infection	1	(0.4)	0	(0.0)
Nosocomial infection	1	(0.4)	0	(0.0)
Lung infection pseudomonal	0	(0.0)	1	(0.3)
Osteomyelitis	0	(0.0)	1	(0.3)
Stoma site infection	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(0.4)**	**3**	**(1.0)**
Tumour haemorrhage	1	(0.4)	3	(1.0)
Nervous system disorders	**3**	**(1.1)**	**0**	**(0.0)**
Carotid artery perforation	1	(0.4)	0	(0.0)
Cerebral ischaemia	1	(0.4)	0	(0.0)
Embolic stroke	1	(0.4)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(2.2)**	**6**	**(2.1)**
Pneumonia aspiration	2	(0.7)	0	(0.0)
Dyspnoea	1	(0.4)	0	(0.0)
Haemoptysis	1	(0.4)	0	(0.0)
Interstitial lung disease	1	(0.4)	0	(0.0)
Pulmonary embolism	1	(0.4)	2	(0.7)
Hypoxia	0	(0.0)	1	(0.3)
Pulmonary artery thrombosis	0	(0.0)	1	(0.3)
Respiratory failure	0	(0.0)	1	(0.3)
Respiratory tract haemorrhage	0	(0.0)	1	(0.3)
Vascular disorders	**1**	**(0.4)**	**0**	**(0.0)**
Haemorrhage	1	(0.4)	0	(0.0)

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

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

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

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

Database Cutoff Date: 13JUN2018.

Source: [P048V01MK3475: adam-adsl; adae]

Table 87: Subjects with AEs resulting in death up to 90 days of last dose (incidence ≥0% in or more treatment groups) Pembro mono vs control (ASaT population)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	300		287	
with one or more adverse events resulting in death	25	(8.3)	27	(9.4)
with no adverse events resulting in death	275	(91.7)	260	(90.6)
Blood and lymphatic system disorders	**1**	**(0.3)**	**0**	**(0.0)**
Disseminated intravascular coagulation	1	(0.3)	0	(0.0)
Cardiac disorders	**3**	**(1.0)**	**3**	**(1.0)**
Myocardial infarction	2	(0.7)	2	(0.7)
Cardiac failure acute	1	(0.3)	0	(0.0)
Acute myocardial infarction	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**1**	**(0.3)**	**0**	**(0.0)**
Gastric haemorrhage	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**4**	**(1.3)**	**2**	**(0.7)**
Death	2	(0.7)	2	(0.7)
Multiple organ dysfunction syndrome	2	(0.7)	0	(0.0)
Immune system disorders	**1**	**(0.3)**	**0**	**(0.0)**
Autoinflammatory disease	1	(0.3)	0	(0.0)
Infections and infestations	**9**	**(3.0)**	**13**	**(4.5)**
Sepsis	3	(1.0)	2	(0.7)
Pneumonia	2	(0.7)	6	(2.1)
Pseudomonal sepsis	1	(0.3)	0	(0.0)
Pulmonary sepsis	1	(0.3)	0	(0.0)
Septic shock	1	(0.3)	2	(0.7)
Soft tissue infection	1	(0.3)	0	(0.0)
Lung infection pseudomonal	0	(0.0)	1	(0.3)
Osteomyelitis	0	(0.0)	1	(0.3)
Stoma site infection	0	(0.0)	1	(0.3)
Urinary tract infection	0	(0.0)	1	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(0.7)**	**3**	**(1.0)**
Tumour haemorrhage	2	(0.7)	3	(1.0)
Respiratory, thoracic and mediastinal disorders	**4**	**(1.3)**	**6**	**(2.1)**
Aspiration	1	(0.3)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Pneumonitis	1	(0.3)	0	(0.0)
Pulmonary embolism	1	(0.3)	2	(0.7)
Hypoxia	0	(0.0)	1	(0.3)
Pulmonary artery thrombosis	0	(0.0)	1	(0.3)
Respiratory failure	0	(0.0)	1	(0.3)
Respiratory tract haemorrhage	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 13JUN2018.

Source: [P048V01MK3475: adam-adsl; adae]

Narratives were provided for all the 57 deaths occurring in the two pembrolizumab-treated arms of KEYNOTE-048 (i.e. 25 in the pembro mono arm and 32 in the pembro combo arm).

Based on the listing provided (data not shown), the AEs leading to death considered as drug-related by investigator in each arm were:

- in the pembro mono arm (n=3): pneumonitis, disseminated intravascular coagulation (DIC), autoinflammatory disease (1 patient each)

- in the pembro combo arm (n=10): septic shock (5 patients), sepsis, interstitial lung disease, tumour hemorrhage, hemorrhage, cerebral ischemia (1 patient each).

At the final analysis cut-off date (25 February 2019), there was one additional patient in the pembro combo arm who died due to a AE (bronchitis) which was classified as treatment related. However, the investigator considered bronchitis (Grade 5) related to carboplatin, but not related to pembrolizumab, or 5-FU.)

- in the control arm (n=8): pneumonia (3 patients), sepsis (2 patients), hypoxia, osteomyelitis, and pulmonary artery thrombosis (1 patient each).

AEOSIs

A prespecified list of PTs was developed to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. These PTs are considered to be medically equivalent to the immune-mediated events and infusion-related reactions.

Table 88: List of AEOSI Preferred Terms, Version 14 (09 May 2018) - based on MedDRA Version 21.0

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	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
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder	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, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption;	Yes
Severe Skin (continued): If Grade 3 or higher:	Rash, Rash erythematous, Rash generalised, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus generalised, Pruritus genital	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy, Dermatomyositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes

Table 89: Adverse event summary AEOSI (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	91	(30.3)	71	(25.7)	68	(23.7)	148	(24.3)	856	(22.3)
with no adverse event	209	(69.7)	205	(74.3)	219	(76.3)	461	(75.7)	2,974	(77.7)
with drug-related† adverse events	70	(23.3)	61	(22.1)	48	(16.7)	114	(18.7)	743	(19.4)
with toxicity grade 3-5 adverse events	20	(6.7)	13	(4.7)	30	(10.5)	27	(4.4)	228	(6.0)
with toxicity grade 3-5 drug-related adverse events	17	(5.7)	11	(4.0)	28	(9.8)	22	(3.6)	195	(5.1)
with serious adverse events	17	(5.7)	12	(4.3)	12	(4.2)	28	(4.6)	227	(5.9)
with serious drug-related adverse events	14	(4.7)	10	(3.6)	11	(3.8)	23	(3.8)	199	(5.2)
with dose modification‡ due to an adverse event	26	(8.7)	21	(7.6)	43	(15.0)	35	(5.7)	311	(8.1)
who died	1	(0.3)	1	(0.4)	0	(0.0)	2	(0.3)	7	(0.2)
who died due to a drug-related adverse event	1	(0.3)	1	(0.4)	0	(0.0)	2	(0.3)	7	(0.2)
discontinued drug due to an adverse event	7	(2.3)	8	(2.9)	19	(6.6)	15	(2.5)	128	(3.3)
discontinued drug due to a drug-related adverse event	7	(2.3)	8	(2.9)	19	(6.6)	15	(2.5)	126	(3.3)
discontinued drug due to a serious adverse event	6	(2.0)	6	(2.2)	9	(3.1)	11	(1.8)	99	(2.6)
discontinued drug due to a serious drug-related adverse event	6	(2.0)	6	(2.2)	9	(3.1)	11	(1.8)	97	(2.5)

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

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

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

‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.

MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)

MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Table 90: (modified) Subjects With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	91	(30.3)	71	(25.7)	68	(23.7)	148	(24.3)	856	(22.3)
Grade 1	30	(10.0)	25	(9.1)	11	(3.8)	41	(6.7)	215	(5.6)
Grade 2	41	(13.7)	33	(12.0)	27	(9.4)	80	(13.1)	413	(10.8)
Grade 3	15	(5.0)	9	(3.3)	27	(9.4)	21	(3.4)	198	(5.2)
Grade 4	4	(1.3)	3	(1.1)	3	(1.0)	4	(0.7)	23	(0.6)
Grade 5	1	(0.3)	1	(0.4)	0	(0.0)	2	(0.3)	7	(0.2)
with no adverse events	209	(69.7)	205	(74.3)	219	(76.3)	461	(75.7)	2,974	(77.7)
Adrenal Insufficiency	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.7)**	**30**	**(0.8)**
Colitis	**3**	**(1.0)**	**7**	**(2.5)**	**2**	**(0.7)**	**4**	**(0.7)**	**74**	**(1.9)**
Encephalitis	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.3)**	**2**	**(0.1)**
Hepatitis	**2**	**(0.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(1.0)**	**24**	**(0.6)**
Hyperthyroidism	**8**	**(2.7)**	**13**	**(4.7)**	**3**	**(1.0)**	**10**	**(1.6)**	**134**	**(3.5)**
Hypophysitis	**1**	**(0.3)**	**1**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**21**	**(0.5)**
Hypothyroidism	**54**	**(18.0)**	**42**	**(15.2)**	**18**	**(6.3)**	**92**	**(15.1)**	**347**	**(9.1)**
Infusion Reactions	**4**	**(1.3)**	**6**	**(2.2)**	**27**	**(9.4)**	**11**	**(1.8)**	**101**	**(2.6)**
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**
Myocarditis	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Myositis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.2)**	**17**	**(0.4)**
Nephritis	**2**	**(0.7)**	**2**	**(0.7)**	**1**	**(0.3)**	**0**	**(0.0)**	**15**	**(0.4)**
Pancreatitis	**2**	**(0.7)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.2)**	**10**	**(0.3)**
Pneumonitis	**18**	**(6.0)**	**15**	**(5.4)**	**3**	**(1.0)**	**23**	**(3.8)**	**142**	**(3.7)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**
Severe Skin Reactions	**8**	**(2.7)**	**2**	**(0.7)**	**20**	**(7.0)**	**9**	**(1.5)**	**54**	**(1.4)**
Thyroiditis	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**3**	**(0.5)**	**27**	**(0.7)**
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.5)**	**12**	**(0.3)**
Uveitis	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**17**	**(0.4)**

Average time to onset of first AEOSI, number of events, and duration of episode are summarized for KEYNOTE-048 treatment arms in the next two tables:

Table 91: Time to onset and duration of AEOSI (pembro combo vs Control) – AsaT population

	Pembrolizumab + Chemotherapy	Cetuximab + Chemotherapy
Subjects in population	**276**	**287**
Subjects with AEOSI (%)	71 (25.7)	68 (23.7)
Time to Onset of First AEOSI (days)†		
Mean (SD)	110.8 (113.7)	55.6 (73.3)
Median	70.0	25.5
Range	1 to 677	1 to 331
Total number of episodes of AEOSI	100	89
Average number of episodes of AEOSI per subject	1.4	1.3
Episode Durations (days)‡		
Median	137.0	25.0
Range	1 to 890+	1 to 912+

Table 92: Time to onset and duration of AEOSI (pembro mono vs Control) – AsaT population

	Pembrolizumab	Cetuximab + Chemotherapy
Subjects in population	**300**	**287**
Subjects with AEOSI (%)	91 (30.3)	68 (23.7)
Time to Onset of First AEOSI (days)[†]		
Mean (SD)	123.6 (114.2)	55.6 (73.3)
Median	85.0	25.5
Range	1 to 652	1 to 331
Total number of episodes of AEOSI	112	89
Average number of episodes of AEOSI per subject	1.2	1.3
Episode Durations (days)[‡]		
Median	232.0	25.0
Range	2 to 909+	1 to 912+

Table 93: (modified) Summary of Outcome for Subjects With AEOSI (Incidence > 0% in One or More Treatment Groups)

		KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[##]		Reference Safety Dataset for MK-3475[###]	
	Outcome	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population		300		276		287		609		3830	
With one or more AEOSI	**Overall**	**91**	**(30.3)**	**71**	**(25.7)**	**68**	**(23.7)**	**148**	**(24.3)**	**856**	**(22.3)**
	Fatal	1	(1.1)	1	(1.4)	0	(0.0)	2	(1.4)	7	(0.8)
	Not Resolved	36	(39.6)	32	(45.1)	13	(19.1)	82	(55.4)	387	(45.2)
	Resolving	18	(19.8)	10	(14.1)	9	(13.2)	16	(10.8)	39	(4.6)
	Unknown	1	(1.1)	0	(0.0)	1	(1.5)	7	(4.7)	18	(2.1)
	Sequelae	4	(4.4)	2	(2.8)	0	(0.0)	2	(1.4)	13	(1.5)
	Resolved	31	(34.1)	26	(36.6)	45	(66.2)	39	(26.4)	392	(45.8)

- Treatment-emergent hypothyroidism

Table 94: Adverse event summary AEOSI – Hypothyroidism (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	54	(18.0)	42	(15.2)	18	(6.3)	92	(15.1)	347	(9.1)
with no adverse event	246	(82.0)	234	(84.8)	269	(93.7)	517	(84.9)	3,483	(90.9)
with drug-related† adverse events	39	(13.0)	35	(12.7)	1	(0.3)	68	(11.2)	310	(8.1)
with toxicity grade 3-5 adverse events	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)	4	(0.1)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)	4	(0.1)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
with dose modification‡ due to an adverse event	3	(1.0)	0	(0.0)	0	(0.0)	1	(0.2)	26	(0.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Among the participants with treatment-emergent hypothyroidism in the pembrolizumab plus chemotherapy and the Pembrolizumab monotherapy datasets, a higher proportion was male and with prior radiation therapy. Median time to onset of hypothyroidism was 83 days in the Pembrolizumab plus chemotherapy dataset and 104 days in the Pembrolizumab monotherapy dataset (it was 106 days in HNSCC pembrolizumab dataset). Three subjects receiving pembrolizumab monotherapy required dose interruption. Hypothyroidism requires long-term thyroid replacement therapy and therefore the median duration has not been reached in any of the safety datasets.

Oedema

The following preferred terms were selected: auricular swelling, ear swelling, eye oedema, eye swelling, orbital oedema, eyelid oedema, periorbital oedema, face oedema, swelling face, laryngeal oedema, laryngotracheal oedema, tracheal oedema, lip oedema, lip swelling, mouth swelling, oedema mouth, circumoral oedema, oedema mucosal, gingival oedema, gingival swelling, oropharyngeal swelling, pharyngeal oedema, epiglottic oedema, palatal oedema, palatal swelling, nasal oedema, swollen tongue, tongue oedema, localized oedema, local swelling, and oropharyngeal oedema.

Table 95: Adverse Event Summary Oedema (Pembro Combo vs Control, Pembro Mono) (ASaT Population)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Pembrolizumab	
	n	(%)	n	(%)	n	(%)
Subjects in population	276		287		300	
with one or more adverse events	20	(7.2)	20	(7.0)	27	(9.0)
with no adverse event	256	(92.8)	267	(93.0)	273	(91.0)
with drug-related[†] adverse events	9	(3.3)	6	(2.1)	5	(1.7)
with toxicity grade 3-5 adverse events	7	(2.5)	1	(0.3)	3	(1.0)
with toxicity grade 3-5 drug-related adverse events	4	(1.4)	0	(0.0)	1	(0.3)
with serious adverse events	5	(1.8)	1	(0.3)	2	(0.7)
with serious drug-related adverse events	3	(1.1)	0	(0.0)	0	(0.0)
with dose modification[‡] due to an adverse event	5	(1.8)	3	(1.0)	1	(0.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	1	(0.3)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

Table 96: (modified)* 5 most common adverse events of oedema regardless of causality (ASaT population)

	KN048 Data for MK-3475 N=300	KN048 Data for MK-3475 + chemotherapy N=276	KN048 Data for SOC N=287	HNSCC Safety dataset for MK-3475 N=609	Reference Safety Dataset for MK-3475 N=3,830
	N (%)	N (%)	N (%)	N (%)	N (%)
Face oedema	12 (4.0)	7 (2.5)	6 (2.1)	27 (4.4)	16 (0.4)
Swelling face	8 (2.7)	3 (1.1)	3 (1.0)	18 (3.0)	7 (0.2)
Laryngeal oedema	2 (0.7)	3 (1.1)	2 (0.7)	3 (0.5)	1 (0.0)
Swollen tongue	0 (0.0)	3 (1.1)	0 (0.0)	7 (1.1)	1 (0.0)
Localised oedema	4 (1.3)	2 (0.7)	3 (1.0)	13 (2.1)	13 (0.3)

*Source: Compiled from Supplemental Statistical Report / CSS

Bleeding From the Tumour Site

Table 97: Subjects with AEs of bleeding from the tumour site by maximum toxicity grade (Incidence >0% in one or more groups) – AsaT population

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[‡‡]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609	
with one or more adverse events	19	(6.3)	24	(8.7)	16	(5.6)	45	(7.4)
Grade 1	7	(2.3)	8	(2.9)	7	(2.4)	15	(2.5)
Grade 2	2	(0.7)	8	(2.9)	3	(1.0)	8	(1.3)
Grade 3	6	(2.0)	4	(1.4)	2	(0.7)	13	(2.1)
Grade 4	2	(0.7)	2	(0.7)	1	(0.3)	6	(1.0)
Grade 5	2	(0.7)	2	(0.7)	3	(1.0)	3	(0.5)
with no adverse events	281	(93.7)	252	(91.3)	271	(94.4)	564	(92.6)
Arterial haemorrhage	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Grade 4	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Carotid artery perforation	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Grade 5	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Haemorrhagic tumour necrosis	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Grade 2	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Laryngeal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Mouth haemorrhage	5	(1.7)	5	(1.8)	6	(2.1)	15	(2.5)
Grade 1	5	(1.7)	3	(1.1)	5	(1.7)	6	(1.0)
Grade 2	0	(0.0)	1	(0.4)	1	(0.3)	2	(0.3)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)
Grade 4	0	(0.0)	1	(0.4)	0	(0.0)	4	(0.7)
Pharyngeal haemorrhage	1	(0.3)	4	(1.4)	0	(0.0)	1	(0.2)
Grade 1	0	(0.0)	2	(0.7)	0	(0.0)	0	(0.0)
Grade 2	1	(0.3)	1	(0.4)	0	(0.0)	1	(0.2)
Grade 3	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Soft tissue haemorrhage	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 1	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Tongue haemorrhage	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 1	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Tracheal haemorrhage	0	(0.0)	3	(1.1)	0	(0.0)	2	(0.3)
Grade 1	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Grade 2	0	(0.0)	2	(0.7)	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
Tumour haemorrhage	12	(4.0)	13	(4.7)	8	(2.8)	24	(3.9)
Grade 1	2	(0.7)	4	(1.4)	2	(0.7)	9	(1.5)
Grade 2	1	(0.3)	4	(1.4)	1	(0.3)	4	(0.7)
Tumour haemorrhage	12	(4.0)	13	(4.7)	8	(2.8)	24	(3.9)
Grade 3	6	(2.0)	3	(1.1)	2	(0.7)	6	(1.0)
Grade 4	1	(0.3)	1	(0.4)	0	(0.0)	2	(0.3)
Grade 5	2	(0.7)	1	(0.4)	3	(1.0)	3	(0.5)
Wound haemorrhage	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)
Grade 1	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 2	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)

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.

Only the highest reported grade of a given adverse event is counted for the individual subject.

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.

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

MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

Source: [ISS: adam-adsl; adae]

Airway Obstruction with dyspnoea

Table 98: Subjects with AEs of airway obstruction with dyspnoea by maximum toxicity grade (Incidence >0% in one or more groups) – AsaT population

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475[#]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609	
with one or more adverse events	3	(1.0)	2	(0.7)	1	(0.3)	13	(2.1)
Grade 1	1	(0.3)	1	(0.4)	1	(0.3)	4	(0.7)
Grade 2	2	(0.7)	0	(0.0)	0	(0.0)	3	(0.5)
Grade 3	0	(0.0)	1	(0.4)	0	(0.0)	4	(0.7)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
with no adverse events	297	(99.0)	274	(99.3)	286	(99.7)	596	(97.9)
Dyspnoea	3	(1.0)	2	(0.7)	1	(0.3)	13	(2.1)
Grade 1	1	(0.3)	1	(0.4)	1	(0.3)	6	(1.0)
Grade 2	2	(0.7)	0	(0.0)	0	(0.0)	5	(0.8)
Grade 3	0	(0.0)	1	(0.4)	0	(0.0)	2	(0.3)
Epiglottic oedema	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Grade 3	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Laryngeal oedema	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 2	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Laryngeal stenosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Stridor	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)
Grade 3	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.5)
Swollen tongue	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Tongue oedema	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.3)
Grade 1	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Wheezing	2	(0.7)	1	(0.4)	1	(0.3)	5	(0.8)
Grade 1	1	(0.3)	1	(0.4)	1	(0.3)	4	(0.7)
Wheezing	2	(0.7)	1	(0.4)	1	(0.3)	5	(0.8)
Grade 2	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.2)

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.
Only the highest reported grade of a given adverse event is counted for the individual subject.
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.
[#] Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 and KN055.
AEs were included if a subject reported both airway obstruction AEs and Dyspnoea AEs. Airway obstruction includes the preferred terms: Epiglottic oedema, Laryngeal obstruction, Laryngeal oedema, Laryngeal stenosis, Laryngeal tracheal oedema, Oropharyngeal swelling, Palatal oedema, Pharyngeal oedema, Stridor, Swollen tongue, Tongue oedema, Tongue swelling, Tracheal oedema, Wheezing.
Dysponea includes the preferred terms: Dyspnoea, Dyspnoea with exertion.
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

Source: [ISS: adam-adsl; adae]

Renal Toxicity events

Table 99: Adverse Event Summary (Pembro Combo vs Control) - ASaT Population (Renal Toxicity)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	276		287		563	
with one or more adverse events	77	(27.9)	56	(19.5)	133	(23.6)
with no adverse event	199	(72.1)	231	(80.5)	430	(76.4)
with drug-related[†] adverse events	55	(19.9)	27	(9.4)	82	(14.6)
with toxicity grade 3-5 adverse events	12	(4.3)	5	(1.7)	17	(3.0)
with toxicity grade 3-5 drug-related adverse events	8	(2.9)	3	(1.0)	11	(2.0)
with serious adverse events	13	(4.7)	3	(1.0)	16	(2.8)
with serious drug-related adverse events	10	(3.6)	2	(0.7)	12	(2.1)
with dose modification[‡] due to an adverse event	28	(10.1)	10	(3.5)	38	(6.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(4.0)	7	(2.4)	18	(3.2)
discontinued drug due to a drug-related adverse event	10	(3.6)	6	(2.1)	16	(2.8)
discontinued drug due to a serious adverse event	2	(0.7)	2	(0.7)	4	(0.7)
discontinued drug due to a serious drug-related adverse event	2	(0.7)	2	(0.7)	4	(0.7)

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

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

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

Grades are based on NCI CTCAE version 4.03.

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.

Renal toxicity include preferred terms which are Acute renal failure SMQ or classified under renal and urinary disorders SOC.

Database Cutoff Date: 13JUN2018

Table 100: Summary of Baseline Renal Function (Pembro Combo vs Control) - ASaT Population - Subjects with Renal Toxicity

	Pembrolizumab + Chemotherapy	Cetuximab + Chemotherapy
Subjects in population	77	56
Baseline Renal Function (mg/dL)		
Subjects with data	77	55
Mean	0.9	0.9
SD	0.2	0.2
Median	0.9	0.9
Range	0.5 to 1.8	0.5 to 1.3

Baseline Renal Function is defined as the blood creatinine level at baseline.
Database Cutoff Date: 13JUN2018

Table 101: Summary of Time to First Renal Toxicity Event (Pembro Combo vs Control) - ASaT Population

	Pembrolizumab + Chemotherapy	Cetuximab + Chemotherapy
Subjects in population	276	287
Time to onset (days)		
Subjects with data	77	56
Mean	67.5	66.1
SD	89.3	72.3
Median	43.0	28.5
Range	3.0 to 692.0	1.0 to 265.0

Renal toxicity include preferred terms which are Acute renal failure SMQ or classified under renal and urinary disorders SOC. Database Cutoff Date: 13JUN2018

Table 102: Summary of Outcome for Subjects With Renal Toxicity Events with incidence > 0% (Pembro Combo vs Control) - ASaT Population

		Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	Outcome	n	(%)	n	(%)
Subjects in population		276		287	
Renal Toxicity Events	**Overall**	**77**	**(27.9)**	**56**	**(19.5)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	21	(27.3)	9	(16.1)
	Resolving	7	(9.1)	5	(8.9)
	Unknown	1	(1.3)	0	(0.0)
	Sequelae	2	(2.6)	0	(0.0)
	Resolved	46	(59.7)	42	(75.0)

Every subject is counted once for each specific Renal Toxicity Events according to the worst outcome; the ordering of the outcomes is as follows: Fatal>Not Resolved>Resolving>Unknown>Sequelae>Resolved.

"Subjects in population" is used for percentage calculation for the Overall row in each section. Within each section, the overall total is used for percentage calculation for each outcome.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

Renal toxicity include preferred terms which are Acute renal failure SMQ or classified under renal and urinary disorders SOC. Database Cutoff Date: 13JUN2018

Table 103: Adverse Event Summary (Pembro Combo vs Control) - ASaT Population-Carboplatin (Renal Toxicity)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	197		202		399	
with one or more adverse events	30	(15.2)	28	(13.9)	58	(14.5)
with no adverse event	167	(84.8)	174	(86.1)	341	(85.5)
with drug-related[†] adverse events	14	(7.1)	8	(4.0)	22	(5.5)
with toxicity grade 3-5 adverse events	2	(1.0)	1	(0.5)	3	(0.8)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	1	(0.5)	0	(0.0)	1	(0.3)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with dose modification[‡] due to an adverse event	3	(1.5)	2	(1.0)	5	(1.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	1	(0.5)	1	(0.3)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

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

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

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

Grades are based on NCI CTCAE version 4.03.

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.

Renal toxicity include preferred terms which are Acute renal failure SMQ or classified under renal and urinary disorders SOC.

Patients who were treated with Carboplatin from first dose or who were initially treated with Cisplatin and later switched to Carboplatin are included.

For patients who switched to Carboplatin during treatment period, adverse events which occurred before first dose of Carboplatin are excluded; for patients who switched to Cisplatin, adverse events on or after the Cisplatin start date are excluded.

Database Cutoff Date: 13JUN2018

Table 104: Adverse Event Summary (Pembro Combo vs Control) - ASaT Population-Cisplatin (Renal Toxicity)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	119		120		239	
with one or more adverse events	53	(44.5)	35	(29.2)	88	(36.8)
with no adverse event	66	(55.5)	85	(70.8)	151	(63.2)
with drug-related[†] adverse events	43	(36.1)	25	(20.8)	68	(28.5)
with toxicity grade 3-5 adverse events	10	(8.4)	4	(3.3)	14	(5.9)
with toxicity grade 3-5 drug-related adverse events	8	(6.7)	3	(2.5)	11	(4.6)
with serious adverse events	12	(10.1)	3	(2.5)	15	(6.3)
with serious drug-related adverse events	10	(8.4)	2	(1.7)	12	(5.0)
with dose modification[‡] due to an adverse event	26	(21.8)	8	(6.7)	34	(14.2)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(9.2)	6	(5.0)	17	(7.1)
discontinued drug due to a drug-related adverse event	10	(8.4)	6	(5.0)	16	(6.7)
discontinued drug due to a serious adverse event	2	(1.7)	2	(1.7)	4	(1.7)
discontinued drug due to a serious drug-related adverse event	2	(1.7)	2	(1.7)	4	(1.7)

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

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

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

Grades are based on NCI CTCAE version 4.03.

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.

Renal toxicity include preferred terms which are Acute renal failure SMQ or classified under renal and urinary disorders SOC.
Patients who were treated with Cisplatin from first dose or who were initially treated with Carboplatin and later switched to Cisplatin are included.
For patients who switched to Carboplatin during treatment period, adverse events which occurred on or after the Carboplatin start date are excluded; for the patient who switched to Cisplatin, adverse events before first dose of Cisplatin are excluded.
Database Cutoff Date: 13JUN2018

Laboratory findings

Pembrolizumab+Chemotherapy versus Standard Treatment

The proportion of most abnormal laboratory findings was comparable among the Pembrolizumab plus Chemotherapy and the Standard Treatment datasets: *Glucose increased* 54.9% and 65.6%; *Haemoglobin decreased* 89.4% and 78.3%; *Leucocytes decreased* 79.3% and 84.8%; *Neutrophils decreased* 67.2% and 71.1%; *Platelets decreased* 73.2 and 76.3%. *Creatinine increased* was found more commonly in combination arm than in the standard of care (36% vs 27%).

Pembrolizumab monotherapy versus Standard Treatment

The proportion of participants with abnormal laboratory findings was either lower (*Haemoglobin decreased* 51.7% vs 78.3%; *Leukocyte decreased* 11.2% vs 74.4%; *Magnesium decreased* 15.8% vs 75.5%; *Neutrophils decreased* 7.3% vs 71.1%; *Platelets decreased* 11.5% vs 76.3%) or comparable in the pembrolizumab monotherapy dataset compared to the Standard Treatment dataset. Incidence of *Calcium increased* was 22.1% in Pembrolizumab monotherapy arm and 12.8% in Standard Treatment arm.

Safety in special populations

Intrinsic Factors

Age

Table 105: AE summary by age category (ASaT population)

	KN048 Data for MK-3475				KN048 Data for MK-3475 + Chemotherapy				KN048 Data for SOC				HNSCC Safety Dataset for MK3475‡‡				Reference Safety Dataset for MK-3475‡‡‡			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	189		111		176		100		183		104		397		212		2,056		1,774	
with one or more adverse events	181	(95.8)	109	(98.2)	173	(98.3)	98	(98.0)	183	(100.0)	103	(99.0)	385	(97.0)	207	(97.6)	1,997	(97.1)	1,723	(97.1)
with no adverse event	8	(4.2)	2	(1.8)	3	(1.7)	2	(2.0)	0	(0.0)	1	(1.0)	12	(3.0)	5	(2.4)	59	(2.9)	51	(2.9)
with drug-related† adverse events	108	(57.1)	67	(60.4)	169	(96.0)	94	(94.0)	180	(98.4)	98	(94.2)	241	(60.7)	146	(68.9)	1,475	(71.7)	1,276	(71.9)
with toxicity grade 3-5 adverse events	97	(51.3)	65	(58.6)	151	(85.8)	83	(83.0)	153	(83.6)	87	(83.7)	233	(58.7)	115	(54.2)	880	(42.8)	922	(52.0)
with toxicity grade 3-5 drug-related adverse events	30	(15.9)	20	(18.0)	124	(70.5)	72	(72.0)	127	(69.4)	71	(68.3)	47	(11.8)	36	(17.0)	271	(13.2)	306	(17.2)
with serious adverse events	73	(38.6)	48	(43.2)	101	(57.4)	61	(61.0)	87	(47.5)	54	(51.9)	181	(45.6)	100	(47.2)	688	(33.5)	762	(43.0)
with serious drug-related adverse events	17	(9.0)	10	(9.0)	62	(35.2)	40	(40.0)	49	(26.8)	24	(23.1)	37	(9.3)	23	(10.8)	191	(9.3)	212	(12.0)
with dose modification‡ due to an adverse event	67	(35.4)	46	(41.4)	145	(82.4)	84	(84.0)	151	(82.5)	89	(85.6)	136	(34.3)	81	(38.2)	602	(29.3)	654	(36.9)
who died	13	(6.9)	12	(10.8)	16	(9.1)	16	(16.0)	15	(8.2)	12	(11.5)	34	(8.6)	20	(9.4)	61	(3.0)	96	(5.4)
who died due to a drug-related adverse event	2	(1.1)	1	(0.9)	6	(3.4)	4	(4.0)	4	(2.2)	4	(3.8)	4	(1.0)	1	(0.5)	7	(0.3)	10	(0.6)
discontinued drug due to an adverse event	19	(10.1)	17	(15.3)	47	(26.7)	38	(38.0)	45	(24.6)	33	(31.7)	50	(12.6)	34	(16.0)	205	(10.0)	247	(13.9)
discontinued drug due to a drug-related adverse event	8	(4.2)	6	(5.4)	37	(21.0)	26	(26.0)	33	(18.0)	24	(23.1)	22	(5.5)	13	(6.1)	92	(4.5)	132	(7.4)
discontinued drug due to a serious adverse event	14	(7.4)	15	(13.5)	27	(15.3)	27	(27.0)	26	(14.2)	22	(21.2)	44	(11.1)	23	(10.8)	154	(7.5)	184	(10.4)
discontinued drug due to a serious drug-related adverse event	4	(2.1)	5	(4.5)	18	(10.2)	13	(13.0)	15	(8.2)	13	(12.5)	16	(4.0)	7	(3.3)	63	(3.1)	86	(4.8)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Table 106: Age-specific AE summary (Pembro combo vs control) – AsaT population

	Pembrolizumab + Chemotherapy							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	176		85		14		1	
with one or more adverse events	173	(98.3)	83	(97.6)	14	(100.0)	1	(100.0)
who died	16	(9.1)	12	(14.1)	3	(21.4)	1	(100.0)
with serious adverse events	101	(57.4)	50	(58.8)	10	(71.4)	1	(100.0)
discontinued† due to an adverse event	47	(26.7)	29	(34.1)	8	(57.1)	1	(100.0)
CNS (confusion/extrapyramidal)	13	(7.4)	12	(14.1)	2	(14.3)	0	(0.0)
AE related to falling	10	(5.7)	9	(10.6)	1	(7.1)	0	(0.0)
CV events	47	(26.7)	24	(28.2)	4	(28.6)	0	(0.0)
Cerebrovascular events	5	(2.8)	2	(2.4)	1	(7.1)	0	(0.0)
Infection	95	(54.0)	48	(56.5)	9	(64.3)	1	(100.0)

Table 107: Age-specific AE summary (Pembro mono vs control) – ASaT population

	Pembrolizumab							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	189		95		15		1	
with one or more adverse events	181	(95.8)	93	(97.9)	15	(100.0)	1	(100.0)
who died	13	(6.9)	10	(10.5)	2	(13.3)	0	(0.0)
with serious adverse events	73	(38.6)	40	(42.1)	8	(53.3)	0	(0.0)
discontinued† due to an adverse event	19	(10.1)	12	(12.6)	5	(33.3)	0	(0.0)
CNS (confusion/extrapyramidal)	14	(7.4)	6	(6.3)	3	(20.0)	0	(0.0)
AE related to falling	16	(8.5)	6	(6.3)	2	(13.3)	0	(0.0)
CV events	22	(11.6)	16	(16.8)	5	(33.3)	1	(100.0)
Cerebrovascular events	3	(1.6)	1	(1.1)	0	(0.0)	0	(0.0)
Infection	78	(41.3)	47	(49.5)	7	(46.7)	0	(0.0)

Table 108: Age-specific AE summary (Pembro combo vs control) – ASaT population

	Cetuximab + Chemotherapy							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	183		77		27		0	
with one or more adverse events	183	(100.0)	76	(98.7)	27	(100.0)	0	(0.0)
who died	15	(8.2)	9	(11.7)	3	(11.1)	0	(0.0)
with serious adverse events	87	(47.5)	40	(51.9)	14	(51.9)	0	(0.0)
discontinued† due to an adverse event	45	(24.6)	28	(36.4)	5	(18.5)	0	(0.0)
CNS (confusion/extrapyramidal)	16	(8.7)	7	(9.1)	3	(11.1)	0	(0.0)
AE related to falling	14	(7.7)	11	(14.3)	5	(18.5)	0	(0.0)
CV events	41	(22.4)	22	(28.6)	9	(33.3)	0	(0.0)
Cerebrovascular events	5	(2.7)	2	(2.6)	1	(3.7)	0	(0.0)
Infection	114	(62.3)	48	(62.3)	15	(55.6)	0	(0.0)

† Study medication withdrawn.
For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 13JUN2018.

Source: [P048V01MK3475: adam-adsl; adae]

Gender

Table 109: AE summary by gender – AsaT population

	KN048 Data for MK-3475				KN048 Data for MK-3475 + Chemotherapy				KN048 Data for SOC				HNSCC Safety Dataset for MK3475‡‡				Reference Safety Dataset for MK-3475‡‡‡			
	M		F		M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	249		51		220		56		249		38		503		106		2,366		1,464	
with one or more adverse events	241	(96.8)	49	(96.1)	217	(98.6)	54	(96.4)	248	(99.6)	38	(100.0)	490	(97.4)	102	(96.2)	2,297	(97.1)	1,423	(97.2)
with no adverse event	8	(3.2)	2	(3.9)	3	(1.4)	2	(3.6)	1	(0.4)	0	(0.0)	13	(2.6)	4	(3.8)	69	(2.9)	41	(2.8)
with drug-related† adverse events	144	(57.8)	31	(60.8)	210	(95.5)	53	(94.6)	242	(97.2)	36	(94.7)	316	(62.8)	71	(67.0)	1,713	(72.4)	1,038	(70.9)
with toxicity grade 3-5 adverse events	135	(54.2)	27	(52.9)	185	(84.1)	49	(87.5)	204	(81.9)	36	(94.7)	286	(56.9)	62	(58.5)	1,124	(47.5)	678	(46.3)
with toxicity grade 3-5 drug-related adverse events	44	(17.7)	6	(11.8)	152	(69.1)	44	(78.6)	170	(68.3)	28	(73.7)	67	(13.3)	16	(15.1)	379	(16.0)	198	(13.5)
with serious adverse events	102	(41.0)	19	(37.3)	123	(55.9)	39	(69.6)	120	(48.2)	21	(55.3)	230	(45.7)	51	(48.1)	924	(39.1)	526	(35.9)
with serious drug-related adverse events	22	(8.8)	5	(9.8)	78	(35.5)	24	(42.9)	61	(24.5)	12	(31.6)	47	(9.3)	13	(12.3)	269	(11.4)	134	(9.2)
with dose modification‡ due to an adverse event	90	(36.1)	23	(45.1)	181	(82.3)	48	(85.7)	205	(82.3)	35	(92.1)	175	(34.8)	42	(39.6)	776	(32.8)	480	(32.8)
who died	19	(7.6)	6	(11.8)	25	(11.4)	7	(12.5)	22	(8.8)	5	(13.2)	40	(8.0)	14	(13.2)	106	(4.5)	51	(3.5)
who died due to a drug-related adverse event	1	(0.4)	2	(3.9)	7	(3.2)	3	(5.4)	6	(2.4)	2	(5.3)	2	(0.4)	3	(2.8)	13	(0.5)	4	(0.3)
discontinued drug due to an adverse event	30	(12.0)	6	(11.8)	69	(31.4)	16	(28.6)	66	(26.5)	12	(31.6)	66	(13.1)	18	(17.0)	284	(12.0)	168	(11.5)
discontinued drug due to a drug-related adverse event	11	(4.4)	3	(5.9)	51	(23.2)	12	(21.4)	48	(19.3)	9	(23.7)	24	(4.8)	11	(10.4)	152	(6.4)	72	(4.9)
discontinued drug due to a serious adverse event	23	(9.2)	6	(11.8)	42	(19.1)	12	(21.4)	39	(15.7)	9	(23.7)	53	(10.5)	14	(13.2)	216	(9.1)	122	(8.3)

ECOG Status

Table 110: AE summary by ECOG performance status – AsaT population

	KN048 Data for MK-3475				KN048 Data for MK-3475 + Chemotherapy				KN048 Data for SOC				HNSCC Safety Dataset for MK3475‡‡				Reference Safety Dataset for MK-3475‡‡‡			
	0		1		0		1		0		1		0		1		0		1	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	118		182		109		167		113		174		176		430		1,811		1,851	
with one or more adverse events	111	(94.1)	179	(98.4)	108	(99.1)	163	(97.6)	113	(100.0)	173	(99.4)	172	(97.7)	417	(97.0)	1,770	(97.7)	1,789	(96.7)
with no adverse event	7	(5.9)	3	(1.6)	1	(0.9)	4	(2.4)	0	(0.0)	1	(0.6)	4	(2.3)	13	(3.0)	41	(2.3)	62	(3.3)
with drug-related† adverse events	69	(58.5)	106	(58.2)	106	(97.2)	157	(94.0)	111	(98.2)	167	(96.0)	118	(67.0)	268	(62.3)	1,400	(77.3)	1,261	(68.1)
with toxicity grade 3-5 adverse events	51	(43.2)	111	(61.0)	91	(83.5)	143	(85.6)	91	(80.5)	149	(85.6)	69	(39.2)	276	(64.2)	743	(41.0)	960	(51.9)
with toxicity grade 3-5 drug-related adverse events	18	(15.3)	32	(17.6)	83	(76.1)	113	(67.7)	79	(69.9)	119	(68.4)	14	(8.0)	68	(15.8)	263	(14.5)	285	(15.4)
with serious adverse events	38	(32.2)	83	(45.6)	57	(52.3)	105	(62.9)	48	(42.5)	93	(53.4)	46	(26.1)	232	(54.0)	587	(32.4)	780	(42.1)
with serious drug-related adverse events	11	(9.3)	16	(8.8)	35	(32.1)	67	(40.1)	21	(18.6)	52	(29.9)	8	(4.5)	51	(11.9)	193	(10.7)	192	(10.4)
with dose modification‡ due to an adverse event	45	(38.1)	68	(37.4)	93	(85.3)	136	(81.4)	91	(80.5)	149	(85.6)	45	(25.6)	171	(39.8)	537	(29.7)	659	(35.6)
who died	6	(5.1)	19	(10.4)	10	(9.2)	22	(13.2)	9	(8.0)	18	(10.3)	5	(2.8)	48	(11.2)	50	(2.8)	95	(5.1)
who died due to a drug-related adverse event	1	(0.8)	2	(1.1)	4	(3.7)	6	(3.6)	2	(1.8)	6	(3.4)	1	(0.6)	4	(0.9)	7	(0.4)	10	(0.5)
discontinued drug due to an adverse event	11	(9.3)	25	(13.7)	26	(23.9)	59	(35.3)	31	(27.4)	47	(27.0)	10	(5.7)	73	(17.0)	182	(10.0)	244	(13.2)
discontinued drug due to a drug-related adverse event	4	(3.4)	10	(5.5)	21	(19.3)	42	(25.1)	25	(22.1)	32	(18.4)	6	(3.4)	29	(6.7)	105	(5.8)	106	(5.7)
discontinued drug due to a serious adverse event	9	(7.6)	20	(11.0)	14	(12.8)	40	(24.0)	14	(12.4)	34	(19.5)	6	(3.4)	60	(14.0)	128	(7.1)	190	(10.3)
discontinued drug due to a serious drug-related adverse event	3	(2.5)	6	(3.3)	8	(7.3)	23	(13.8)	7	(6.2)	21	(12.1)	3	(1.7)	20	(4.7)	66	(3.6)	74	(4.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Extrinsic Factors

Region

Table 111: AE summary by region – AsaT population

	KN048 Data for MK-3475						KN048 Data for MK-3475 + Chemotherapy						KN048 Data for SOC						HNSCC Safety Dataset for MK3475‡‡						Reference Safety Dataset for MK-3475‡‡‡					
	North America		European Union		Rest of the World		North America		European Union		Rest of the World		North America		European Union		Rest of the World		North America		European Union		Rest of the World		North America		European Union		Rest of the World	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	75		86		139		58		88		130		56		102		129		388		153		68		1,727		1,384		719	
with one or more adverse events	72	(96.0)	83	(96.5)	135	(97.1)	57	(98.3)	87	(98.9)	127	(97.7)	56	(100.0)	102	(100.0)	128	(99.2)	378	(97.4)	147	(96.1)	67	(98.5)	1,693	(98.0)	1,334	(96.4)	693	(96.4)
with no adverse event	3	(4.0)	3	(3.5)	4	(2.9)	1	(1.7)	1	(1.1)	3	(2.3)	0	(0.0)	0	(0.0)	1	(0.8)	10	(2.6)	6	(3.9)	1	(1.5)	34	(2.0)	50	(3.6)	26	(3.6)
with drug-related† adverse events	44	(58.7)	47	(54.7)	84	(60.4)	56	(96.6)	83	(94.3)	124	(95.4)	53	(94.6)	99	(97.1)	126	(97.7)	251	(64.7)	102	(66.7)	34	(50.0)	1,296	(75.0)	946	(68.4)	509	(70.8)
with toxicity grade 3-5 adverse events	37	(49.3)	40	(46.5)	85	(61.2)	52	(89.7)	73	(83.0)	109	(83.8)	48	(85.7)	81	(79.4)	111	(86.0)	224	(57.7)	87	(56.9)	37	(54.4)	823	(47.7)	644	(46.5)	335	(46.6)
with toxicity grade 3-5 drug-related adverse events	11	(14.7)	6	(7.0)	33	(23.7)	48	(82.8)	60	(68.2)	88	(67.7)	39	(69.6)	69	(67.6)	90	(69.8)	54	(13.9)	22	(14.4)	7	(10.3)	249	(14.4)	213	(15.4)	115	(16.0)
with serious adverse events	28	(37.3)	32	(37.2)	61	(43.9)	36	(62.1)	59	(67.0)	67	(51.5)	22	(39.3)	54	(52.9)	65	(50.4)	178	(45.9)	70	(45.8)	33	(48.5)	625	(36.2)	550	(39.7)	275	(38.2)
with serious drug-related adverse events	6	(8.0)	2	(2.3)	19	(13.7)	20	(34.5)	39	(44.3)	43	(33.1)	9	(16.1)	30	(29.4)	34	(26.4)	38	(9.8)	18	(11.8)	4	(5.9)	149	(8.6)	163	(11.8)	91	(12.7)
with dose modification† due to an adverse event	25	(33.3)	33	(38.4)	55	(39.6)	49	(84.5)	74	(84.1)	106	(81.5)	49	(87.5)	83	(81.4)	108	(83.7)	137	(35.3)	53	(34.6)	27	(39.7)	549	(31.8)	454	(32.8)	253	(35.2)
who died	1	(1.3)	6	(7.0)	18	(12.9)	9	(15.5)	8	(9.1)	15	(11.5)	4	(7.1)	9	(8.8)	14	(10.9)	37	(9.5)	12	(7.8)	5	(7.4)	42	(2.4)	68	(4.9)	47	(6.5)
who died due to a drug-related adverse event	1	(1.3)	0	(0.0)	2	(1.4)	2	(3.4)	0	(0.0)	8	(6.2)	1	(1.8)	3	(2.9)	4	(3.1)	1	(0.3)	4	(2.6)	0	(0.0)	3	(0.2)	6	(0.4)	8	(1.1)
discontinued drug due to an adverse event	3	(4.0)	9	(10.5)	24	(17.3)	23	(39.7)	30	(34.1)	32	(24.6)	20	(35.7)	35	(34.3)	23	(17.8)	57	(14.7)	18	(11.8)	9	(13.2)	208	(12.0)	160	(11.6)	84	(11.7)
discontinued drug due to a drug-related adverse event	2	(2.7)	2	(2.3)	10	(7.2)	19	(32.8)	22	(25.0)	22	(16.9)	16	(28.6)	28	(27.5)	13	(10.1)	22	(5.7)	11	(7.2)	2	(2.9)	99	(5.7)	84	(6.1)	41	(5.7)
discontinued drug due to a serious adverse event	2	(2.7)	8	(9.3)	19	(13.7)	13	(22.4)	18	(20.5)	23	(17.7)	10	(17.9)	17	(16.7)	21	(16.3)	44	(11.3)	15	(9.8)	8	(11.8)	142	(8.2)	127	(9.2)	69	(9.6)
discontinued drug due to a serious drug-related adverse event	1	(1.3)	2	(2.3)	6	(4.3)	8	(13.8)	9	(10.2)	14	(10.8)	7	(12.5)	11	(10.8)	10	(7.8)	13	(3.4)	8	(5.2)	2	(2.9)	59	(3.4)	60	(4.3)	30	(4.2)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡‡ Includes all subjects who received at least one dose of MK-3475 in KN012 Cohorts B and B2, KN040 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, KN013-Cohort 3, KN024, KN045, KN052 and KN087.
MK-3475 Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
MK-3475 Database Cutoff Date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JULY2017)
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)
MK-3475 Database Cutoff Date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
MK-3475 Database Cutoff Date for Bladder (KN045: 18JAN2017, KN052: 09MAR2017)

Source: [ISS: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

See clinical pharmacology section.

Discontinuation due to adverse events

All drug-related AEs leading to Treatment Discontinuation

The proportion of subjects with AEs leading to treatment discontinuation was 30.8%, 12%, and 27.2% in respectively the Pembrolizumab+Chemotherapy, Pembrolizumab monotherapy and the Standard Treatment arms.

Drug-related AEs Leading to Treatment Discontinuation

Table 112: Subjects with drug-related adverse events resulting in treatment discontinuation (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term from KN048 Combo (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	14	(4.7)	63	(22.8)	57	(19.9)	35	(5.7)	224	(5.8)
with no adverse events	286	(95.3)	213	(77.2)	230	(80.1)	574	(94.3)	3,606	(94.2)

In the Pembrolizumab + Chemotherapy arm, the most frequently reported (≥1.0% incidence) drug-related AEs leading to discontinuation of Pembrolizumab plus Chemotherapy were *Blood creatinine increased* (5 patients; 1.8%, vs 0.3% in control arm), *Mucosal inflammation, Neutropenia, Septic shock, Pneumonia* (4 patients each; 1.4%), *Pneumonitis, Thrombocytopenia*, *Nausea, Tinnitus* and *peripheral sensory neuropathy* (3 patients each; 1.1%). Rate of renal and urinary disorders SOC was similar in pembro combo and standard treatment arm (1.8% vs 2.1%).

In the Pembrolizumab monotherapy arm, the most frequently reported drug-related AEs leading to discontinuation of pembrolizumab included *Pneumonitis* and *Autoimmune hepatitis* reported in 0.7% (2 patients) each. Of the 2 Grade 4 autoimmune hepatitis events, 1 had resolved and 1 was resolving. Of the 2 pneumonitis events, 1 was not resolved and 1 was fatal.

The most common drug-related AE resulting in the discontinuation of study treatment was infusion related reaction and rash and anemia in the standard treatment group.

All AEs leading to Treatment Interruption

While proportions of subjects with AEs resulting in interruption of study intervention were 64.1% and 63.4% in the Pembrolizumab+Chemotherapy and the Standard Treatment arms, it was 30.7% in the Pembrolizumab monotherapy arm.

Drug-related Adverse Events Leading to Treatment Interruption

Table 113: Subjects with drug-related adverse events resulting in treatment interruption (incidence >0% in one or more treatment groups) by decreasing frequency of preferred term from KN048 Combo (ASaT population)

	KN048 Data for MK-3475		KN048 Data for MK-3475 + Chemotherapy		KN048 Data for SOC		HNSCC Safety Dataset for MK3475‡‡		Reference Safety Dataset for MK-3475‡‡‡	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	300		276		287		609		3,830	
with one or more adverse events	53	(17.7)	148	(53.6)	145	(50.5)	62	(10.2)	509	(13.3)
with no adverse events	247	(82.3)	128	(46.4)	142	(49.5)	547	(89.8)	3,321	(86.7)

The most common drug-related AEs leading to interruption of study intervention were *Neutropenia* (15.9% and 15.3%) and *Thrombocytopenia* (11.6% and 6.6%) in both the Pembrolizumab+Chemotherapy and the Standard Treatment arms. Drug-related *Anaemia* (11.6% vs 4.5%), *Platelet count decreased* (7.6% vs 2.8%), *Neutrophil count decreased* (7.2% vs 5.9%) *White blood cell count decreased* (2.9% vs 1.0%), *Blood creatinine increased* (2.5% vs 0.0%) resulted more often cause of treatment interruption in the Pembrolizumab+Chemotherapy group compared with the Standard treatment group. A higher proportion of participants with drug-related *Infusion-related reaction* (3.5% vs 0.4%), *Nausea* (2.8% vs 0.4%), *Rash* (2.8% vs 0.4%), and *Dermatitis acneiform* (2.8% vs 0.0%) resulted in study intervention interruption in the standard treatment versus the combination group.

In the Pembrolizumab monotherapy arm compared to the Standard Treatment arm, *Pneumonitis* (2.3% vs 0.0%) was the only AE leading to treatment interruption in more than 2% of subjects.

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 4 March 2018 to 3 September 2018.

2.5.1. Discussion on clinical safety

Pembrolizumab+Chemotherapy versus Standard Treatment

Proportions of subjects in the adverse event summary show consistent results in the Pembrolizumab+Chemotherapy and the Standard Treatment study arms for overall AEs (98.2% and 99.7%), drug-related AEs (98.2% and 99.7%), Grade 3-5 AEs (95.3% and 96.9%), Grade 3-5 drug-related AEs (84.8% and 83.6%). Differently, the rates of SAEs (58.7% vs 49.1%) and of drug-related SAEs (37% vs 25.4%), overall deaths (11.6% vs 9.4%), deaths due to drug-related AE (3.6% vs 2.8%), drug discontinuation due to AE (30.8% vs 27.2%), drug discontinuation due to drug-related AE (22.8% vs 19.9%), drug discontinuation due to SAE (19.6% vs 11%), and drug discontinuation due to drug-related SAE (11.2% vs 3.8%) were increased in subjects treated with the pembrolizumab combination treatment than in those receiving standard of care. After adjusting for exposure and including multiple occurrence of events, the higher incidence rates in SAEs (179 vs 158/100 person-years) and in drug-related SAEs (86 vs 69/100 person-years) among subjects receiving Pembrolizumab+Chemotherapy in respect to those treated with Standard Treatment were confirmed.

In the Pembrolizumab+Chemotherapy and the Standard Treatment arms, the pattern and frequency of most common AEs were similar and consistent with that expected for platinum-based chemotherapy. Pembrolizumab+Chemotherapy compared favourably to chemotherapy in skin-related AEs, Hypomagnesaemia, and Hypokalaemia. This is consistent with the known toxicity profile of cetuximab, used in the control arm. The standard treatment was of advantage for Anaemia, Hypothyroidism, and Blood creatinine increased. Other AEs with a higher incidence in the pembrolizumab chemotherapy group compared to the standard treatment group were acute kidney injury (6.5% versus 3.1%), peripheral neuropathy (5.8% versus 2.8%), peripheral sensory neuropathy (5.8% versus 2.4%) and paraesthesia (4.0% versus 2.8%).

The overall proportion of Grade 3-5 AEs (84.8% and 83.6%) as well as exposure-adjusted incidence rates (238 and 289/100 p-y) were comparable among the Pembrolizumab+Chemotherapy and the standard treatment datasets. When adjusted for exposure, rates of Grade 3 to 5 events, stomatitis and mucosal inflammation were higher (events/100 person-years) in subjects on pembrolizumab plus chemotherapy compared to subjects on standard treatment, 13.1 versus 6.6 and 15.7 versus 8.9, respectively.

The incidence of drug-related AEs was comparable in the two arms (95.3% vs 96.9%). Drug-related AEs more frequently reported in the pembrolizumab-combination arm when compared to Standard Treatment were: Anaemia (48.2% vs 41.1%), Thrombocytopenia (27.2% vs 22.0%), Hypothyroidism (12.7% vs 0.3%), Blood creatinine increased (10.9% vs 5.2%), Peripheral sensory neuropathy (5.4% vs 2.1%), Malaise (6.5% 3.1%), and Acute kidney injury (5.4% vs 2.1%). On the contrary, chemotherapy-treated subjects compared to those receiving pembro combo treatment displayed an increased frequency of various skin -related PTs (e.g. *Rash* 35.2% vs 8.0%), electrolyte alterations, and infusion-related reactions.

Proportions of subjects with Grade 3-5 drug-related AEs and median time to first event were comparable in the Pembrolizumab+Chemotherapy and the Standard Treatment (71.0% and 69.0%) datasets. In the pembrolizumab combination arm, *Acute kidney injury* (4 patients, 1.4%) and *Septic shock* (6 patients,

2.2%) were reported more often than in the standard treatment arm (0.3% and 0.0%, respectively).

Incidences of SAEs and exposure-adjusted SAE rates were higher in the pembrolizumab plus chemotherapy group than in the standard treatment group (58.7% and 179.40 events/100 person-years, respectively, versus 49.1% and 158.49 events/100person-years). Febrile neutropenia (5.8% vs 4.9%), Pneumonia (5.4% vs 6.3%), Anaemia (5.1% vs 3.1%), and Lung infection (3.3% vs 0.7%) were the most commonly observed SAEs in the pembrolizumab combination arm. Incidences of drug-related SAEs were higher in pembrolizumab-treated subjects (37.0% versus 25.4%). The most frequently reported drug-related SAEs (≥2.0% incidence) in the pembrolizumab plus chemotherapy group were febrile Neutropenia (5.1%), Anaemia (4.0%), Stomatitis (2.9%), Neutropenia (2.5%), Mucosal inflammation, Nausea, Septic shock and Thrombocytopenia (2.2% each) in the pembrolizumab plus chemotherapy group.

There were few more deaths due to AEs in the Pembrolizumab+Chemotherapy arm than in the Standard Treatment arm [11.6% (32 patients) vs 9.4% (27 patients)]. When adjusted for exposure, event rates were similar (16.79 versus 16.68 events/100 person-years).

Drug-related AEs leading to treatment discontinuation (22.8% and 19.9%) or interruption (53.6% and 50.5%) were equally frequent among the Pembrolizumab+Chemotherapy and the Chemotherapy arms.

Based on the overall data provided, a concern was raised regarding the renal toxicity of pembrolizumab in combination with chemotherapy, in particular related to higher frequencies of blood creatinine increased, Acute kidney injury and Acute renal failure in the pembro combo arm compared to standard chemotherapy. Review of renal toxicity by SMQ showed in participants treated with pembrolizumab+chemotherapy compared to subjects receiving standard of care, higher proportions of overall Renal AEs (27.9% vs 19.5%, respectively) as well as of all related AE categories. When stratifying for type of platinum compound, differences between combination treatment and standard of care were larger in participants treated with cisplatin than in those with carboplatin. No baseline factor predictive of renal toxicity was identified, but average time to onset was longer for the pembrolizumab+chemotherapy arm in comparison to the cetuximab+chemotherapy arm, leading to the hypothesis of a diverse etiopathogenesis (proximal tubule cell toxicity vs immune-mediated). In light of the above described findings, the MAH was requested to provide more detailed information for renal toxicity events with unfavourable outcome (not resolved or resolved with sequelae) [data not shown]. Overall, the proportion of subjects with renal toxicity were higher in patients treated with pembrolizumab+cisplatin (14/119; 11.8%) or with pembrolizumab+carboplatin (9/197; 4.5%) when compared to those receiving cetuximab+carboplatin (6/202; 2.9%) or cetuximab+cisplatin (3/120; 2.5%). However, when looking at exposure-adjusted incidences the difference between treatment arms was small. Among subjects with unfavourable renal events, the vast majority reported non-immune-related events (none was treated with corticosteroids) and had events of mild to moderate grade in maximum toxicity. Further, a similar proportion of subjects among treatment arms received subsequent antineoplastic treatment, and generally the cause of death was not due to renal events. Thus, it is agreed with the MAH that evidences are insufficient to support changes to the SmPC.

Regarding the safety profile of the pembrolizumab combination treatment in relation to type of chemotherapy used (cisplatin/carboplatin), also within each platinum compound strata a higher proportion of SAEs (Carboplatin: 51.3% vs 43.6%; Cisplatin: 61.3% vs 45.8%) and of drug-related SAEs (Carboplatin: 26.4% vs 15.8%; Cisplatin: 45.5% vs 35.0%) are found in the Pembrolizumab+Chemotherapy in respect to Standard of Care group. Furthermore, regardless of pembrolizumab use, almost all AEs frequencies were higher in subjects treated with pembrolizumab-cisplatin than in those receiving pembrolizumab-carboplatin. As these findings seem to reflect known tolerability differences between platinum agents and due to limitations (a priori investigator's selection of chemotherapeutic agent, limited sample size, and post hoc analysis), no

definitive conclusions can be drawn on pembrolizumab's safety when combined with different chemotherapeutic agent.

Pembrolizumab monotherapy versus Standard Treatment

In the adverse event summary, although the proportion of patients who experienced AEs was similar in pembro mono vs the control arm, the pembrolizumab monotherapy arm showed lower rates of almost all AE categories. Adverse Event rates adjusted for exposure confirmed the favourable safety profile of pembrolizumab monotherapy compared to chemotherapy.

In the pembrolizumab monotherapy arm, most common AEs with incidence ≥20% were Fatigue (27.7% vs 35.5%) and Anaemia (21.0% vs 46.0%). A clear advantage of pembro mono over standard treatment is seen for most the AEs with exception of Hypothyroidism, as already expected for pembrolizumab.

The proportion of Grade 3-5 AEs was considerably lower in the Pembrolizumab monotherapy dataset compared with in the Standard Treatment (54.0% versus 83.6%, respectively). The most common Grade 3-5 AEs in the Pembrolizumab monotherapy dataset (>5% incidence) were Hyponatremia (5.7%) and Pneumonia (5.3%), whereas Neutropenia, Anaemia, and Neutrophil count decreased were the most commonly reported events in the Standard Treatment dataset (>10% incidence). Exposure-adjusted rates (34.33 and 265.74/100 p-y) confirmed the better safety profile of Pembrolizumab monotherapy compared to Standard Treatment.

Frequency of drug-related AEs (58.3% vs 96.9%) and Grade 3-5 drug-related AEs (16.7% vs 69%) was clearly lower for Pembrolizumab monotherapy in respect to standard treatment. The most common drug-related AEs recorded with pembrolizumab were Hyponatraemia (5.7%) and Pneumonia (5.3%). However, with the exception of Hypothyroidism (13% vs 0.3%), overall single drug-related AEs were more frequently observed with chemotherapy than with pembrolizumab; all hypothyroidism events were grade 1-2. Few more events of grade 3-5 drug-related pneumonitis were reported in pembrolizumab-treated patients [1.3% (4 cases) vs 0.3% (1 case)]. Median time to first Grade 3-5 drug-related AE was considerably longer in the Pembrolizumab monotherapy arm in respect to the Standard Treatment arm (62.5 vs 22 days).

Both SAEs (40.3% vs 49.1%) and drug-related SAEs (9.0% versus 25.4%), were less common in the Pembrolizumab monotherapy arm when compared to the Standard Treatment arm. The most common drug-related SAEs in the pembrolizumab monotherapy arm were *pneumonitis* (1%, 3 patients) and *acute kidney injury* (0.7%, 2 patients). Both events occurred in only 1 patient each in the SOC arm (0.3%).

AEs resulting in death were less frequently observed in participants assigned to the Pembrolizumab monotherapy arm when compared to standard treatment [8.3% (25 patients) vs 9.4% (27 patients)]. The most common SOC was *Infections* (3.0% vs 4.5%), with *Sepsis* (1.0% vs 0.7%) as the most common PT in the pembro arm, and *Pneumonia* (1.7% vs 2.1%) the most common PT in the chemotherapy arm. Three fatal events were classified as due to pembrolizumab-related AEs by the investigator (*Pneumonitis, disseminated intravascular coagulation (DIC)* and *autoinflammatory disease*). The MAH will continue monitoring of DIC cases through routine pharmacovigilance activities in clinical studies and the post-marketing environment.

With regard to the event "autoinflammatory disease", this occurred in a subject after 1 cycle of pembrolizumab. In this complex case, the subject experienced also a grade 3 encephalitis, considered a treatment related AEOSI by the MAH (already included as ADR in Keytruda SmPC), and a possible diagnosis of Hemophagocytic lymphohistiocytosis (HLH). The risk of HLH has been added to the list of ADRs in section 4.8 of the SmPC with the frequency of "rare" following the most recent PSUR procedure (EMEA/H/C/PSUSA/00010403/201809, CHMP opinion adopted on 28 March 2019).

Drug-related AEs leading to treatment discontinuation (4.7% versus 19.9%) were less frequent in the

Pembrolizumab monotherapy arm if compared to standard of care and most common PTs were *Pneumonitis* and *Autoimmune hepatitis* reported in 0.7% (2 patients) each. Both events are known ADR for pembrolizumab. Drug-related AEs leading to treatment interruption mirrored the same finding: Pembrolizumab monotherapy 17.7% versus Standard Treatment 50.5%.

AEOSIs

Frequency of overall AEOSIs, SAEs and deaths due to AEOSIs were not noticeably dissimilar among KEYNOTE-048 arms. Type and frequency of specific AEOSIs were consistent with known safety profiles, showing as most common events Hypothyroidism (15.2% and 18.0% in pembro combo and pembro mono, respectively), Pneumonitis (5.4% and 6.0%), and Hyperthyroidism (4.7% and 2.7%).

Drug-related hypothyroidism occurred in approximately 13% of pembrolizumab-treated subjects regardless whether chemotherapy was given in association. Male gender and prior radiation therapy were more frequently observed in subjects experiencing this event. With the exception of a slightly shorter median time to onset of hypothyroidism in patients receiving pembro combo compared to pembro mono (83 and 104 days, respectively), overall the addition of chemotherapy to pembrolizumab did not change the pattern of hypothyroidism in HNSCC. As seen in the HNSCC pembro monotherapy RSD, in KEYNOTE-048 study the higher incidence of this AEOSI in the HNSCC setting compared to other disease site is confirmed and this has been reflected in section 4.8 of the SmPC.

Incidences of *Pneumonitis* were higher in the pembrolizumab monotherapy and pembrolizumab plus chemotherapy groups (6.0% and 5.4%) compared to the standard treatment group (1.0%) in study KN048. These incidences were also higher when compared to the pembrolizumab monotherapy HNSCC and RSD datasets (3.8% and 3.7%, respectively). The frequency of pneumonitis was higher in the pembrolizumab and the pembro combo arm in participants that had prior radiation (general). Numbers of participants with explicit prior radiation to the lung were far too small, 8 of 863, to be meaningful. Radiation of advanced HNSCC may involve intrathoracic radiation, which is associated with a risk of pneumonitis. Thus, the higher frequency of pneumonitis recorded in participants with prior radiation is considered to be in line with the observed increases of pneumonitis events after prior thoracic radiation across several other indications (also reflected in section 4.8. of the SmPC). Considering the overall data for KN048, a special wording with regard to the frequencies of pneumonitis in HNSCC is not warranted (updated frequency of pneumonitis in SmPC now 4.3%).

Other events

Facial oedema (Face oedema and Swelling face) occurred with higher rates in the Pembrolizumab monotherapy arm (pembro mono 6.0%, pembro combo 3.6%, standard treatment 3.1%), although comparable with the HNSCC pembrolizumab monotherapy dataset (7.2%). Severity was Grade 1-2 in most cases.

The proportion of participants with events of Bleeding from the tumour site was higher in the Pembrolizumab+Chemotherapy (8.7%) and Pembrolizumab monotherapy (6.3%) datasets in comparison with Standard treatment (5.6%) arm. Monitoring of fatal hemorrhages through routine pharmacovigilance activities in clinical studies and the post-marketing environment is recommended.

Airway obstruction events with dyspnea occurred rarely but were more common in pembrolizumab-based treatments [1% (3 patients) in Pembrolizumab monotherapy, 0.7% (2 patients) in Pembrolizumab+Chemotherapy]) than in Standard Treatment arm (0.3%, 1 patient). Longer time to onset than in standard of care and partial or complete treatment response at the time of event in most subjects are not suggestive of causal relationship with drug exposure.

Laboratory findings

Incidence of most all-grades abnormal laboratory findings was comparable among

Pembrolizumab+Chemotherapy and Standard Treatment arms. Notably however, *Creatinine increased* was more often reported for subjects receiving pembrolizumab combination treatment in respect to standard of care (36% vs 27%, respectively).

When compared to Standard Treatment, while none of the abnormal laboratory findings, except for *Calcium increased*, exceeded in the pembrolizumab monotherapy arm, abnormalities related to myelotoxicity were all strongly reduced (*Haemoglobin decreased* 51.7% vs 78.3%; *Leukocyte decreased* 11.2% vs 74.4%; *Neutrophils decreased* 7.3% vs 71.1%; *Platelets decreased* 11.5% vs 76.3%).

Safety in special populations

Comparison of safety profiles by intrinsic factors, showed enlarging proportions of subjects in both pembrolizumab-containing arms who discontinued treatment, experienced SAEs, and who died with increasing age groups (<65, 65-74, 75-84). Similar observation is made in the control group when considering patients <65 years and between 65-74 years, while no relevant differences are seen between 65-74 and 75-84. This could be related to a more limited number of subjects in the 75-84 class.

Also keeping in mind, the proportions of females enrolled in KEYNOTE-048 study arms (56% pembrolizumab+Chemotherapy, 51% Pembrolizumab monotherapy, 38% Standard Treatment), analysis by Gender showed that female versus male participants of the Pembrolizumab+Chemotherapy arm had higher frequency of Grade 3 to 5 drug-related AEs (78.6% vs 69.1%), SAEs (69.6% vs 55.9%), and drug-related SAEs (42.9% vs 35.5%). The same trend was observed in the standard chemotherapy arm, and not in the Pembrolizumab monotherapy arm, suggesting a contribution of chemotherapy to the observation.

As expected, participants with an ECOG status of 1 displayed a higher proportion of subjects with SAEs and AEs leading to study intervention discontinuations. AEs summary by Region of enrolment did not document significant differences among KEYNOTE-048 study arms.

Comparison of KEYNOTE-048 study with pooled datasets

Median duration of exposure was longest in the pembrolizumab plus chemotherapy group (5.78 months), whereas the median duration of exposure was shorter in the pembrolizumab monotherapy group (3.50 months) than in the Reference Safety Dataset (4.71 months), but longer than in the HNSCC Safety Dataset (2.83 months). This may reflect the progression of disease in subjects treated second-line for HNSCC, and the different indications in the RSD.

While frequency of overall AEs was comparable across datasets, proportions of all other AE categories in the Pembrolizumab+Chemotherapy arm, being comparable to those of the Chemotherapy arm, were higher than in pooled datasets. Drug-related AEs were 95.3% in Pembrolizumab+Chemotherapy and lower in the Pembrolizumab monotherapy RSD (71.8%) and HNSCC pembrolizumab monotherapy (63.5%) datasets. Incidence and pattern of common drug-related AEs reported for the Pembrolizumab+Chemotherapy arm differed from those found for pooled pembrolizumab datasets. Most common drug-related AEs observed in the KEYNOTE-048 Pembrolizumab monotherapy arm were similar to the Pembrolizumab monotherapy RSD, with the exception of a higher rate of *Hypothyroidism* events (13% vs 8.1%), which instead was consistent with the HNSCC pembrolizumab monotherapy dataset (11.2%).

Overall incidence of drug-related Grade 3 to 5 AEs (71%, 15.1%, and 13.6%) and of drug-related SAEs (37.0%, 10.5%, and 9.9%) was higher in the Pembrolizumab plus Chemotherapy dataset when compared to the Pembrolizumab monotherapy RSD and HNSCC pembrolizumab datasets. In the Pembrolizumab monotherapy dataset, incidences of drug-related Grade 3 to 5 AEs (16.7%) and of drug-related SAEs (9.0%) were similar.

In comparison to the Pembrolizumab monotherapy RSD (4.1%) and HNSCC pembrolizumab

monotherapy (8.9%) datasets, the overall incidence of AEs leading to death was higher in the Pembrolizumab plus Chemotherapy dataset (11.6%). Event frequency was in the Pembrolizumab monotherapy arm (8.3%) higher compared to the Pembrolizumab monotherapy RSD, but comparable to the HNSCC pembrolizumab monotherapy dataset.

Proportions of deaths were higher in the indication R/M HNSCC (KN048 pembrolizumab monotherapy group [8.3%], KN048 pembrolizumab plus chemotherapy group [11.6%] and in the HNSCC Safety Dataset [8.9%]) when compared to the Reference Safety Dataset (4.1%).

2.5.2. Conclusions on clinical safety

In the 1L treatment of subjects with R/M HNSCC, Pembrolizumab+Chemotherapy compared to cetuximab-based chemotherapy showed an overall similar safety profile. The toxicity pattern of the combination pembrolizumab + platinum/5-FU appears consistent with the known safety profile of pembrolizumab monotherapy and the cytotoxic agents used. Of note is the higher incidence of SAEs recorded with pembrolizumab plus chemotherapy compared to standard treatment. SAEs which contributed to the higher overall incidence were distributed across several SOCs with no individual SAE raising special concern. Incidences of Grade 3 to 5 adverse events and of drug-related Grade 3 to 5 AEs were comparable. When adjusted for exposure, hypothyroidism, pyrexia, and blood creatinine increase were higher in the pembrolizumab plus chemotherapy than in the standard treatment group.

The safety profile of pembrolizumab monotherapy in 1L R/M HNSCC is consistent with the established safety profile of pembrolizumab monotherapy in 2L R/M HNSCC and other indications. Pembrolizumab monotherapy for the treatment of 1L R/M HNSCC favourably compared to standard treatment, as expected, taking also into account the known toxicity of the poly-chemotherapy regimen EXTREME used as control.

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 27.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)

Summary of safety concerns	
Missing information	Long term safety

Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities

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 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) -Important potential risks (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT) -Missing information (Long term safety)	Final Study Report	Dec 2019
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT.	Important potential risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	PSUR	2019
Started	Clinical trial A Phase I/II Study of MK-3475 in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma (KN021)	To determine the recommended Phase II dose for MK-3475 in combination with chemotherapy or immunotherapy in subjects with unresectable or metastatic NSCLC.	-Important identified risks (Immune-related adverse reactions) -Important potential risk (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Apr 2020
Started	Clinical Trial A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KN189)	To evaluate the antitumour activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy and to evaluate the antitumour activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy	-Important identified risks (Immune-related adverse reactions) -Important potential risk (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Jun 2021

On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
		using OS.			

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trials (KN087, KN204).
GVHD after pembrolizumab	Routine risk minimisation measures:	Routine pharmacovigilance activities

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
administration in patients with a history of allogeneic SCT	▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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.
Missing Information		
Long term safety	No risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing MAH-sponsored clinical trial in NSCLC (KN042) for pembrolizumab

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning with regard to the higher frequency of ADRs reported with pembrolizumab in combination with chemotherapy compared to pembrolizumab monotherapy or chemotherapy alone has been added to the product information together with a recommendation to consider available treatment options before initiating treatment. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The only change in the leaflet is the addition of one paragraph regarding the combination products in section 1 "What KEYTRUDA is and what it is used for". There are no other proposed changes to the content of the package leaflet; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Head and neck cancers describe an anatomically heterogeneous group of cancers characterized by an aggressive behaviour and very high mortality rate, usually with squamous histology (i.e. HNSCC), and overall accounting for 6% of cancer cases. Median age of diagnosis is in the late 60s and 70s, prevalently

in male. Tobacco, alcohol, male gender and older age are considered risk factors for HNSCC, together with HPV infection for cancers located in the oropharynx.

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, with median survival of 10-14 months. In clinical practice, other combinations, such as a taxane or cisplatin plus cetuximab, are also sometimes used when patients are not fit enough for the EXTREME regimen. For patients who are asymptomatic, treatment is usually monotherapy to balance the side-effects recorded with combination regimens. Options for first-line single agent treatment include platinum-based chemotherapy, 5-FU, paclitaxel, docetaxel, methotrexate, cetuximab, gemcitabine and capecitabine.

In the EXTREME study, the addition of cetuximab to cisplatin/carboplatin plus 5 FU resulted in a significant increase in OS compared to cisplatin/carboplatin plus 5 FU (10.1 months versus 7.4 months, respectively, HR of 0.80, 95% CI: 0.64, 0.99; p=0.04). The cetuximab combination regimen was associated with a frequency of Grade 3 to 4 AEs comparable to the comparator regimen (82% versus 76%, p=0.19, respectively). The EXTREME regimen is the only Category 1 evidence-supported combination regimen recommended by NCCN as 1L treatment for subjects with R/M HNSCC. The EHNS-ESMO-ESTRO Clinical Practice Guidelines also recommend the 1L option of cetuximab with carboplatin or cisplatin plus 5-FU.

Although the EXTREME study resulted in an improved OS, it is still palliative, as the disease remains incurable, and newer therapeutic options are necessary to address the unmet medical needs of this incurable population of R/M HNSCC patients with poor prognosis.

3.1.3. Main clinical studies

The evidence submitted for the new indication is KEYNOTE-048, a randomized, multi-centre, open-label trial investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC.

3.2. Favourable effects

Pembrolizumab plus platinum/5FU:

Statistically significant OS superiority was demonstrated for pembro combo vs control in all the 3 pre-specified populations: ITT: HR 0.72 (0.60, 0.87); median OS 13.0 vs 10.7 months; CPS≥1: HR 0.65 (0.53, 0.80); median OS 13.6 vs 10.4 months and CPS≥20: HR 0.60 (0.45, 0.82); median OS 14.7 vs 11 months.

In the CPS<20 and CPS≥1 to <20 populations, OS results were slightly in favour of Pembro Combo with, respectively, a median OS of 11.8 months vs 10.2 months (HR 0.83 [95%CI: 0.65, 1.05]) and median OS 12.7 months vs 9.9 months (HR 0.71 [95%CI: 0.54, 0.94]).

For the CPS ≥ 1 population, median PFS was 5.1 vs 5.0 months in Pembro Combo vs standard arm (HR=0.84, 95% CI: 0.69, 1.02. In the ITT PFS rates at 6 months were similar in both arms, while PFS rates at 9 and 12 months were in favour of Pembro Combo. In the CPS ≥1 and CPS ≥20 populations PFS rates at 6, 9 and 12 months were in favour of Pembro Combo.

In the CPS ≥1 population, ORR was 36% in both arms. In the ITT, CPS ≥1 and CPS ≥20 populations, a higher CR rate was observed. Median DOR and higher proportion of responders ≥6 months observed in Pembro Combo arm in the ITT, CPS ≥1 and CPS ≥20 populations.

Pembrolizumab monotherapy:

OS was non-inferior for Pembro Mono compared to standard treatment in the ITT population (HR=0.83, 95% CI: 0.70, 0.99). OS rate at 12 months was 48.7% vs 44.4%.

In the CPS≥1 population, statistically significant OS benefit for the Pembro Mono was shown with median OS 12.3 months (95% CI: 10.8, 14.3) versus 10.3 months (95% CI: 9.0, 11.5). The HR was 0.74 (95% CI: 0.61, 0.90). OS rate at 12 months was 50.4% versus 43.6%. OS rate at 24 months was 28.9% versus 17.4%. Median response duration was longer in the Pembro Mono arm compared to standard treatment (22.6 vs 4.5 months) in the ITT, (23.4 vs 4.5 months) CPS≥1 and (22.6 vs 4.2 months) CPS≥20 populations, with higher proportion of long (≥6 months) responders (ITT: 77.8% vs 38.8% of those with a response).

3.3. Uncertainties and limitations about favourable effects

Pembrolizumab plus platinum/5FU:

In the CPS<1 population, no OS benefit was observed. Compared to the IA2, OS results seem to worsen with longer follow-up at the final analysis (median OS of 11.3 vs 10.7 months; at the final analysis OS HR=1.21, 95%CI: 0.76, 1.94; OS rate at 12 months 41.0% vs 46.5%, OS rate at 24 months 20.5% vs 25.6% in favour of the standard arm.

There was no statistically significant improvement in PFS in the ITT or CPS ≥20 populations, therefore, PFS in the CPS ≥1 population was not tested as per the multiplicity strategy. For the CPS<1, CPS≥1 to <20 and CPS<20 populations, no PFS benefit was observed (HR 1.46, HR 0.93 and HR 1.05, respectively).

A slightly higher rate of PD was observed in the Pembro Combo for the ITT (17.1% vs 11.9%), CPS ≥ 1 (17.4% vs 12.3%) and CPS ≥ 20 (15.1% vs 8.2%) populations. In the CPS<20, CPS≥1 to <20, CPS<1 populations, ORR was lower in the Pembro Combo arm compared to standard treatment. For the CPS<1 population, the median duration of response was higher in the Pembro Combo arm, however the estimated response duration ≥6 months was lower in the Pembro Combo compared to standard.

As a consequence of these results the indication was restricted to patients with CPS≥ 1.

Pembrolizumab monotherapy:

Pembro mono did not show statistical superiority on OS in the ITT population, but was associated with a higher risk of early death compared to standard treatment as reflected in the KM curves crossing at month 8. Although OS was statistically significant in the PD-L1 expressing populations (CPS≥1 and CPS≥20), a higher risk of early death during the first 6 months after randomization was confirmed / also seen in this subset of pembro mono treated patients, compared to patients receiving EXTREME.

At the moment no specific recommendation can be included in the SmPC, since consistency of results obtained from different studies is needed to make the results strong and convincing. OS and all efficacy results were in favour of standard treatment in the CPS<1 population. The pembro mono indication was therefore restricted to CPS≥1.

For all populations, PFS results were in favour of standard treatment. The ORR was lower in the Pembro Mono arm compared to standard treatment in the ITT, CPS<1, CPS≥1 to <20 and CPS<20 populations. The median duration of response of pembro mono was shorter for the CPS<1.

Both pembrolizumab combo and mono:

No direct comparison was performed between pembrolizumab when used as monotherapy or in combination with chemotherapy. Appropriate information to help physicians in the choice among the two alternative treatments has been included in sections 4.4 and 5.1 of the SmPC.

The availability of only limited data on patients over 75 years has been reflected in the SmPC.

3.4. Unfavourable effects

Pembrolizumab plus platinum/5FU:

Pembrolizumab combination showed an overall comparable safety profile with the SOC, with higher incidence of SAE (both all causality and drug-related), AE (both all causality and drug related) leading to deaths and leading to drug discontinuation in the pembrolizumab combination arm compared to chemotherapy alone. Such trend was confirmed in the exposure-adjusted analysis for all SAEs and drug-related SAEs.

Most common AEs were Anaemia (58.3% vs 46.7%), Nausea (51.1% vs 51.2%), Constipation (37% vs 33.1%), Fatigue (34.4% vs 35.5%), Neutropenia (33.7% vs 32.8%), Vomiting (32.6% vs 27.9%), and Mucosal inflammation (30.8% vs 28.2%).

Higher incidence of hypothyroidism, anaemia and blood creatinine increase was seen in the pembro combo arm vs control. When adjusted for exposure, hypothyroidism, pyrexia, and blood creatinine increase were higher in the pembrolizumab plus chemotherapy than in the standard treatment group. On the contrary, increased frequency of skin-related AEs, electrolyte alterations, and infusion-related reactions was observed with standard treatment vs pembro combo, consistent with the known toxicities of cetuximab included in the control regimen.

Pembrolizumab monotherapy:

A favourable safety profile of pembrolizumab monotherapy as compared to the EXTREME regime was demonstrated, with the exception of hypothyroidism (reflected in the SmPC).

3.5. Uncertainties and limitations about unfavourable effects

The interpretation of safety data in the age group ≥75 years is limited by the low number of elderly subjects included in the ASaT population (15 in pembro combo and 16 subjects in pembro mono group).

3.6. Effects Table

Table 114: Effects Table for Keytruda in 1L R/M HNSCC (KEYNOTE-048, OS from Final analysis data cut-off: 25 Feb 2019)

Effect	Short description	unit treatment control	Uncertainties / Strength of evidence	Ref
Favourable Effects				
Pembrolizumab + cisplatin/carboplatin + 5-FU				
OS (ITT)	Time from randomization to death due to any cause	HR=0.72 (0.60, 0.87)	Dual primary endpoints. ITT, CPS≥1 and CPS≥20: Statistically significant superiority. *Exploratory subgroup CPS<1*	CSR
OS (CPS≥1)		HR=0.65 (0.53, 0.80)		
OS (CPS<1)		*HR=1.21 (0.76, 1.94)*		
PFS (ITT)	Time from randomization to first PD (based on BICR) or death due to any cause	HR=0.93 (0.78, 1.11)	Dual primary endpoints. PFS not statistically significant in all populations; Similar PFS rate in ITT at 6 months, higher PFS rates at 9, 12 months, higher PFS rates at 6, 9 and 12 months in CPS ⩾ 1 and CPS ⩾20, but not inCPS<1	
PFS (CPS≥1)		HR=0.84 (0.69, 1.02)		
PFS (CPS<1)		*HR=1.46 (0.93, 2.30)*		
Pembrolizumab				

Effect	Short description	unit	treatment	control	Uncertainties / Strength of evidence	Ref
OS (ITT)	Time from randomization to death due to any cause	HR=0.83 (0.70, 0.99)			OS in ITT non-inferior (but not statistically superior) Crossing KM survival curves at months 7-8 with early favourable OS effect for standard treatment OS in CPS≥1 statistically significant	CSR
OS (CPS≥1)		HR=0.74 (0.61, 0.90)				
OS (CPS<1)		*HR=1.51 (0.96, 2.37)*				
Unfavourable Effects						
		P+C	P	C		
Drug-related anaemia	%	48.2	4	41.1	No new safety concerns with pembrolizumab treatment were identified in 1L R/M HNSCC	
Drug-related nausea		44.9	4	45.6		
Drug-related neutropenia		33	1	31.4		
Drug-related hypothyroidism		12.7	13	0.3		
Drug-related G3-5 AEs		71	16.7	69		
Drug-related SAE		37	9	25.4		
Drug-related deaths		3.6	1	2.8		

Abbreviations: OS: overall survival; PFS: progression free survival; ORR: objective response rate; CR: complete response; PR: partial response; DOR: duration of response; CPS: combined positive score; ITT: intention to treat; HNSCC: head and neck squamous cell carcinoma; R/M: recurrent/metastatic; CSR: clinical study report; AE: adverse event; P+C= pembrolizumab + chemotherapy; P= pembrolizumab; C=control

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pembrolizumab plus platinum/5FU:

When cetuximab is replaced by pembrolizumab in the association with platinum/5FU for the 1L treatment of R/M HNSCC, a statistically significant advantage in overall survival is seen in the ITT population at the final analysis. KM OS curves are overlapping up to month 8, but reassuringly a crossing is not visually apparent. Lack of PFS and ORR advantages does not fully support the positive OS trend, but there is some advantage in duration of response for pembro combo vs standard treatment.

The benefit of the pembrolizumab combination over EXTREME regimen appear more pronounced the higher the PD-L1 expression by CPS score is (of the ITT population, about 85% of subjects had CPS≥1 score and 42% were CPS≥20). In both populations, a statistically significant advantage in OS was reached. Overall, imbalances observed between treatment arms in the two populations CPS≥1 and CPS≥20 had no relevant impact on the treatment HR estimates. However, although acknowledging the small sample size of an exploratory subgroup for which the study was not powered, concern is raised by the absence of an observable OS improvement / negative results in the exploratory CPS<1 subgroup (15% of the ITT population). OS worsened in CPS<1 population with longer follow-up from the IA2 to the FA. In addition, inferior PFS and ORR results, together with no DOR advantage were observed. The lack of biological plausibility of using pembrolizumab in PD-L1 negative patients and the negative results of pembrolizumab monotherapy and combination therapy in CPS<1 subjects, do not satisfactorily support the substitution of cetuximab with pembrolizumab in combination with platinum/5-FU chemotherapy, representing a potentially less active combination, with no clear advantage in terms of tolerability.

Toxicity of both experimental and control arms appears substantial. The safety profile of pembro combo is overall consistent with the known toxic effects of each agent used in the combination. While lacking of

the typical AEs associated with cetuximab, the pembro combo arm appears characterized by a higher incidence of hypothyroidism (known ADR of pembrolizumab), as well as pyrexia and renal toxicity.

Pembrolizumab monotherapy:

Pembrolizumab monotherapy, although statistically non-inferior to the EXTREME regimen, demonstrated a detrimental effect during the first 8 months from randomization, and a small OS benefit afterwards. During the procedure, the MAH restricted the sought indication of pembrolizumab monotherapy from all patients to those whose tumour express PD-L1 with CPS≥1 score. A statistically significant OS benefit was observed in the CPS≥1 and CPS≥20 populations. Nevertheless, crossing survival curves in the PD-L1 expressing patients (more pronounced in CPS≥1) display that OS is in favour of standard treatment during the first 7-8 months. Only in patients surviving longer than 7-8 months, OS rates favour Pembro Mono at months 12 and 18. The higher risk of death within 6 months from randomization in subjects treated with pembro mono vs standard treatment was confirmed. In the CPS >1 to <20 population, the number of subjects who died from PD in the first 6 months of treatment was double in pembro mono compared to control. However, at the moment no specific recommendation can be included in the SmPC, since consistency of results obtained from different studies is needed to make the results strong and convincing. PFS failed to show improvement, and ORR was lower in pembrolizumab-treated patients, although the patients who respond showed considerably higher chance to have durable response.

As expected, the safety profile of pembrolizumab monotherapy compares favourably with the toxicity of the EXTREME regimen.

3.7.2. Balance of benefits and risks

For the pembrolizumab combination, acknowledging the small sample size of the exploratory subgroup of PD-L1 CPS<1, for which the study was not powered, the lack of biological plausibility in using pembrolizumab in negative PD-L1 disease, together with the overall similar/slightly inferior results in CPS<1 population for pembrolizumab combination over EXTREME, do not satisfactorily support the substitution of cetuximab with pembrolizumab in combination with platinum/5-FU chemotherapy, which represent a potentially less active combination, with no clear advantage in terms of tolerability. In patients whose disease expresses PD-L1 with CPS score ≥1, the B/R of pembrolizumab when used in combination with platinum/5-FU chemotherapy is favourable since the survival benefits outweighed the risk in this population with dismal prognosis.

For pembrolizumab monotherapy, an indication restricted to CPS≥1 patients is considered acceptable.

3.8. Conclusions

The overall B/R of pembrolizumab as monotherapy and in combination with platinum/5-FU chemotherapy for the first line treatment of R/M HNSCC PD-L1 expressing CPS⩾1 is positive.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication to include, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose disease expresses PD-L1 with CPS score ≥1, based on the results from KEYNOTE-048, a randomized, multi-centre, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line metastatic or unresectable recurrent HNSCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated version of the RMP (Version 27.0) has also been agreed.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose disease expresses PD-L1 with CPS score ≥1, based on the results from KEYNOTE-048, a randomized, multi-centre, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line metastatic or unresectable recurrent HNSCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated version of the RMP (Version 27.0) has also been agreed.

Summary

Please refer to the Scientific Discussion Keytruda-EMEA-H-C-3820-II-0065.