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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

PEMBROLIZUMAB (KEYTRUDA)

(Merck Canada)

Indication: For the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.

For the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

1L	First line
2L	Second line
5-FU	5-fluorouracil
AE	Adverse event
ANC	Absolute neutrophil count
ALT	Alanin aminotransferase
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
AUC	Area under the curve
BICR	Blind independent central review
CCI	Cross Cancer Institute
CCO	Cancer Care Ontario
CET	Cetuximab
CET-chemo	Cetuximab plus cisplatin and 5-fluoruracil
CGP	Clinical Guidance Panel
CNS	Central nervous system
CPS	Combined Positive Score
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DIC	Difference Information Criterion
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECOG QLQ-C30	Eastern Cooperative Oncology Group quality of life questionnaire of cancer patients
ECOG QLQ H&N35	Eastern Cooperative Oncology Group quality of life questionnaire module for head and neck cancer
EGFR	Epidermal growth factor receptor
EPAR	European public assessment report
EQ-5D	EuroQol 5-dimension
FA	Final analysis
FAS	Full Analysis Set
FU	Fluorouracil
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
HRQoL	Health related quality of life
IA1	Interim analysis 1
IA2	Interim analysis 2
INR	International normalized ratio
ITC	Indirect treatment comparison

ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan Meier
LS	Least squares
LSTN	Life Saving Therapies Network
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NMA	Network meta analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	Pan-Canadian Drug Review
PD	Progressive disease
PEMB	Pembrolizumab
PEMB-chemo	Pembrolizumab plus cisplatin and 5-fluoruracil
PEMB mono	Pembrolizumab monotherapy
pERC	pCODR Expert Review Committee
PFS	Progression free survival
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
PD-L1	Programmed death-ligand 1
RCT	Randomized controlled trial
RECIST	Response evaluation criteria in solid tumours
R/M	Relapsed or metastatic
RSMT	Restricted mean survival time
SAE	Serious adverse event
SD	Stable disease
SEER	Surveillance, epidemiology, and end results program
SR	Systematic review
TPS	Tumour proportion score
TTD	Time to deterioration
TTFS	Time to failure of strategy
ULN	Upper limit of normal
VAS	Visual analog scale
WDAE	Withdrawal due to adverse event

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pembrolizumab (KEYTRUDA) for head and neck squamous cell carcinoma (HNSCC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of pembrolizumab (Keytruda) for the first-line treatment of metastatic or unresectable recurrent HNSCC both in combination with platinum and fluorouracil (FU) chemotherapy for all patients, and as monotherapy for patients who tumours have PD-L1 expression CPS ≥ 1.

Health Canada has issued market authorization, without conditions, for pembrolizumab for:

- First-line treatment of metastatic or unresectable recurrent HNSCC as monotherapy, in adult patients whose tumours have PD-L1 expression [Combined Positive Score (CPS) ≥ 1] as determined by a validated test, and
- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

The Health Canada indication aligns with the CADTH requested reimbursement criteria.

Pembrolizumab is a selective humanized monoclonal antibody that enhances immune system detection of tumours and facilitates tumour regression via the programmed cell death receptor 1 (PD-1) pathway. The Health Canada recommended dose is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression. When pembrolizumab is given in combination with chemotherapy, pembrolizumab should be given prior to chemotherapy when given on the same day.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

A single trial, KEYNOTE-048, met the inclusion criteria for the systematic review. KEYNOTE-048 is an ongoing, international, phase 3, open-label, three-arm, randomized trial of pembrolizumab monotherapy (PEMB-mono) or pembrolizumab plus platinum chemotherapy plus 5-fluorouracil (PEMB-chemo) compared with cetuximab plus platinum chemotherapy plus 5-fluorouracil (CET chemo). Platinum chemotherapy for patients receiving either PEMB-chemo or CET-chemo could be either cisplatin or carboplatin, by investigator decision. Patients were eligible if they had pathologically confirmed squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx that was recurrent or metastatic and was not considered curable by local therapies. They could not have received systemic therapy for recurrent/metastatic disease and had to have completed chemotherapy for locoregionally advanced disease at least 6 months before study entry. Patients were to have an ECOG performance status score of 0 or 1 and patients with oropharyngeal cancer had to have known HPV status.

Patients were randomized to the three treatments, with randomization stratified by PD-L1 tumour proportion score (TPS, TPS≥50% versus <50%), ECOG status (0 or 1), and HPV status (yes versus no for oropharyngeal cancers, while other cancers were assumed to be HPV p16-negative). Treatment was given in 21-day cycles. Chemotherapy could be given for six cycles, pembrolizumab for 35 cycles, and cetuximab was not restricted in length. Crossover between treatment arms was not permitted. Patients who had started on cisplatin chemotherapy were allowed to cross over to carboplatin if toxicities occurred and could receive an additional two dose modifications of carboplatin. Patients who had complete response were allowed to discontinue study treatment, and those who had received pembrolizumab had the option to resume treatment upon progression.

Multiple protocol amendments were made in the early stages of the trial, amending the definition of the PD-L1 subgroups of interest and introducing additional hypotheses with a parallel and hierarchical testing scheme. The treatment comparisons are between PEMB-mono and CET-chemo and PEMB-chemo and CET-chemo; there was no comparison between PEMB-mono and PEMB-chemo. The co-primary endpoints are OS and PFS, tested in three populations, ITT, PD-L1 combined proportion score (CPS) ≥1 and PD-L1 CPS≥20. The proportion of patients who are progression-free for 6 and 12 months and overall response rate (ORR) were secondary endpoints, and duration of response (DOR) was an exploratory endpoint. PRO secondary endpoints were mean change from baseline and time to deterioration (TTD) in European Organization for Research and Treatment of Cancer (EORTC) quality of life (QLQ)-C30 global health status/QoL and TTD in pain and swallowing as measured by EORTC QLQ-H&N35. Pre-specified exploratory endpoints were additional analyses of the EORTC QLQ-C30 and EORTC QLQ-H&N35 domains, and health utilities using the EuroQol 5-dimension (EQ-5D).

In total, 882 patients were randomized, 301 to PEMB-mono, 281 to PEMB-chemo, and 300 to CET-chemo. The majority of patients were male (85.0%), White or Asian (73.3% and 18.6%, respectively), and not Hispanic or Latino (77.2%). Most had metastatic disease (69.7%) and tumours with PD-L1 expression (PD-L1 CPS≥1 85.2%). For the ITT and PD-L1 CPS≥1 populations, the balance at baseline was good. For the smaller PD-L1 CPS≥20 population there were larger baseline differences, but sensitivity analyses reported by the sponsor suggest that the impact was minimal.

The trial was open-label but well-conducted, with allocation concealment, objective primary endpoints, and low loss to follow-up. The trial was stratified using PD-L1 TPS, however, biomarker-defined subgroups were later on redefined to be based on PD-L1 CPS rather than PD-L1 TPS, based on external information from other pembrolizumab trials that suggested that CPS was a better predictor of outcome. While the revised definition using PD-L1 CPS may potentially compromise baseline balance, the balance of reported variables was good. Crossover of the survival curves for PEMB-mono versus CET-chemo and divergence of the survival curves for PEMB-mono versus CET-chemo and statistical testing for treatment-time interaction both suggested violation of the proportional hazards assumption. Sensitivity analyses produced findings consistent with the primary analysis.

Table 1 summarizes the key outcomes for the KEYNOTE-048 trial for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the final analysis. For OS in the ITT population, PEMB-mono was non-inferior but not statistically significantly superior to CET-chemo for survival. For OS in both the PD-L1 CPS≥1 and CPS≥20 populations, PEMB-mono was statistically significantly superior to CET-chemo. There was no statistically significant difference between the two treatments for PFS in any of the populations. For OS, PEMB-chemo was statistically significantly superior to CET-chemo in all three populations. There was no statistically significant difference for PFS in any of the populations. Health related quality of life measures showed minimal difference between groups in the comparisons for any of the groups.

A lower proportion of patients who received PEMB-mono had grade 3 to 5 adverse events, SAEs, and discontinuation of any treatment due to an AE, compared with those receiving CET-chemo, with the exception of hypothyroidism. A higher proportion of patients receiving PEMB-chemo experienced SAEs and discontinuation of any treatment due to an AE, compared with CET-chemo, while the proportions of patients with grade 3 to 5 AEs were similar in the two groups. The proportion of patients with AEs leading to death were similar in the three groups.

Limitations:

- Study was open-label, with measures applied to control bias.
- Stratification of randomization was not preserved in the PD-L1 CPS≥1 and PD-L1 CPS≥20 subgroups, as the variable used to stratify randomization PD-L1 TPS was not identical to that used to define the subgroups.

- Survival curves deviated from the proportional hazards assumption that underlies standard methods for survival comparisons, meaning that HRs could be over- or under-estimated. Results of sensitivity analyses were generally consistent with the proportional hazards analysis.
- As a result of ongoing follow-up and low long-term survival in these patients, estimates of long-term effect are imprecise.

Table 1: Highlights of Key Outcomes

	KEYNOTE-048			
	PEMB mono (N = 301)	CET-chemo (N = 300)	PEMB-chemo (N = 281)	CET-chemo (N = 278)
Data cut-off date	February 25, 2019 (Final analysis)			
Median follow-up time, months (range)	11.5 (0.2, 45.7)	10.7 (0.1, 41.8)	13.0 (0.1, 43.4)	10.7 (0.1, 40.7)
ITT population				
OS in months, median	11.5 (10.3, 13.4)	10.7 (9.3, 11.7)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
HR (95%CI)	0.83 (0.70, 0.99)		0.72 (0.60, 0.87)	
p-value	0.01985		0.00025	
PFS in months, median	2.3 (2.2, 3.3)	5.2 (4.9, 6.1)	4.9 (4.7, 6.1)	5.1 (4.9, 6.1)
HR (95% CI)	1.29 (1.09, 1.53)		0.93 (0.78, 1.11)	
p-value	0.9983		0.21211	
ORR (95% CI)	16.9 (12.9, 21.7)	36.0 (30.6, 41.7)	35.6 (30.0, 41.5)	36.3 (30.7, 42.3)
Difference in % versus control	-19.0 (-25.8, -12.1)		-0.8 (-8.7, 7.2)	
PD CPS≥1 population				
OS in months, median	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
HR (95%CI)	0.74 (0.61, 0.90)		0.65 (0.53, 0.80)	
p-value	0.00133		0.00002	
PFS in months, median	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
HR (95%CI)	1.13 (0.94, 1.36)		0.84 (0.69, 1.02)	
p-value	0.8958		0.03697	
ORR (95% CI)	19.1 (14.5, 24.4)	34.9 (29.9, 41.1)	36.4 (30.3, 42.8)	35.7 (29.6, 42.2)
PD CPS≥20 population				
OS in months, median	14.8 (11.5, 20.6)	10.7 (8.8, 12.8)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)
HR (95%CI)	0.58 (0.44, 0.78)		0.60 (0.45, 0.82)	
p-value	0.0001		0.00044	
PFS in months, median	3.4 (3.2, 3.8)	5.3 (4.8, 6.3)	5.8 (4.7, 7.6)	5.3 (4.9, 6.3)
HR (95%CI)	0.99 (0.76, 1.29)		0.84 (0.69, 1.02)	
p-value	0.46791		0.03697	
ORR (95% CI)	23.3 (16.4, 31.4)	36.1 (27.6, 45.3)	42.9 (34.1, 52.0)	38.2 (29.1, 47.9)
HrQoL (PRO FAS population)				
EOTRC QLQ-30 Global health status Change from baseline to Week 15 (95% CI)	0.85 (-1.90, 3.59)	0.60 (-2.19, 3.40)	1.17 (-1.79, 4.12)	0.77 (-2.22, 3.76)
Difference in LS means	0.24 (-3.34, 3.40)		0.40 (-3.46, 4.26)	

	KEYNOTE-048			
Time to deterioration EORTC QLQ-30 Global Health Status	1.38 (0.95, 2.00)		1.37 (0.94, 2.00)	
Time to deterioration EORTC QLQ-H&N35 Pain	0.80 (0.53, 1.21)		1.37 (0.93, 2.02)	
Time to deterioration EORTC QLQ-H&N35 Swallowing	1.26 (0.85, 1.88)		1.05 (0.69, 1.59)	
Harms Outcome, n (%) (ASaT population)	PEMB-mono (N = 300)	CET-chemo (N = 276)	PEMB-chemo (N= 287)	CET-chemo (N= 276)
Patients with one or more drug-related AEs, n (%)	175 (58.3)	278 (96.9)	264 (95.7)	278 (96.9)
Patients with one or more grade 3-5 AEs, n (%)	164 (54.7)	239 (83.3)	235 (85.1)	239 (83.3)
Patients who died due to an AE, n (%)	25 (8.3)	28 (9.8)	32 (11.6)	28 (9.8)
Patients with SAEs	123 (41.0)	141 (49.1)	165 (59.8)	141 (49.1)
Patients who discontinued any drug due to an adverse event, n (%)	36 (12.0)	79 (27.5)	90 (32.6)	79 (27.5)
Patients who discontinued all components			23 (8.3)	26 (9.1)

AE = adverse event, ASaT = All Subjects as Treated, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, PRO FAS = Patient Reported Outcomes Full Analysis Set, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

HR < 1 favours PEMB / PEMB-chemo

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient group, Life Saving Therapies Network (LSTN) provided patient input on pembrolizumab (Keytruda) for the first-line treatment of patients with recurrent or metastatic HNSCC as monotherapy or in combination with platinum and fluorouracil (FU) chemotherapy. LSTN is a network of patients, patient advocacy groups, policy experts, oncologists, health economists, law experts, pharmaceutical industry representatives and federal regulators. LSTN focuses on clinical research reform to facilitate faster access to new therapies, regulatory reform to develop precision treatments and reimbursement reform for the effective treatment of diseases. LSTN solicited patient input from a total of 13 respondents from a variety of means.

Out of the 13 respondents, two survey respondents and one interviewee were treated with pembrolizumab in the first line setting for recurrent or metastatic HNSCC. From a patient perspective, HNSCC can cause a significant physical and emotional impact on the lives of patients. LSTN highlighted that an unmet exists for HNSCC patients in Canada due to limited therapeutic options and lack of community supports. Side-effects of HNSCC reported by patients are pain and discomfort in the head and neck region, difficulty breathing, excessive coughing, difficulty chewing and swallowing meals. Patients expressed great concern about the impact of the disease on their ability to perform their day-today tasks. LSTN also highlighted the social impact of HNSCC as this type of cancer can limit patients' social outings and interactions. Anxiety, depression, panic attacks and fear of recurrence are common complaints reported by patients. Current treatments available for patients with HNSCC include nivolumab, methotrexate, hydroxyurea and docetaxel in combination with cisplatin, and fluorouracil. LSTN commented that these treatments are often associated with significant side-effects that can affect patients' quality of life. Three patients reported having experience with pembrolizumab, all of whom reported a positive experience. These patients did not report any side effects associated with pembrolizumab and noted that it was effective in controlling their cancer. One patient was previously taking cetuximab in combination with radiation therapy. After switching to pembrolizumab, the patient reported that her quality of life had drastically improved and that she was able to continue her daily activities with ease. Additionally, two patients did not have experience with pembrolizumab but reported that they were aware of the treatment and expressed a strong desire to be able to access the drug. Overall, patients value increased effectiveness of treatments, a better side-effect profile and an improvement in quality of life that will enable them to continue their day-to-day tasks while undergoing treatment. LSTN highly supports the reimbursement of pembrolizumab in Canada due to the positive patient experiences and limited availability of effective treatments.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary
Input was obtained from all **nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:
- Place in therapy and sequencing with currently available treatments
- Target population of add-on chemotherapy

Economic factors:
- Clarity on dosing schedule and treatment duration
- Need for PD-L1 testing

Please see below for more details

Registered Clinician Input

A total of three registered clinician inputs were provided for the review of pembrolizumab (Keytruda) for the first-line treatment of patients with recurrent or metastatic HNSCC as monotherapy or in combination with platinum and fluorouracil (FU) chemotherapy: two individual inputs from a clinician from Cross Cancer Institute (CCI), a clinician from the National Cancer Institute (NCI) and one joint input from Cancer Care Ontario (CCO) comprised of two clinicians. All clinicians agreed that pembrolizumab, with or without chemotherapy should be made available for first line treatment for all patients with recurrent or metastatic HNSCC. Patient populations of particular interest are patients with a PD-L1 CPS (combined positive score) < 1 or patients with PD-L1 CPS > 20 The clinicians stated that the decision to add chemotherapy to pembrolizumab depends on the patients' PD-L1 CPS status; patients with PD-L1 CPS > 1 could be treated with PEMB-mono, whereas patients with PD-L1 CPS <1 could be treated with PEMB-chemo. However, the clinicians noted that patient factors such as comorbidities and age should also be taken into consideration when deciding between pembrolizumab alone or PEMB-chemo. All clinicians emphasized the importance of funding for PD-L1 testing, as it can identify patients who are eligible for PEMB-mono, which could minimize toxicity from chemotherapy. Contraindications to pembrolizumab identified by clinicians were patients with severe active autoimmune disorders and those with solid organ transplants. Clinicians described possible sequencing options: if PEMB-mono is prescribed in the first line setting, then the second line option would be platinum-based chemotherapy. If PEMB-chemo is prescribed in the first line, then the second line option would be non-platinum-based chemotherapy. Patients who are ineligible or intolerant to platinum-based therapy may receive either pembrolizumab or nivolumab as there is no evidence to suggest the use of one drug over the other. Clinicians noted that re-treatment with pembrolizumab after reaching the 2-year time-period can be considered; however, they noted that there is limited evidence on re-treatment with pembrolizumab. Although there is currently no evidence to inform the discontinuation of pembrolizumab earlier than the 2-year time-period, the clinicians noted that treatment may be discontinued earlier due to reasons such as toxicity or as per the clinical judgment. Clinicians commented that alternative dosing can be considered but it is preferable to use the same dosing as in the clinical trial.

Summary of Supplemental Questions

The comparator used in the single identified trial (KEYNOTE-048) is CET-chemo. As cetuximab is not broadly available for HNSCC in Canada, current standard of care is represented by platinum doublet chemotherapy, with a minority of patients receiving cetuximab through provincial case-by-case reviews or patient access programs where available. Single agent cisplatin, methotrexate, capecitabine or docetaxel are options considered for patients for whom doublet chemotherapy is not appropriate. A sponsor-provided SR followed by an ITC compared PEMB-mono and PEMB-chemo with other treatments, including platinum doublet chemotherapy.

Thirty-one trials met the systematic review inclusion criteria as studies conducted in the first-line population of patients with metastatic or unresectable recurrent HNSCC, and 23 included patients with at least 6 months between systemic therapy given for locoregional disease. Of these 23, 7 formed a connected network for OS and 3 for PFS, for comparisons with both PEMB-mono and PEMB-chemo. One further study was excluded for OS on account of its age. Available comparators for OS were platinum plus 5-FU, 5-FU, methotrexate, cisplatin, cisplatin plus paclitaxel, CET-chemo, and cetuximab plus platinum plus docetaxel. Available

comparators for PFS were platinum plus 5-FU, CET-chemo, and cetuximab plus platinum plus docetaxel. Two sets of analyses were conducted, using the ITT populations for all trials and using the PD-L1 CPS≥1 population of the KEYNOTE-048 trial with the ITT populations of all other trials, since a PD-L1 selected population was not available.

In the analysis using the ITT population, PEMB-mono had lower hazard of death compared with 5-FU, 5-FU, methotrexate, cisplatin, and CET-chemo after six or nine months. No difference was seen for cisplatin plus paclitaxel (with the exception of one time-point) or cetuximab plus platinum plus docetaxel. In the analysis using the KEYNOTE-048 PD-L1 CPS≥1 population, PEMB-mono had lower hazard of death compared with six comparators from the sixth month on, and for cisplatin plus docetaxel plus cetuximab from the eighteenth month on. In the PFS analyses for both populations, PEMB-mono had lower hazard of progression from six to fifteen months on for all comparisons, but no difference or higher hazard in the early months.

In the analysis using the ITT population, PEMB-chemo had lower hazard of death compared with 5-FU, 5-FU, methotrexate, cisplatin, and CET-chemo after six or nine months, and for early time-points for cisplatin plus paclitaxel and later time-points for cetuximab plus cisplatin plus docetaxel. Results for analyses using the KEYNOTE-048 PD-L1 CPS≥1 population were similar. In the PFS analyses for both populations, PEMB-mono had lower hazard of progression from three to six months on for CET-chemo and platinum plus 5-FU, but not for cetuximab plus cisplatin plus docetaxel.

The SR was well conducted and documented and the NMA used appropriate methods to model survival in the presence of proportional hazards. The NMA had the following limitations: Only a minority of trials could be incorporated into a connected network, and the included comparators did not represent other PD-L1 targeting therapies. The dataset was relatively sparse, meaning that only fixed effects analyses could be conducted and no adjustment done for baseline clinical heterogeneity (ECOG status and recurrent/metastatic) or potential effect modifiers. Data representing the PD-L1 CPS≥1 population were only available for the KEYNOTE-048 trial, so the comparison of that subgroup assumed that the presence of PD-L1 expression would not influence response to comparators. In addition, the stratification factor for PD-L1 expression in KEYNOTE-048 was PD-L1 TPS, which was related to but not the same as the stratification factor for selecting the subgroup, indicating that randomization was not preserved and introducing the potential for bias. Survival data were not mature for all trials, resulting in the need to extrapolate survival, with results for the time-varying analyses that are uncertain and sensitive to model selection. Due to the above limitations, the comparative efficacy estimates obtained may be biased, and it is not possible to quantify or identify the direction of the bias. Results of this NMA must be interpreted with caution.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for PEMB-mono and PEMB-chemo

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Age</td><td>Trial recruited adults, aged ≥ 18 years.

Age distribution comparison of PEMB-mono with CET-chemo, ITT population
<table>
<tr><th>Age</th><th>PEMB-mono N = 300</th><th>CET-chemo N = 301</th></tr>
<tr><td><65 years, n (%)</td><td>190 (63.1)</td><td>195 (65.0)</td></tr>
<tr><td>≥65 years, n (%)</td><td>111 (36.9)</td><td>105 (35.0)</td></tr>
<tr><td>Median, years</td><td>62</td><td>61</td></tr>
<tr><td>Range</td><td>22 to 94</td><td>24 to 84</td></tr>
</table>
Age distribution for the comparison of PEMB-chemo with CET-chemo, ITT population
<table>
<tr><th>Age</th><th>PEMB-chemo N = 281</th><th>CET-chemo N = 278</th></tr>
<tr><td><65 years, n (%)</td><td>180 (64.1)</td><td>181 (65.1)</td></tr>
<tr><td>≥65 years, n (%)</td><td>101 (35.9)</td><td>97 (34.9)</td></tr>
<tr><td>Median, years</td><td>61.0</td><td>61.0</td></tr>
<tr><td>Range</td><td>20 to 85</td><td>24 to 84</td></tr>
</table>
Subgroup analyses were conducted by age group.</td><td>Is this representative of patients in Canadian clinical practice?

Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>The age of the patients recruited to KEYNOTE-048 is representative of a Canadian population. With the increase on HPV associated HNSCC versus carcinogen related exposure the median age is decreasing over time. The restriction to patients over 18 does not influence the interpretation of the trial results with respect to the Canadian population.</td></tr>
<tr><td>Organ dysfunction</td><td>Patients had to have adequate organ function on screening labs defined as:
ANC ≥1,500/µL
Platelets ≥100,000/µL
Hemoglobin ≥9 g/dL
Creatinine ≤1.5 ULN or creatinine clearance 60 mL/min if >1.5 ULN
Total bilirubin ≤1.5 ULN or direct bili ≤ ULN if total bili >1.5 ULN
AST and ALT ≤2.5 ULN or ≤5 ULN for patients with liver metastases
INR or PT ≤1.5 ULN unless anticoagulant therapy; otherwise within therapeutic range
aPTT or PPT ≤1.5 ULN unless anticoagulant therapy; otherwise within therapeutic range</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Given the favorable safety profile of PEMB-mono the CGP recommends discretion of the treating physician for: (1) use of PEMB-mono in patients with lab parameters beyond those outlined in the trial and (2) use of carboplatin instead of cisplatin when offering PEMB-chemo in patients with lab parameters beyond those outlined in the trial.</td></tr>
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<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Outcomes</td><td>Assessment of Key Outcomes</td><td>PFS, ORR, duration of response (exploratory) were assessed according to RECIST v1.1, with modification (confirmatory scan following PD) in patients receiving pembrolizumab, since patients receiving immunotherapy can show apparent progression. HRQoL assessed by EORTC-QLQ and EORTC H&N35.</td><td>If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?</td><td>The CGP agreed that assessment of outcomes were applicable to Canadian clinical practice.</td></tr>
<tr><td>Setting</td><td>Ethnicity or Demographics</td><td>Sex for PEMB-mono versus CET-chemo
<table><tr><td>Sex</td><td>PEMB-mono N = 300</td><td>CET-chemo N = 301</td></tr><tr><td>Male</td><td>250 (83.1)</td><td>261 (87.0)</td></tr><tr><td>Female</td><td>51 (16.9)</td><td>39 (13.0)</td></tr></table>
Sex for PEMB-chemo versus CET-chemo
<table><tr><td>Sex</td><td>PEMB-chemo N = 281</td><td>CET-chemo N = 278</td></tr><tr><td>Male</td><td>224 (79.7)</td><td>242 (87.1)</td></tr><tr><td>Female</td><td>57 (20.3)</td><td>36 (12.9)</td></tr></table>
Race/ethnicity at baseline for the comparison of PEMB-mono with CET-chemo, ITT population
<table><tr><td>Race/ ethnicity</td><td>PEMB-mono N = 300</td><td>CET-chemo N = 301</td></tr><tr><td>American Indian Or Alaska Native</td><td>5 (1.7)</td><td>6 (2.0)</td></tr><tr><td>Asian</td><td>58 (19.3)</td><td>54 (18.0)</td></tr><tr><td>Black or African American</td><td>4 (1.3)</td><td>6 (2.0)</td></tr><tr><td>Multi-Racial</td><td>12 (4.0)</td><td>9 (3.0)</td></tr><tr><td>White</td><td>219 (72.8)</td><td>224 (74.7)</td></tr><tr><td>Hispanic or Latino</td><td>46 (15.3)</td><td>44 (14.7)</td></tr><tr><td>Not Hispanic or Latino</td><td>233 (77.4)</td><td>231 (77.0)</td></tr></table></td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.</td><td>The trial results are fully applicable to the Canadian landscape. The CGP does not expect different treatment effect based on ethnicity or different disease management practices across countries. HNSCC is more commonly diagnosed in men however, the data is applicable to women. It is anticipated that this treatment is effective regardless of race.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>Race/ethnicity at baseline for the comparison of PEMB-chemo with CET-chemo, ITT population
<table>
<tr><th>Race/ ethnicity</th><th>PEMB-chemo N = 281</th><th>CET-chemo N = 278</th></tr>
<tr><td>American Indian Or Alaska Native</td><td>3 (1.1)</td><td>6 (2.2)</td></tr>
<tr><td>Asian</td><td>60 (21.4)</td><td>49 (17.6)</td></tr>
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<tr><td>White</td><td>203 (72.2)</td><td>207 (74.5)</td></tr>
<tr><td>Hispanic or Latino</td><td>45 (16.0)</td><td>44 (15.8)</td></tr>
<tr><td>Not Hispanic or Latino</td><td>213 (75.8)</td><td>211 (75.9)</td></tr>
</table></td><td></td><td></td></tr>
<tr><td></td><td>Concurrent use of radiation</td><td>Subjects were prohibited from receiving radiation therapy.

Radiation for a symptomatic solitary lesion or to the brain was considered on a case by case basis after consultation with the sponsor. Subject had to have clear measurable disease outside the radiation field. Administration of palliative radiation therapy was considered clinical progression for determination of PFS.</td><td>Are the trial results generalizable patients who receive concurrent radiation therapy?</td><td>As concurrent use of radiation was not allowed in the trial, there are no data to support the generalizability of treatment benefit in patients with concurrent use of radiation. The CGP does not support generalization to this patient group.</td></tr>
</table>

1.2.4 Interpretation

Burden of Illness and Need

Although it is expected that at least 1,600 Canadians will suffer and die due to recurrent and metastatic squamous cell carcinoma of the head and neck (RMSCCHN) this year, these patients will not have access to the most effective 1st-line systemic therapies potentially available. In 2008 the EXTREME trial demonstrated superior overall survival for the first time in RMSCCHN with the addition of cetuximab to platinum/5FU chemotherapy.[2] However, regulatory approval for use of cetuximab for RMSCCHN was never pursued in Canada. Nivolumab is publicly available for the 2nd-line treatment of RMSCCHN patients suffering cancer progression on or after platinum-based chemotherapy, including progression within 6 months of platinum-based chemoradiation in the majority of jurisdictions.[3] A natural progression of this line of inquiry was the study of PD-1 inhibitors in the 1st-line RMSCCHN setting, and a number of large randomized clinical trials were initiated. However, in the absence of access to cetuximab, most RMSCCHN patients in Canada continue to receive platinum-based doublet chemotherapy which has not been shown to improve either overall survival or HRQoL.

Effectiveness

From the perspective of the current standard of care in Canada, the results of the KEYNOTE-048 RCT are compelling.[1] The most important results of KEYNOTE-048 were observations that patients receiving pembrolizumab plus platinum/5FU lived longer on average than patients receiving CET-chemo. In all patients, regardless of tumor PD-L1 expression, the risk of death was reduced by 23% during the trial observation period (HR 0.77 (95% CI 0.63 to 0.93), p=0·0034) and four times more patients were alive at 4 years (19.4% versus 4.5%) suggesting a durable survival benefit.[4] Similar results were seen with PEMB-mono compared to CET-chemo in patients with tumor PD-L1 CPS score $\geq$1 (85% of the patients) with the risk of death reduced by 22% during the trial observation period (HR: 0.78, (95% CI 0.64 to 0.96), p=0·0086), and nearly three-fold improvement in 4-year overall survival (16.7% versus 5.9%).[4] This treatment effect became more extreme in association with higher CPS score. Although median OS improvements might appear modest (2-2.3 months), these are within the range of other accepted life-prolonging cancer therapies, are associated with a unique observation of long term survival in this population and are made in comparison to a more active control therapy not currently available to Canadian patients. For the comparison of PEMB-mono versus CET-chemo for the PD-L1 CPS≥1 population the difference in OS was statistically significant at IA2, favouring PEMB-mono. The median OS was 12.3 months (95% CI 10.8 to 14.9 months) for PEMB-mono, compared with 10.3 months (95% CI 9.0 to 11.5 months) for CET-chemo. For the comparison of PEMB-chemo versus CET-chemo for the ITT population, the difference in OS was statistically significant at IA2, favouring PEMB-chemo. Median OS was 13.0 months (95% CI 10.9 to 14.7 months) for PEMB-chemo, compared with 10.7 months (95% CI 9.3 to 11.7 months) for CET-chemo. At the IA2 PEMB-mono was non-inferior to CET-chemo in the total population (HR: 0.85 [95% CI 0.71−1.03] p=0.0456) but not superior. In the small subset of patients (n=89) with CPS score <1, a trend toward worse overall survival was reported (HR: 1.51 [0.96-2.37]).[5] This may be related to higher early mortality with PEMB-mono compared to the CET-chemo in patients with lower CPS scores reflected in crossing of the OS KM curves during the first 6-9 months on trial.[1] This observation was not seen with PEMB-chemo, has been seen in several other mono-immunotherapy trials, and is unexplained. Progression-free survival was not improved with pembrolizumab either with or without chemotherapy compared with CET-chemo. These PFS Kaplan-Meier curves showed qualitative differences in treatment effect over time with pronounced crossover between 6-12 months after starting treatment. This PFS finding has been frequently observed in immunotherapy trials in cancer and is of uncertain clinical significance. It is notable that improved overall survival was observed despite this. Measures of patient reported HRQoL with pembrolizumab either with or without chemotherapy were similar to CET-chemo, with neither clinically significant improvement nor deterioration during the observation period of the trial.

Safety

PEMB-mono had far fewer adverse effects than CET-chemo. However, replacing cetuximab with pembrolizumab in combination with platinum/5FU changed some types but not the incidence of treatment toxicity. Severe adverse effects (grade 3 or higher) attributed to study treatment by the investigator occurred 17%, 72%, and 69% of patients treated with pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and CET-chemo, respectively. Treatment-related deaths occurred in 1%, 4%, and 3% pf patients, respectively. Fatigue and hypothyroidism were the most common treatment-related adverse events reported with pembrolizumab monotherapy. The most common treatment-related adverse effects seen with pembrolizumab plus chemotherapy were anemia, hypothyroidism, and cough; and with CET-chemo were hypokalemia, hypomagnesemia, rash, and acneiform

dermatitis. The CGP agreed that toxicity with PEMB-mono was manageable and much less than with CET-chemo; notwithstanding the potential for uncommon but severe immune mediated adverse effects. It can be assumed that the safety profile of PEMB-mono is better than standard of care platinum-based combination chemotherapies currently used in Canada for the treatment of RMSCCHN; although not based on direct observation in RMSCCHN, this has been observed in similar comparisons done in lung cancer.[6] The toxicity profile with PEMB-chemo was similar to CET-chemo but was manageable. The safety profile of PEMB-chemo is likely more severe than currently used standard of care platinum-based combination chemotherapies as uncommon but severe immune-mediated toxicities could occur and toxicity severity was similar to CET-chemo which is known to have more toxicity than chemotherapy alone.[2]

Limitations and Generalizability

Enrollment was limited to patients with RMSCCHN of the conventional mucosal sites who had not received prior systemic therapy for metastatic disease and/or who had progressed more than 6 months after curative chemoradiation treatment and were of good performance status (ECOG 0 or 1). 70% had metastatic disease and 29% had recurrent disease only. Choice of cisplatin or carboplatin was at the investigator's discretion, and 58% of patients received carboplatin. The CGP considered these data generalizable to patients with squamous cell carcinomas of less common mucosal sites that were not included in the trial, including squamous cell carcinomas of uncertain primary site, of the nasal cavity and paranasal sinuses, and EBER-negative nasopharyngeal cancer, but not to primary skin cancers. The curative and metastatic treatment of squamous cell cancer of the nasal cavity and paranasal sinuses as well as non-EBER expressing nasopharyngeal cancer aligns with the treatment of HNSCC in general. The favorable safety profile suggested that PEMB-mono was a reasonable choice in patients with ECOG 2 performance status. The results should only be generalized to patients with localized disease if they refuse or cannot be treated with curative intent definitive local treatment and are intended to be treated non-curatively.

An obvious limitation of generalizing the KEYNOTE-048 data to Canadian practice is the non-standard control arm using CET-chemo, which has not been available for most Canadian patients. However, as CET-chemo provides improved survival and tumor response compared to platinum/5FU chemotherapy, in the absence of direct comparison of pembrolizumab either with or without chemotherapy to platinum/5FU alone, it would be expected that the survival benefits of pembrolizumab-based treatment could be liberally generalized to Canadian RMSCCHN patients.

The strengths of the KEYNOTE-048 trial included the selection of overall survival as the primary endpoint, and no treatment crossover at the time of cancer progression. Lack of blinding of investigators and patients to treatment received is a common practice in oncology trials and a weakness of the trial design. This raises potential for ascertainment bias that could lead to earlier discontinuation of control treatment compared to pembrolizumab-based treatment and may explain in part the unusual PFS findings. Often patients receiving immune checkpoint inhibitor therapy who are clinically well may continue treatment despite evidence of tumor growth on imaging due to the possibility of "pseudo-progression" due to tumor inflammation; whereas patients on the CET-chemo would always have treatment discontinued. The CGP considered the potential effect of this on the results uncertain.

Health Canada has approved PEMB-mono in adult patients whose cancers have PD-L1 expression CPS ≥ 1 as determined by a validated test and PEMB-chemo regardless of the PD-L1 status. The CGP agreed that PD-L1 status is not currently being tested in head and neck cancer patients and is not required prior to nivolumab monotherapy in the post-adjuvant or second line setting. The CGP acknowledged that based on the HC approved indication PD-L1 CPS testing would be required to identify patients qualifying for PEMB-mono. Although 85% of patients had tumor CPS score ≥1 and overall survival with PEMB-mono appeared non-inferior to control in all patients, exploratory subgroup analyses suggested a potential detrimental effect in patients with tumor CPS core <1. While these exploratory analyses must be interpreted with caution, the CGP supported CPS testing and use of PEMB-mono only in patients with tumor CPS score ≥1. The decision to use pembrolizumab either as monotherapy with CPS testing or in combination with chemotherapy without CPS testing should be done at the treating physician's discretion based on clinical factors and patient preferences. The CGP noted that some of the patients with tumour CPS≥1 may require PEMB-chemo for clinical reason, such as critical organ metastases, symptomatic local recurrence, or situations where more rapid and certain tumor regression is of value.

KEYNOTE-048 was an international RCT that included Canadian participants, enhancing its generalizability. The study would have been conducted mainly in academic centres, but the CGP did not consider this a limitation due to the widespread adoption of pembrolizumab as treatment for other cancer indications common in community practice. Pembrolizumab should be prescribed by

clinicians knowledgeable about its immune-mediated adverse effects, and clinicians supervising these patients should be alert to the spectrum of these effects and their treatment.

The CET-chemo regimen consists of platinum/FU in combination with cetuximab. As cisplatin/paclitaxel has been shown equally effective and less toxic than cisplatin/5FU in a large clinical trial,[7] the CGP considered the use of pembrolizumab in combination with cisplatin/paclitaxel a reasonable generalization. Furthermore, 58% of patients in KEYNOTE-048 received carboplatin instead of cisplatin. This consistent with Canadian practice, with a majority of RMSCCHN patients ineligible for cisplatin either due to performance status, comorbidity, or residual cisplatin adverse effects. In view of this, the CGP also considered the use of pembrolizumab in combination with carboplatin/paclitaxel a reasonable generalization to Canadian practice from the KEYNOTE-048 trial.

1.3 Conclusions

The Clinical Guidance Panel concluded that, compared with CET-chemo there is a net clinical benefit to:

- PEMB-mono in the first-line treatment of adult patients with metastatic or unresectable recurrent HNSCC whose tumours have PD-L1 expression CPS ≥ 1 as determined by a validated test;
- PEMB-chemo in the first-line treatment of adult patients with metastatic or unresectable recurrent HNSCC.

Based on one high-quality randomized controlled trial that demonstrated a clinically meaningful and statistically significant benefit in OS for pembrolizumab either alone (in patients with tumor CPS score ≥1) or in combination with platinum/5FU (all patients) compared to CET-chemo. The improvements in OS are compelling and important for patients with this incurable disease as current median OS ranges from 5.0 to 8.7 months with platinum-based combination chemotherapies which have been the standard of care in Canada for several decades. According to patient reported outcomes data quality of life was stable with no improvements or detriments observed with either PEMB-mono or PEMB-chemo compared with CET-chemo. The adverse event profiles of PEMB-mono and PEMB-chemo were overall manageable with PEMB-mono therapy having less toxicity compared with CET-chemo.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Patients with HIV and known hepatitis B or C infection were excluded from the trial. The CGP agreed that the trial results were considered generalizable to patients with these infections provided their infection was under control and treatment decision was at the discretion of their treating physician. As pembrolizumab may induce autoimmune effects it is considered contraindicated in patients with organ allografts requiring immunosuppression. Treatment of patients with active autoimmune and inflammatory conditions that may be exacerbated by pembrolizumab should be at the discretion of the treating physician.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
Currently Funded Treatments	
Initial treatments for recurrent or metastatic heck and neck squamous cell carcinoma (R/M HNSCC) include single-agent chemotherapy or combination chemotherapy. The more commonly used therapies in Canada for first-line treatment of R/M HNSCC are platinum agents plus 5-FU or docetaxel, or carboplatin plus paclitaxel. Cetuximab with or without platinum–fluorouracil chemotherapy or radiation therapy is another option for these patients. Non platinum-based chemotherapies and nivolumab are available to patients with significant intolerance or contraindication to platinum-based chemotherapies. Patients can also be eligible for nivolumab if they have recurred within six months of platinum-based therapy. PAG observed that this population does not overlap	

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
with patients included in KEYNOTE-048 since the latter could not have received systemic therapy ≤ 6 months before initiation of the new treatment, as per trial inclusion criteria.	
• PAG noted that the KEYNOTE-048 trial compared PEMB-mono or PEMB-chemo to CET-chemo. PAG is also seeking comparative information of pembrolizumab versus platinum-based chemotherapies.	• Currently, only indirect comparisons can be made between pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy and platinum-based chemotherapies as no trial to date has directly compared these drugs in R/M HNSCC. However, these have compared favorably in several lung cancer trials.[6] Refer to Section 7 for summary and critical appraisals of a sponsor-submitted network meta analysis for patients with R/M HNSCC. The CGP noted that results of the sponsor-provided network meta-analysis (NMA) suggested that for the analysis using the KEYNOTE-048 PD-L1 Combined Positive Score (CPS) ≥1 population, estimates of overall survival (OS) hazard ratio (HR) favoured PEMB-mono over platinum plus 5-FU and cisplatin plus paclitaxel for most time-points from six months on, although the difference was lost for cisplatin plus paclitaxel at later time-points. Estimates of OS HR favoured PEMB-chemo over platinum plus 5-FU in the ITT population for most time-points from six months on. PEMB-chemo was favoured over cisplatin plus paclitaxel at the early time-points (before 18 months) but not the later. However, the CGP agreed with the CADTH Methods Team, that due to limitations identified in the NMA caution must be used in interpreting the comparative efficacy estimates. The CGP noted that as CET-chemo provides improved survival and tumor response compared to platinum/5-FU chemotherapy,[2] it would be expected that the survival benefits of pembrolizumab-based treatment could be liberally generalized to Canadian patients with R/M HNSCC receiving standard care with platinum-based chemotherapy.
Eligible Patient Population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with PEMB-mono and PEMB-chemo:	
• Patients with an Eastern Cooperative Oncology Group (ECOG) Performance status greater than 2.	• KEYNOTE-048 trial included patients with ECOG PS of 0 or 1. Most patients in the trial had ECOG PS of 1. The CGP noted that approximately half of the patients seen in clinical practice have worse performance status than patients included in the KEYNOTE-048 trial (ECOG ≥ 2). While the CGP agreed that the benefit for patients with an ECOG status of 2 or greater cannot be formally concluded from the KEYNOTE-048 trial, the CGP felt it would be reasonable to offer PEMB-mono to patients with ECOG PS of 2 or greater or who might be considered ineligible for platinum-based combination therapy based on patient preferences and the judgement of the treating clinician.
• Patients with central nervous system (CNS) metastases	

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
• Patients with squamous cell cancer of the sinus cavity.	• KEYNOTE-048 trial excluded patients with known active CNS metastases and/or carcinomatous meningitis. The CGP noted that patients with active CNS disease and carcinomatous meningitis were excluded due to the poor prognosis associated with these conditions. Patients with effectively treated CNS metastases were eligible for the trial. Patients with asymptomatic CNS disease would be a reasonable population to include for treatment as small lesions may not require immediate treatment with stereotactic radiosurgery (SRS) or radiotherapy particularly if the burden of systemic disease is prominent and needs to be addressed. • KEYNOTE-048 trial excluded patients with squamous cancer of the sinus cavity. The curative and metastatic treatment of squamous cell cancer of the nasal cavity and paranasal sinuses as well as non-EBER expressing nasopharyngeal cancer aligns with the treatment of HNSCC in general. Generalizing to this population therefore seems appropriate.
PAG is seeking guidance on whether patients with R/M HNSCC patients who are not amenable to local therapy and who have started first-line non-curative chemotherapies, or who are unable to tolerate treatment, could switch to pembrolizumab as their first-line treatment. Should switching be acceptable, PAG would like clarity on the types of first-line therapies that would be applicable and whether these include CET-chemo.	In patients who are not amendable to local therapy and who have initiated first-line chemotherapy prior to funded access to pembrolizumab, the addition of PEMB-mono to combination chemotherapy is reasonable. Combination chemotherapy should be platinum-based. In case patients have started on CET-chemo, a switch to PEMB-chemo would be reasonable. For patients who are unable to tolerate combination chemotherapy and require ongoing treatment, the data supporting nivolumab as second-line therapy are probably more directly generalizable, and this treatment should be considered. However, it would be reasonable to consider pembrolizumab if nivolumab was not available.
PAG noted that HNSCC patients having recurred within 6 months of potentially curative neoadjuvant/adjuvant platinum-based therapy for locally advanced malignancies are eligible to receive nivolumab (another PD-1 inhibitor) and is seeking guidance on whether pembrolizumab could be used in the same fashion despite the exclusion of such patients from the trial. PAG is unsure if this population would be eligible as per the wording of the reimbursement request.	The KEYNOTE-48 trial excluded patients who have recurred within 6 months of potentially curative neoadjuvant/adjuvant platinum-based therapy had prior systemic treatment for advanced/metastatic disease. The CGP noted that nivolumab received a pERC conditional positive recommendation in 2017 for above patient population. Therefore, nivolumab would be the preferred option in this setting.
PAG is also concerned about potential indication creep to: • Patients who experienced prior non-curative chemotherapy or immunotherapy • Patients in the locally or regionally advanced setting (as neoadjuvant or adjuvant therapy).	• The KEYNOTE-048 trial results are in the first line recurrent/metastatic setting and there is insufficient evidence to extrapolate to the second line or greater setting if previously treated with chemotherapy or immunotherapy. • The KEYNOTE-048 trial included patients with recurrent or metastatic disease and treatment was with palliative intent. The CGP noted that the KEYNOTE-048 trial results are not generalizable to patients with locally or regionally advanced disease in the curative intent setting. Trials are currently underway to address the addition of immunotherapy in the locally advanced setting with concurrent treatment.
Implementation Factors	

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
The proposed dose of pembrolizumab for HNSCC is 200 mg. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight-based dose for HNSCC(i.e., 2mg/kg up to 200mg) given the high cost of fixed dose compared to weight-based dose for patients weighing less than 100 kg. PAG also identified emerging data of dosing pembrolizumab at 400 mg every 6 weeks. PAG noted that a CADTH Technology Review suggests that weight-based doses of pembrolizumab and corresponding flat doses have similar effects. PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400 mg or 4 mg/kg up to a maximum of 400 mg every 6 weeks).	Weight-based dosing (e.g., 2mg/kg up to 200mg every 3 weeks) of pembrolizumab would be reasonable for the present target population in line with the findings from a CADTH's Technology Review on Dosing and Timing of Immuno-Oncology Drugs (https://www.cadth.ca/sites/default/files/ou-tr/ho0008-dosing-timing-immuno-oncology-drugs.pdf; November 2019) that suggested weight-based doses and corresponding flat doses of pembrolizumab have similar effects. Furthermore, the CGP noted that there is promising evidence emerging in melanoma (KEYNOTE 555 study)[8] in support of an alternate dosing scheduling for pembrolizumab based on 400 mg every 6 weeks and agreed that it would seem reasonable to generalize the 400 mg every 6 weeks schedule of pembrolizumab to the present target population. However, the CGP noted that there is currently insufficient evidence to inform a recommendation on the use of a weight-based dosing schedule of 4 mg/kg up to a flat dose cap of 400 mg every 6 week in the present target population.
PAG is seeking guidance on treatment discontinuation as per the KEYNOTE-048 trial treatment of "once every 3 weeks until disease progression, intolerable toxicity, physician or participant decision, or 35 cycles, whichever occurred first".	In the KEYNOTE-048 trial treatment after initial radiographic progression was possible until a repeat tumor assessment 4 weeks later confirmed progressive disease. Patients who were awaiting radiologic confirmation of progression were able to continue treatment at the investigator's discretion if they were clinically stable. The CGP agreed that the trial parameters in the KEYNOTE-048 trial set for treatment discontinuation are reasonable and reflective of clinical practice.
For patients who do not tolerate the PEMB-chemo combination, PAG is seeking guidance on whether PEMB-mono can be attempted before electing to discontinue therapy.	The CGP noted that pembrolizumab could be continued if chemotherapy needs to be discontinued due to intolerance and the patient is benefiting from treatment and is considered likely to continue to benefit.
PAG would also like to confirm whether the evidence is generalizable: • to any chemotherapy backbone • and to concurrent use with radiation	• Although the KEYNOTE-048 trial did not evaluate pembrolizumab in combination with carboplatin plus paclitaxel the CGP agreed that the results of the trial can be generalized to pembrolizumab in combination with carboplatin plus paclitaxel or other platinum doublet agents (carboplatin/5-FU, paclitaxel/cisplatin) commonly used in HNSCC. Benefit with other platinum doublets has been demonstrated in lung cancer trials. Most clinicians would consider platinum plus 5-FU and carboplatin plus paclitaxel as interchangeable in the management of HNSCC. Clinicians may choose carboplatin plus paclitaxel over 5-FU for ease of administration. Carboplatin/paclitaxel is a single day infusion every 3 weeks consistent with the administration of pembrolizumab. Platinum/5-FU is delivered as a multiday infusion and requires placement of a venous access device like a port-a-cath. This would be particularly relevant for example for patients who travel far distances for delivery of therapy, have issues with thrombosis (indwelling venous access device). • As concurrent use of radiation was not allowed in the KEYNOTE-048 trial, there are no data to support the

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	generalizability of treatment benefit in patients with concurrent use of radiation. The CGP does not support generalization to this patient group.
Is there evidence to inform and recommendations for which patients are most likely to benefit from pembrolizumab +/- chemotherapy in R/M HNSCC?	The CGP noted that beyond trends to greater benefit with PEMB-mono with increasing CPS score, there is no robust evidence to inform which patients are most likely to benefit from PEMB-mono versus PEMB-chemo.
How frequently should patients on pembrolizumab for R/M HNSCC be monitored for disease progression, and with which tests?	The CGP noted that ideally response to treatment is monitored by evaluating changes in clinical symptoms, signs, and imaging. Symptoms and signs are monitored regularly in the course of clinical care, usually at each visit for treatment (every three to four weeks). Imaging should be done at a minimum of every 12 weeks.
Is there evidence to inform if there are any groups of patients that could discontinue pembrolizumab earlier than 2 years (35 cycles), such as any that achieve a complete response?	The CGP noted that there is lack of evidence to define a clinical situation in which patients may discontinue pembrolizumab earlier than 2 years. However, despite insufficient evidence, the CGP felt it would be reasonable to discontinue pembrolizumab earlier than 2 years in patients that have achieved a complete response as is commonly being done in clinical practice and was allowed in the KEYNOTE-048 trial. However, the CGP noted that these patients should be considered for pembrolizumab re-challenge if they experience tumor progression, as they have not demonstrated the development of drug resistance.
Sequencing and Priority of Treatment	
Circumstances that would justify preferred use of PEMB-mono versus PEMB-chemo versus other standard of care therapies, including patient factors driving the decision to combine chemotherapy with pembrolizumab	The CGP noted that PEMB-mono would be the preferred choice for most patients. Clinical circumstance in which PEMB-chemo would be preferred would be organ critical or symptomatic metastatic disease requiring high probability of tumor response to therapy. The main regulatory circumstance for PEMB-chemo would be CPS score <1 or lack of CPS data. The main circumstance for standard of care would be absolute contraindications to pembrolizumab immunotherapy.
Possibility and timing of re-treatment with pembrolizumab in relapsed patient who had completed therapy after 35 cycles or 2 years, or who had confirmed complete response and received at least 24 weeks of therapy, including two doses of pembrolizumab beyond the first evidence of complete response, and discontinued pembrolizumab.	The CGP noted that generally, if a patient's tumor was in remission at the time of discontinuing pembrolizumab (patient who has completed therapy for 2 years or a patient with complete response who received at least 24 weeks of pembrolizumab therapy), it is reasonable to re-challenge with the drug at the time of disease progression. However, there is limited data on the effectiveness of this approach, and this was not directly studied in the KEYNOTE-048 trial. The KEYNOTE-048 trial allowed patients who achieved complete response and were treated for at least 24 weeks with pembrolizumab before discontinuing therapy to receive a second course of pembrolizumab for up to a year. In an exploratory analysis of KEYNOTE-048 data with four-year follow-up reported in abstract form (data cut-off March 25, 2020),[4] a total of 11 patients (6 randomized to PEMB mono) received second course PEMB, with overall response rate of 36.4%.

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	Extrapolation from other disease sites such as NSCLC have demonstrated disease control rates of 70-80% at re-challenge (KEYNOTE 024 WCLC 2019[9] and 010 SEMO 2018[10])
Are there clinical situations where it would be appropriate to continue pembrolizumab beyond the 2-year (35 cycle) time duration?	The CGP noted that there are no data supporting situations in which it would be appropriate to continue pembrolizumab beyond the 2-year time duration. However, in rare clinical situation with an ongoing very delayed clinical response the treating clinician may consider taking this approach.
Confirmation that patients who progress on PD-1/PD-L1 inhibitor therapy would not be eligible for subsequent therapy with an alternative PD-1/PD-L1 inhibitor (i.e., patients who progress on pembrolizumab, with or without chemotherapy, would not be eligible for subsequent nivolumab).	The CGP noted that there is currently no clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with PEMB-mono or PEMB-chemo. In the absence of evidence of benefit, patients who progress on pembrolizumab should not be treated with nivolumab as they are unlikely to benefit due to the similar mechanism of action of these drugs.
Using PEMB-mono in the first line and reserving platinum-based chemotherapy for subsequent line.	The CGP noted that using PEMB-mono in the first line and reserving platinum-based chemotherapy for subsequent lines would seem reasonable for most patients.
Choice of downstream platinum and non-platinum-based chemotherapies	The CGP noted that there is currently insufficient clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with PEMB-mono or PEMB-chemo. The CGP noted that based on clinical expert opinion, patients who progress on pembrolizumab-based treatment, may be treated with a choice of chemotherapy at the treating clinician's discretion or offered participation in clinical trials. Usually this choice would be based on the timing and type of prior chemotherapy exposure, the sites of tumor progression, and patient factors such as organ function and performance status.
Use of CET-chemo in patients who received single agent pembrolizumab and experienced disease progression.	The CGP noted that there is currently insufficient clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with PEMB-mono or PEMB-chemo. CET-chemo would be a reasonable option in this situation. However, cetuximab is not currently funded for use in this situation and many patients cannot tolerate the toxicity of this regimen and receive alternative chemotherapy such as paclitaxel/carboplatin.
Is there evidence to inform the choice of nivolumab or pembrolizumab in patients ineligible or intolerant to platinum-based therapy?	In untreated first-line R/M HNSCC patients ineligible for platinum-based therapy with CPS $\geq$1 expressing tumors, pembrolizumab would be the preferred option based on data from KEYNOTE-048. In such patients with CPS <1, there is an evidence gap. Pembrolizumab could be considered but evidence of benefit is less certain. R/M HNSCC patients who are intolerant of first-line platinum-based chemotherapy and have stable or responding disease could be considered for pembrolizumab based on extrapolation of the KEYNOTE-048 trial data. Such patients with progressing disease should be offered nivolumab as per current funding guidelines.
Companion Diagnostic Testing	
PAG seeks clarity on any requirement for p16 testing for pembrolizumab eligibility.	Immunohistochemical testing of HNSCC tumors for p16 expression is of value in the diagnosis and prognostic staging of localized oropharyngeal cancer being considered for curative

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	treatment. It is not currently validated as a prognostic or predictive biomarker for R/M HNSCC, so there is no requirement for testing in this population.

PAG = Provincial Advisory Group, CGP = Clinical Guidance Panel, PEMB-mono = pembrolizumab monotherapy; PEMB-chemo = pembrolizumab plus platinum chemotherapy plus 5-fluorouracil; CET-chemo = cetuximab plus platinum chemotherapy plus 5-fluorouracil, R/M HNSCC = metastatic or unresectable recurrent HNSCC

2 Background Clinical Information

This section was prepared by the pCODR Head and Neck Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

In Canada, an estimated 5,400 people are diagnosed with head and neck cancers every year and an estimated 1,500 Canadians died from it in 2020.[11] Approximately 90% to 95% of head and neck cancers are squamous cell carcinomas.[12] The majority of patients will present with metastatic disease (regional nodal involvement in 43% and distant metastasis in 10%).[13] Of the patients with lymph node involvement who are at highest risk of recurrence, the progression-free survival at 3 years is estimated to be 38% in carcinogen-associated cancers and 74% in human papilloma virus (HPV)-related cancers when treated with concurrent chemoradiation.[14] Patients with distant metastases have a median survival of about 10 months.[15] Therefore, a significant proportion of HNSCC patients will present with or develop metastatic disease and will require further therapy. While HNSCC represents a small proportion of total cancer diagnoses in Canada, it is associated with significant morbidity due to its anatomical location and effective treatment options are necessary. HNSCC is now recognized to be comprised of two distinct entities: primarily carcinogen-induced disease related to smoking, alcohol and direct toxin exposure that typically involves the oral cavity, larynx and hypopharynx; and HPV-related disease that usually presents as oropharyngeal cancer involving the base of tongue or tonsil. The incidence of HNSCC is increasing largely attributable to an increase in HPV-related oropharyngeal cancer. The impact of HPV vaccination strategies will not be seen for years given the long latency period before disease development.

2.2 Accepted Clinical Practice

Recurrent and metastatic squamous cell carcinoma of the head and neck poses a treatment challenge due to the limited therapeutic options. Patients have frequently received extensive pre-treatment, with surgery, radiotherapy, and possibly systemic chemotherapy. Local recurrence is often associated with significant morbidity owing to the functional location of the disease, with tumour growth impeding eating, swallowing, and even breathing. These tumours may be bulky and ulcerated, increasing the risk of superinfection. Patients become debilitated because the disease impedes their ability to take in adequate nutrition and fluids, which further limits their treatment options. Many patients decline treatment with cisplatin-based systemic chemotherapy, due to its poor efficacy and toxicity. Referral patterns contribute as well, as surgeons or radiation oncologists are typically the first contact for newly diagnosed patients, and they may decide not to refer a patient for chemotherapy, or the patient themselves may decline the referral. Some patients seen by medical oncologists may not be considered suitable candidates for chemotherapy due to their medical status. Salvage surgical resection and/or re-irradiation are usually considered but are often not feasible. Use of palliative radiation may be limited due to prior high dose radiotherapy given with curative intent earlier in the course of disease management.

Phase II trials of single agent chemotherapy drugs in HNSCC demonstrated a superior response rate and suggested a survival benefit with cisplatin compared to bleomycin or methotrexate, the standard of care since the 1950s.[16,17] Subsequently, cisplatin became the backbone of doublet chemotherapy. However, although response rates and toxicity risks differed between regimens, no chemotherapy regimens gave a clear survival benefit over methotrexate in adequately powered randomized trials (RCTs). Recent analyses of these RCTs suggest that the efficacy of first-line chemotherapy may be less than anticipated, likely due to patient selection and more aggressive initial curative treatment, and there is no evidence of health-related quality of life benefits.[18]

In 2008, the EXTREME trial of first-line platinum/fluorouracil (5-FU) with and without cetuximab in recurrent or metastatic HNSCC demonstrated an improvement in median survival from 7.4 to 10.1 months (HR 0.8, 95% CI 0.64 to 0.99 p=0.04) with the addition of epidermal growth factor receptor (EGFR)-directed therapy.[2] This was the first adequately powered RCT of first-line drug treatment for recurrent or metastatic HNSCC to report an overall survival benefit. The manufacturers of cetuximab have not pursued Health Canada approval for its use in Canada. Therefore, CET-chemo as per the CET-chemo protocol currently does not have HC approval and access is variable und unreliable (i.e., provincial case-by-case reviews or patient access programs where available). In Canada a platinum-based chemotherapy doublet alone remains standard first-line treatment in Canada. This is typically cisplatin/5-FU, or carboplatin in combination with either FU or paclitaxel in patients who are less fit or cisplatin ineligible.[7] Single agent cisplatin, methotrexate, capecitabine or docetaxel are options considered for patients for whom doublet chemotherapy is not appropriate due

to frailty, comorbidity, or desire to avoid toxicity. The median overall survival with platinum-based combination regimens ranges from 5.0 to 8.7 months across trials.[7,19]

For patients with recurrent or metastatic HNSCC cancer, who progress despite platinum double chemotherapy, there is no consensus on the optimal management. Docetaxel, paclitaxel methotrexate and fluoropyrimidines are commonly used, and one randomized phase II trial showed that docetaxel had a superior response rate compared to methotrexate.[20]

Capecitabine and paclitaxel with or without carboplatin may also be considered but on the basis of limited evidence.[21] In some jurisdictions in Canada cetuximab has been provided via private insurance.

In 2016, based on the results of the CheckMate 141 trial[3] and the KEYNOTE-012 study,[22] PD-L1 inhibitors nivolumab[23] and pembrolizumab[24] received FDA approval for patients with recurrent or metastatic HNSCC with progression on or after a platinum-based therapy. Health Canada approval for nivolumab for the same indication followed in May 2017. In 2020, based on results of the KEYNOTE-048 trial, pembrolizumab received FDA approval for the first line treatment of patients with recurrent or metastatic HNSCC both in combination with platinum and fluorouracil for all patients, and as monotherapy for patients whose tumours overexpress PD-L1 (Combined Positive Score [CPS] ≥ 1 as determined by an FDA approved test. In 2020 Health Canada approved pembrolizumab for the first-line treatment of metastatic or unresectable recurrent HNSCC both in combination with platinum and fluorouracil (FU) chemotherapy for all patients, and as monotherapy for patients who tumours have PD-L1 expression CPS ≥ 1 as determined by a validated test. With regards to PEMB mono therapy a precautionary approach was considered due to uncertainties regarding efficacy in patients whose tumours have a negative PD-L1 expression (i.e. CPS<1) which deemed the benefit-risk profile to be positive only for patients whose tumours have PD-L1 expression CPS ≥ 1.

3 Summary of Patient Advocacy Group Input

One patient group, Life Saving Therapies Network (LSTN) provided patient input on Pembrolizumab (Keytruda) for the first-line treatment of patients with recurrent or metastatic HNSCC as monotherapy or in combination with platinum and fluorouracil (FU) chemotherapy. LSTN is a network of patients, patient advocacy groups, policy experts, oncologists, health economists, law experts, pharmaceutical industry representatives and federal regulators. LSTN focuses on clinical research reform to facilitate faster access to new therapies, regulatory reform to develop precision treatments and reimbursement reform for the effective treatment of diseases. LSTN solicited patient input from a total of 13 respondents from a variety of means as follows:

- The co-founder of LSTN is a HNSCC survivor who provided input regarding the patient experience with HNSCC and/or the therapy under review. Several patient advocacy groups were contacted by LSTN. LSTN collaborated with HeadWay, a patient advocacy group in Alberta for HNSCC and an organization called HPV Awareness.
- An online survey was circulated in two official languages. The survey was promoted on social media platforms for HNSCC patients to respond. The survey generated a total of eight responses.
- LSTN contacted authors of online testimonials of pembrolizumab through social media to either fill out the survey or conduct an interview with. LSTN attempted to collect input from patients in Canada and the USA. LSTN conducted one-on-one interviews with two authors of online testimonials.

Out of the 13 respondents, two survey respondents and one interviewee were treated with pembrolizumab in the first line setting for recurrent or metastatic HNSCC. From a patient perspective, HNSCC can cause a significant physical and emotional impact on the lives of patients. LSTN highlighted that an unmet exists for HNSCC patients in Canada due to limited therapeutic options and lack of community supports. Side-effects of HNSCC reported by patients are pain and discomfort in the head and neck region, difficulty breathing, excessive coughing, difficulty chewing and swallowing meals. Patients expressed great concern about the impact of the disease on their ability to perform their day-today tasks. LSTN also highlighted the social impact of HNSCC as this type of cancer can limit patients' social outings and interactions. Anxiety, depression, panic attacks and fear of recurrence are common complaints reported by patients. Current treatments available for patients with HNSCC include nivolumab, methotrexate, hydroxyurea and docetaxel in combination with cisplatin, and fluorouracil. LSTN commented that these treatments are often associated with significant side-effects that can affect patients' quality of life. Three patients reported having experience with pembrolizumab, all of whom reported a positive experience. These patients did not report any side effects associated with pembrolizumab and noted that it was effective in controlling their cancer. One patient was previously taking cetuximab in combination with radiation therapy. After switching to pembrolizumab, the patient reported that her quality of life had drastically improved and that she was able to continue her daily activities with ease. Additionally, two patients did not have experience with pembrolizumab but reported that they were aware of the treatment and expressed a strong desire to be able to access the drug. Overall, patients value increased effectiveness of treatments, a better side-effect profile and an improvement in quality of life that will enable them to continue their day-to-day tasks while undergoing treatment. LSTN highly supports the reimbursement of pembrolizumab in Canada due to the positive patient experiences and limited availability of effective treatments.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

LSTN presented current research on HNSCC and shared experiences of patients. According to the Canadian Society of Otolaryngology – Head and Neck Surgery, more than 4300 Canadians are expected to be diagnosed with HNSCC in 2020 and more than 1600 will die from the disease. LSTN commented that currently there is no national patient advocacy support group in Canada specifically for patients with HNSCC and noted a significant unmet need for these patients. Some head and neck cancers are also associated with the Human Papilloma Virus (HPV). LSTN did not provide the actual number of patients who reported each side-effect. Physical symptoms of HNSCC include pain, soreness and discomfort in the head and neck region. Muscle cramps in the neck

were also reported by some patients, as well as dry mouth and reduced saliva. LSTN commented that patients who undergo surgery may suffer from facial and neck disfigurement. Difficulty breathing, excessive coughing, difficulty chewing, and difficulty with swallowing meals are some of the functional impairments caused by HNSCC. Insomnia was also reported by some patients. Survey respondents expressed concerns about the impact of the cancer on their daily activities. Many reported a reduction in their ability to work, travel, exercise and their ability to meet familial obligations and complete daily chores. Many patients also expressed concerns about their decreased ability to bathe and dress themselves without the help of a family member.

LSTN also commented on the social impact of HNSCC. Patients may have difficulty speaking which can affect their ability to socialize. A social stigma exists with HNSCC treatments that affect facial appearances which can impact patients' social life by limiting their social outings. Patients reported anxiety, depression and panic attacks as a result of the cancer and many fear a recurrence of the cancer. Many patients also expressed concerns about their intimate lives due to the prevalence of HPV.

3.1.2 Patients' Experiences with Current Therapy

Current treatments for HNSCC identified by LSTN include nivolumab, methotrexate, hydroxyurea and docetaxel in combination with cisplatin, and fluorouracil. LSTN commented that while the success rates of these treatments vary, they are often associated with debilitating side-effects that can impair the quality of life of patients.

One patient reported having experience with cetuximab in combination with radiation therapy. The patient reported acne breakouts on the face, chest and head regions, as well as blisters in the mouth while undergoing the treatment. The patient was unable to consume solid foods and as a result had to modify her diet which resulted in weight loss. The patient reported that after switching to pembrolizumab, she was able to enjoy a relatively normal life and continue her day-to-day activities.

LSTN stated that some severe side effects of cetuximab include cardiovascular and respiratory problems. Many patients reported gastrointestinal side-effects such as vomiting and diarrhea.

3.1.3 Impact on Caregivers

LSTN was not able to collect input from caregivers but commented on the impact of the disease on caregivers. Caregivers are often stressed while caring for patients with HNSCC. In some cases, caregivers have had to travel long distances and even from different countries to care for their loved ones. Caregiver duties can affect their work and social life, which can impact the overall financial and emotional wellbeing of the family. LSTN also commented on the changing nature of the relationship between patients and caregivers during the course of the illness. Caregiving duties can negatively affect the day-to-day interactions with patients. Being faced with new and challenging caregiving responsibilities can cause tension in family relationships. LSTN noted that a lack of external support can often increase the difficulties faced by families.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

LSTN emphasized that patients expect therapies that are more clinically effective with improved side-effect profiles. Patients also seek treatments that will improve their quality of life and enable them to continue their daily activities while receiving treatment. LSTN asserted that immunotherapy can be a promising treatment for improving patient outcomes and their quality of life. It can allow for the multidisciplinary approach to healthcare preferred by patients as it poses less restrictions on the day-today living of patients while enabling them to receive care from oncologists, mental health specialists and community groups. LSTN commented that new therapies that lead to better outcomes for patients should be the new standard of care for first and second line treatment of HNSCC, as well as combination therapy with other treatment options.

Two patients who responded to the LSTN survey and had not used pembrolizumab stated that they are aware of the treatment and would be interested in accessing it. One Canadian patient commented "It will help me in so many ways" and "Please, I need to have it." LSTN emphasized that a lack to access to novel treatments can affect patients' ability to cope with the disease. The knowledge that there are better treatments available but not being able to access them can place a burden on patients' mental health.

3.2.2 Patient Experiences to Date

Two survey respondents (25%) and one interviewee had reported having experience with pembrolizumab. Pembrolizumab was accessed from a clinical trial outside of Canada. The respondents rated the dug as extremely effective in controlling the cancer and reported a high quality of life and experienced normal living while being on the treatment. LSTN reported that the drug was administered to the patients through a blood infusion for approximately 30 minutes. The frequency of treatment was different for each patient and was often accompanied by a blood test to monitor for side-effects. LSTN commented that treatment with pembrolizumab is less intensive and exhausting than other currently available treatments for HNSCC, as it enables patients to return to day-to-day activities while undergoing treatment. The patients reported no side-effects while undergoing treatment and considered that pembrolizumab has an acceptable side effect profile. Patients emphasized that maintaining relationships with loved ones and the returning to work and performing their daily tasks while undergoing treatment is of utmost importance to them. All respondents commented that they were better able to perform their daily tasks and continue normal living following treatment with pembrolizumab. Since the drug was accessed through a clinical trial, patients emphasized that pembrolizumab should be widely accessible for HNSCC patients so that more patients can benefit from the treatment.

3.3 Companion Diagnostic Testing

None identified.

3.4 Additional Information

Based on the patient input, LSTN provided some additional comments for CADTH's consideration. LSTN emphasized that HNSCC is often associated with a poor prognosis, significantly affecting the quality of life of patients, as well as their caregivers. Pembrolizumab represents a significant advancement in the treatment for HNSCC compared to other currently available therapies that is not only effective at controlling the cancer but also has an acceptable side effect profile that allows patients to continue to live a normal life when undergoing treatment. Patients expressed support for increased access to pembrolizumab for patients with HNSCC. Finally, LSTN noted that pembrolizumab for HNSCC can extend patients' lives and also improve their quality of life.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all **nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Place in therapy and sequencing with currently available treatments
- Target population of add-on chemotherapy

Economic factors:

- Clarity on dosing schedule and treatment duration
- Need for PD-L1 testing

Please see below for more details.

4.1 Currently Funded Treatments

Initial treatments for recurrent or metastatic HNSCC include single-agent chemotherapy or combination chemotherapy. The more commonly used therapies in Canada for first-line treatment of R/M HNSCC are platinum agents plus 5-FU or docetaxel, or carboplatin plus paclitaxel. Cetuximab with or without platinum–fluorouracil chemotherapy or radiation therapy is another option for these patients. Non platinum-based chemotherapies and nivolumab are available to patients with significant intolerance or contraindication to platinum-based chemotherapies. Patients can also be eligible for nivolumab if they have recurred within six months of platinum-based therapy. PAG observed that this population does not overlap with patients included in KEYNOTE-048 since the latter could not have received systemic therapy ≤ 6 months before initiation of the new treatment, as per trial inclusion criteria.

PAG noted that the KEYNOTE-048 trial compared pembrolizumab monotherapy to pembrolizumab + platinum doublet + 5-FU and to cetuximab + platinum doublet + 5-FU. PAG is also seeking comparative information of pembrolizumab versus platinum-based chemotherapies.

4.2 Eligible Patient Population

The reimbursement request is for the first-line treatment of patients with recurrent or metastatic HNSCC as monotherapy or in combination with platinum and FU chemotherapy. Patients would qualify for monotherapy only if their tumours have PD-L1 expression (CPS ≥ 1). PAG is seeking clarity on whether patients with an ECOG performance score equal or greater than 2 would be eligible for treatment with pembrolizumab.

PAG is seeking guidance on whether R/M patients who are not amenable to local therapy and who have started first-line non-curative chemotherapies, or who are unable to tolerate treatment, could switch to pembrolizumab as their first-line treatment. Should switching be acceptable, PAG would like clarity on the types of first-line therapies that would be applicable and whether these include cetuximab + platinum + 5-FU. Additionally, PAG would like to know if the clinical evidence can be generalized to patients with CNS metastases or squamous cell cancer of the sinus cavity.

PAG noted that HNSCC patients having recurred within six months of potentially curative neoadjuvant/adjuvant platinum-based therapy for locally advanced malignancies are eligible to receive nivolumab (another PD-1 inhibitor) and is seeking guidance on whether pembrolizumab could be used in the same fashion despite the exclusion of such patients from the trial. PAG is unsure if this population would be eligible as per the wording of the reimbursement request. PAG is also concerned about potential indication creep to patients who experienced prior non-curative chemotherapy or immunotherapy and to patients in the locally or regionally advanced setting (as neoadjuvant).

4.3 Implementation Factors

The proposed dose of pembrolizumab for HNSCC is 200 mg. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight-based dose for R/M HNSCC (i.e., 2mg/kg up to 200mg) given the high cost of fixed dose compared to weight-based dose for patients weighing less than 100 kg. PAG also identified emerging data of dosing pembrolizumab at 400 mg every 6 weeks. PAG noted that a CADTH Technology Review suggests that weight-based doses of pembrolizumab and corresponding flat doses have similar effects. PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400 mg or 4 mg/kg up to a maximum of 400 mg every 6 weeks).

PAG noted that the use 100 mg vials may result in wastage, particularly in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is utilized. As pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing.

PAG is seeking guidance on treatment discontinuation as per the KEYNOTE-048 trial treatment of "once every 3 weeks until disease progression, intolerable toxicity, physician or participant decision, or 35 cycles, whichever occurred first". PAG identified the maximum of ~2 years of therapy as an enabler to implementation. PAG further noted that a 6-week schedule (if recommended as a dosing option) would be more convenient for patients and use less chemotherapy chair time resources.

For patients who do not tolerate the pembrolizumab plus chemotherapy combination, PAG is seeking guidance on whether pembrolizumab monotherapy can be attempted before electing to discontinue therapy. PAG would also like to confirm whether the evidence is generalizable to any chemotherapy backbone, and to concurrent use with radiation.

Pembrolizumab is an add-on intravenous therapy requiring 30 minutes of infusion time every three weeks for two years. As a result, it may significantly increase demands for chair time and clinic visits. Incremental resources would be required to monitor and treat infusion reactions, immune related adverse effects and other toxicities associated with immunotherapies. In the case of pembrolizumab monotherapy, replacement of first line IV chemotherapies may mitigate some issues related with management of specific sides effects. Pembrolizumab would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy and sequencing with other drug regimens for R/M HNSCC. In particular:

- Circumstances that would justify preferred use of pembrolizumab monotherapy vs. pembrolizumab-chemotherapy vs. other standard of care therapies, including patient factors driving the decision to combine chemotherapy with pembrolizumab.
- Possibility and timing of re-treatment with pembrolizumab in relapsed patient who had completed therapy after 35 cycles or 2 years, or who had confirmed complete response and received at least 24 weeks of therapy, including two doses of pembrolizumab beyond the first evidence of complete response, and discontinued pembrolizumab. Confirmation that patients who progress on PD-1/PD-L1 inhibitor therapy would not be eligible for subsequent therapy with an alternative PD-1/PD-L1 inhibitor (i.e., patients who progress on pembrolizumab, with or without chemotherapy, would not be eligible for subsequent nivolumab).
- Using pembrolizumab monotherapy in the first line and reserving platinum-based chemotherapy for subsequent line.
- Choice of downstream platinum and non platinum-based chemotherapies
- Use of cetuximab + platinum + fluorouracil in patients who received single agent pembrolizumab and experienced disease progression.

4.5 Companion Diagnostic Testing

PD-L1 status is not currently being tested in head and neck cancer patients and is not required prior to nivolumab monotherapy in the post-adjuvant or second line setting. PAG remarked that since PD-L1 CPS testing is required to identify patients qualifying for pembrolizumab monotherapy, some jurisdictions may not have validated testing in place for the combined positive score (tumor staining plus tumor infiltrating cell staining) and may be required to send tissue samples out of province. Finally, PAG seeks clarity on any requirement for p16 testing for pembrolizumab eligibility.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of three registered clinician inputs were provided for the review of pembrolizumab (Keytruda) for the first-line treatment of patients with recurrent or metastatic HNSCC as monotherapy or in combination with platinum and fluorouracil (FU) chemotherapy: two individual inputs from a clinician from Cross Cancer Institute (CCI), a clinician from the National Cancer Institute (NCI) and one joint input from Cancer Care Ontario (CCO) comprised of two clinicians. All clinicians agreed that pembrolizumab, with or without chemotherapy should be made available for first line treatment for all patients with recurrent or metastatic HNSCC. Patient populations of particular interest are patients with a PD-L1 CPS (combined positive score) < 1 or patients with PD-L1 CPS > 20 The clinicians stated that the decision to add chemotherapy to pembrolizumab depends on the patients' PD-L1 CPS status ; patients with PD-L1 CPS > 1 could be treated with pembrolizumab alone, whereas patients with PD-L1 CPS <1 could be treated with pembrolizumab and chemotherapy. However, the clinicians noted that patient factors such as comorbidities and age should also be taken into consideration when deciding between pembrolizumab alone or pembrolizumab with chemotherapy. All clinicians emphasized the importance of funding for PD-L1 testing, as it can identify patients who are eligible for pembrolizumab monotherapy, which could minimize toxicity from chemotherapy. Contraindications to pembrolizumab identified by clinicians were patients with severe active autoimmune disorders and those with solid organ transplants. Clinicians described possible sequencing options: if pembrolizumab monotherapy is prescribed in the first line setting, then the second line option would be platinum-based chemotherapy. If pembrolizumab plus chemotherapy is prescribed in the first line, then the second line option would be non-platinum-based chemotherapy. Patients who are ineligible or intolerant to platinum-based therapy may receive either pembrolizumab or nivolumab as there is no evidence to suggest the use of one drug over the other. Clinicians noted that re-treatment with pembrolizumab after reaching the 2-year time-period can be considered; however, they noted that there is limited evidence on re-treatment with pembrolizumab. Although there is currently no evidence to inform the discontinuation of pembrolizumab earlier than the 2-year time-period, the clinicians noted that treatment may be discontinued earlier due to reasons such as toxicity or as per the clinical judgment. Clinicians commented that alternative dosing can be considered but it is preferable to use the same dosing as in the clinical trial.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s)

The clinician from CCI noted that the most appropriate comparators for pembrolizumab are platinum (cisplatin or carboplatin) plus 5FU and platinum with paclitaxel. The clinician further commented that platinum (cisplatin or carboplatin) plus paclitaxel are the most commonly used in their clinical practice as intergroup trials have demonstrated similar outcomes between cisplatin/5FU and cisplatin/paclitaxel. The clinicians from CCO mentioned carboplatin plus paclitaxel or platinum+5FU for patients who have relapsed after six months from chemoradiotherapy, and nivolumab for patients who relapse within six months of chemoradiotherapy.

The clinicians from CCI and NCI both noted that cetuximab is not currently reimbursed for the indication under review. The clinician from NCI further commented that cetuximab in combination with platinum doublet chemotherapy is the standard of care around the world and patients in Ontario have minimal access to cetuximab in combination with platinum doublet chemotherapy (platinum 5-FU).

5.2 Eligible Patient Population

The clinicians from CCO stated that the ideal patient population for this regimen would be patients who are metastatic at presentation or patients who relapse after chemoradiotherapy at any point. Both clinicians from NCI and CCO noted that the use of pembrolizumab alone or in combination with chemotherapy depends on patients' PD-L1 CPS status if PD-L1 testing is available. The clinician from NCI noted that patients with PD-L1 CPS < 1 or unknown would generally be treated with pembrolizumab plus chemotherapy, whereas patients with PD-L1 CPS > 1 could receive pembrolizumab alone or with chemotherapy, as judged by the clinician. The clinicians from CCO noted that patients with PD-L1 CPS > 1 and who are not in need of an immediate response could benefit from pembrolizumab alone instead of the combination given it is less toxic and has a longer duration of response. The clinician from NCI stated that patients with a PD-L1 CPS > 20 can be considered for pembrolizumab alone and therefore avoid chemotherapy.

The clinicians from CCI and NCI both asserted that there exists an unmet need for the patient population in the reimbursement request. The clinician from CCI noted that overall survival is limited even with treatment. Both clinicians also agreed that the inclusion and exclusion criteria of the clinical trial can be applied to clinical practice. The clinician from CCI further noted that the reimbursement request should be expanded to include pembrolizumab in combination with platinum (cisplatin or carboplatin) plus paclitaxel. Additionally, the clinician noted that treatment should be extended to patients with recurrent or metastatic HNSCC of unknown primary and patients who have an intolerance or a contraindication to platinum-based chemotherapy.

5.3 Relevance to Clinical Practice

All three groups of clinicians stated that pembrolizumab should ideally be available to all patients in the first line recurrent or metastatic HNSCC setting. The clinicians from CCO specified that recurrence could be at any time from curative intent therapy. The clinician from NCI noted that the population of interest is specifically those with PD-L1 CPS >20 and those with PD-L1 CPS <1. However, patients with PD-L1 CPS between 1 and 20 would still be eligible for pembrolizumab with or without chemotherapy. The clinician from CCI commented that pembrolizumab monotherapy has less toxicity compared to chemotherapy alone and that pembrolizumab with chemotherapy has better efficacy and is not significantly more toxic than chemotherapy alone. Similarly, the clinician from NCI stated that pembrolizumab with or without chemotherapy has better efficacy, safety and tolerability compared to chemotherapy. Both clinicians from CCI and NCI stated that the main contraindications to pembrolizumab are patients with certain autoimmune diseases and patients with solid organ transplants.

5.3.1 In the clinical trial interpretation by the investigators, it is stated that pembrolizumab monotherapy is an appropriate first-line treatment for patients that are PD-L1 positive, and pembrolizumab plus chemotherapy is an appropriate first-line treatment for all patients with recurrent or metastatic HNSCC – do clinicians agree with these interpretations, as the submitter has not limited the request to PD-L1 subsets, yet has included both pembrolizumab monotherapy and pembrolizumab plus chemotherapy in the request? Is there any evidence to inform when pembrolizumab should be prescribed as monotherapy vs. in combination with chemotherapy for recurrent or metastatic HNSCC?

The clinicians from CCO and CCI both agreed with the above interpretation of the clinical trial investigators. The clinicians from CCO emphasized the importance of PD-L1 testing upfront as it can identify patients who are eligible for single agent pembrolizumab, which would minimize toxicity from chemotherapy. They noted that according to the results of the KEYNOTE-048 trial, treatment with single agent pembrolizumab may also result in a longer duration of response. The clinician from CCI explained that the funding for PD-L1 testing will depend on the cost of implementing CPS testing. The clinicians from CCO and CCI both commented that the choice of pembrolizumab monotherapy versus pembrolizumab in combination with chemotherapy is judged by the clinician based on individual patient factors such as burden of disease, rate of progression and CPS status. The clinician from NCI further commented that patients with highly positive PD-L1 tumours (PD-L1 CPS > 20) could benefit from single agent pembrolizumab and those with PD-L1 negative tumours (PD-L1 CPS <1) would benefit from the combination of pembrolizumab and chemotherapy. The choice of single agent pembrolizumab or the combination of pembrolizumab and chemotherapy would be based on clinical judgment for patients with a PD-L1 CPS between 1 and 20. The clinician also noted that in some cases a patient may have a PD-L1 positive tumor, but the size and location of the disease may warrant the need for chemotherapy to facilitate a larger response. The clinician further commented that in these types of cases, clinicians may not be inclined to treat patients with immunotherapy alone, due to rapid disease progression. Additionally, some patients with a PD-L1 CPS > 1 may not be a candidate for chemotherapy due to factors such as comorbidities or age, and therefore may only be treated with pembrolizumab. Therefore, the clinician noted that having the option to treat with single agent pembrolizumab or the combination of pembrolizumab plus chemotherapy provides clinicians with the best options for treating patients based on individual patient needs.

5.3.2 Is there evidence to inform the choice of nivolumab or pembrolizumab in patients ineligible or intolerant to platinum-based therapy?

The clinicians NCI and CCI both responded that there is currently no evidence to inform the choice of nivolumab or pembrolizumab in patients ineligible or intolerant to platinum-based therapy. Both drugs are reasonable options for this patient population.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

All clinicians stated that pembrolizumab would be used in the first line setting and replace the current standard of care for recurrent or metastatic HNSCC. The clinicians from NCI and CCI both noted that if pembrolizumab monotherapy is used in the first line, second line options would be platinum-based chemotherapy. Both clinicians also stated that if pembrolizumab in combination with chemotherapy are used, then second-line options would be non-platinum-based chemotherapy (ex. taxane). Cetuximab is also a reasonable alternative in provinces where it is funded. The clinician from CCO further stated that if pembrolizumab is given in the first line setting, nivolumab would not be given in the second line setting.

5.5 Companion Diagnostic Testing

All clinicians stated PD-L1 testing as the companion diagnostic test. The clinicians from NCI and CCI noted that currently the test is available but not funded in Ontario. The clinician from NCI believes that testing on any tissue is appropriate and would not require a new diagnostic sample to be taken for testing before treatment. Additionally, the clinician strongly supports the funding of PD-L1 testing for all patients with head and neck cancer. The clinician from CCI noted that PD-L1 testing would also require the training of pathologists to report CPS and would be an additional cost to Lab Medicine.

5.6 Implementation Questions

5.6.1 If treatment with pembrolizumab for recurrent or metastatic HNSCC is discontinued due to reaching the 2-year (35 cycles) time period as per the KEYNOTE-048 study, is there evidence to inform or is it appropriate to consider re-treatment at the time of disease progression? Are there clinical situations where it would be appropriate to continue pembrolizumab beyond the 2-year (35 cycle) time duration?

The clinicians from CCO commented that currently there is no evidence to consider re-treatment at the time of disease progression. The clinician from NCI noted that there is limited data to inform re-treatment with pembrolizumab at the time of disease progression. In the KEYNOTE-010 trial in NSCLC, retreatment after two years showed some effect, but the sample size of patients was small. The clinician concluded that allowing re-treatment with pembrolizumab after completing 2 years of treatment may be a reasonable option; however, there is no data to indicate whether continuous treatment of pembrolizumab is appropriate beyond the two-year time horizon. Alternatively, the clinician from CCI felt that it would be appropriate to consider re-treatment of pembrolizumab at the time of disease progression.

5.6.2 Is there evidence to inform if there are there any groups of patients that could discontinue pembrolizumab earlier than 2 years (35 cycles), such as any that achieve a complete response?

The clinicians from CCO commented that currently there is no evidence to inform discontinuing pembrolizumab earlier than 2 years (35 cycles). The clinician from CCI commented that although currently there is no evidence, it may be reasonable based on clinician's judgement and not on evidence. The clinician from NCI stated that while early discontinuation may be possible for patients with complete response, there is limited data to implement this as a standard. The clinician noted that the NSCLC Checkmate-153 trial showed better overall survival for patients treated continuously than for patients who stopped after one year of treatment of nivolumab. Therefore, other than for toxicity reasons, it is unclear whether pembrolizumab should be stopped earlier than two years.

5.6.3 Is weight-based dosing up to a cap a viable alternative to flat dosing of pembrolizumab? Would an alternate dosing schedule (i.e., 400 mg or 4 mg/kg up to a maximum of 400 mg every 6 weeks) be appropriate?

The clinician from CCI commented that weight-based dosing up to a cap as an alternative to flat dosing of pembrolizumab should be based on the decision of provincial cancer pharmacies. The clinician commented that dosing of 400 mg every six weeks was not evaluated in the clinical trial. The clinician from NCI noted that it is preferred to use the same dosing as in the clinical trial, but alternative dosing could be an appropriate consideration.

5.7 Additional Information

Not Applicable.

6 Systematic Review

6.1 Objectives

To review the efficacy and safety of pembrolizumab (Keytruda) for the first-line treatment of metastatic or unresectable recurrent HNSCC both in combination with platinum and fluorouracil (FU) chemotherapy for all patients, and as monotherapy for patients who tumours have PD-L1 expression CPS ≥ 1.

Supplemental Questions most relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in section 7.

- Review and critical appraisal of sponsor-submitted network meta-analysis (NMA) of the comparative efficacy and safety of pembrolizumab as monotherapy or in combination with platinum plus 5-FU versus platinum plus 5-FU, the current Canadian standard of care, for the first line systemic treatment of patients with recurrent or metastatic HNSCC. Interventions of interest were: cisplatin/carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, cetuximab, gemcitabine or capecitabine, either as monotherapy or in combination with one another; nivolumab, ipilimumab, durvalumab, tremelimumab, in-class immuno-oncology, and other systemic therapies.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 4. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 4: Systematic review selection criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of pembrolizumab should be included.	Patients with recurrent or metastatic HNSCC. **Subgroups:** • PD-L1 expression • HPV-16 status (positive vs negative) • Smoking status • Time since completion of definitive therapy • Age • Sex	Pembrolizumab monotherapy OR Pembrolizumab in combination with platinum and fluoruracil chemotherapy	• Platinum chemotherapy plus taxane* (platinum doublet chemotherapy) • Any single or combination targeted agent and/or chemotherapy.	• **OS** • **PFS** • **HRQoL** • **PRO** • ORR • DOR • DCR • AEs • SAEs • WDAEs • Autoimmune AEs

* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).

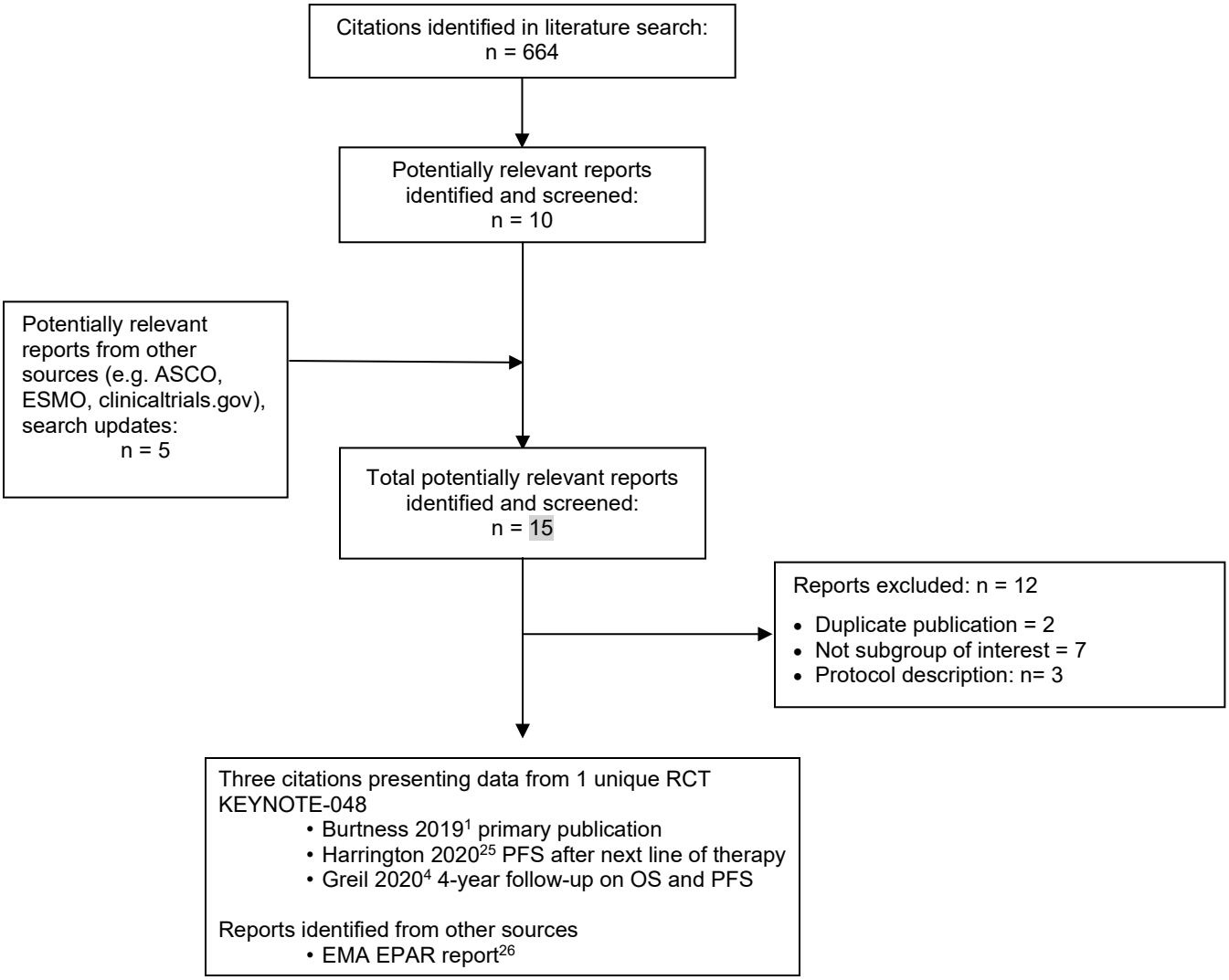
Abbreviations: AE = adverse events, DCR=disease control rate, DOR=duration of response, HNSCC = squamous cell carcinoma of the head and neck, HPV-16 = Human papillomavirus type 16, ORR=objective response rate, PD-L1 = Programmed death-ligand 1, PRO=Patient related outcomes, RCT=randomized controlled trial, SAE=serious adverse events, WDAE=withdrawals due to adverse events

6.3 Results

6.3.1 Literature Search Results

Of the 308 potentially relevant reports identified in the initial search, 6 were identified and screened, with an additional 5 identified in abstract and update searches. Three reports of one RCT were included in the pCODR systematic review.[1,4,25] Reports were excluded because were post-hoc analyses of subgroups other than those identified as being of interest, described the protocol only, or had duplicate information.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to KEYNOTE-048 were also obtained through requests to the Sponsor by CADTH[27-29]

6.3.2 Summary of Included Studies

One trial (KEYNOTE-048), described in three publications, met the eligibility criteria and was included.

6.3.2.1 Detailed Trial Characteristics

Table 5 summarizes the trial characteristics for KEYNOTE-048, and Table 6 the findings of quality appraisal.

Table 5: Summary of Trial Characteristics for KEYNOTE-048 trial of PEMB-mono or PEMB-chemo versus CET-chemo in HNSCC

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic HNSCC (MK-3475- 048/KEYNOTE-048, NCT02358031) Phase 3, open-label, 1:1:1 randomized (stratified by PD-L1 expression, p16 expression, ECOG) N = 882 (PEMB mono = 301, PEMB-chemo = 281, CET-chemo = 300); N treated = 863 (PEMB mono = 300, PEMB-chemo = 276, CET-chemo = 287) 200 centres, 37 countries (Argentina, Australia, Austria, Brazil, Canada, Chile, Columbia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, United States.) Patients enrolled between April 20, 2015 to January 17, 2017. Most recent data cut-off: Interim analysis 2: June 13, 2018 Prespecified final analysis: February 25, 2019 Estimated final completion date: January 17th, 2021[29] Status: trial ongoing **Funding:** Merck Sharp and Dohme Corp	**Key Inclusion Criteria**: • Adults (≥18 years) with recurrent or metastatic HNSCC (oropharynx, oral cavity, hypopharynx, larynx) • No prior systemic therapy for recurrent or metastatic disease. Systemic therapy for locally advanced disease allowed, if completed >6 months prior • Measurable disease per RECIST 1.1 • ECOG performance status 0 or 1 • Results available for tumour p16 expression for tumours of oropharynx; tissue for PD-L1 **Key Exclusion Criteria**: • Disease progression within 6 months of completion of systemic treatment for locoregionally advanced HNSCC • Known active CNS metastases and/or carcinomatous meningitis • Active autoimmune disease requiring systemic treatment, other than replacement therapy • Diagnosed immunodeficiency or receiving systemic steroid therapy or immunosuppressive therapy • Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy **Prohibited therapies** • Non-protocol antineoplastic systemic therapy, biological therapy, chemotherapy • Systemic glucocorticoids for other than treating AE or replacement (physiologic doses allowed). • Radiation therapy. Allowed for exceptional cases to treat	**Intervention**: *PEMB mono* Pembrolizumab monotherapy, 200 mg IV every 3 weeks OR *PEMB-chemo* Pembrolizumab 200 mg IV plus cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV plus 5-FU 1000 mg/m^2/day (day 1 to 4) IV, every 3 weeks **Comparator**: *CET-chemo* Cetuximab 400 mg/m^2 (day 1) IV followed by 250 mg/m^2 IV weekly, plus cisplatin 100 mg/m^2 IV or carboplatin AUC 5 IV plus 5-FU 1000 mg/m^2/day (day 1 to 4) IV, every 3 weeks	All efficacy outcomes assessed for ITT, CPS≥1, CPS≥20 populations, unless noted. **Primary**: • OS • PFS **Secondary**: • Proportion progression-free • ORR • Change from baseline global health status • Time to deterioration global health status, pain, swallowing **Safety**: • AEs • Study drug discontinuations Assessments of tumour response by RECIST 1.1, BICR, unless otherwise noted.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	symptomatic solitary lesion or to brain.		

Abbreviations: 5-FU = 5-fluorouracil, AE = adverse event, AUC = area under the curve, BICR = blind independent central review, CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CNS = central nervous system, IV = intravenous, ORR = objective response rate, OS = overall survival, PD-L1 = programmed death ligand 1, PD-L2 = programmed death ligand 2, PEMB = pembrolizumab, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PFS = progression free survival, RECIST = Response Evaluation Criteria in Solid Tumours

Data source: EPAR 2019,[26] Burtness 2019,[1] Checkpoint meeting responses[29]

Table 6: Select quality characteristics of the KEYNOTE-048 trial of pembrolizumab monotherapy or pembrolizumab plus chemotherapy versus cetuximab with chemotherapy in HNSCC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KEYNOTE-048	PEMB or PEMB-chemo versus CET-chemo	OS, PFS (ITT, CPS≥1, CPS≥20)	Yes	882	Yes†	Yes	No	Yes	Yes	No	Yes

† Randomization was stratified by percentage of PD-L1-expressing tumour cells (≥50% versus <50%), p16 status (yes versus no) for oropharyngeal cancers (while other cancers were assumed to be p16-negative), and by ECOG performance status (0 versus 1).

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, OS = overall survival, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PFS = progression free survival

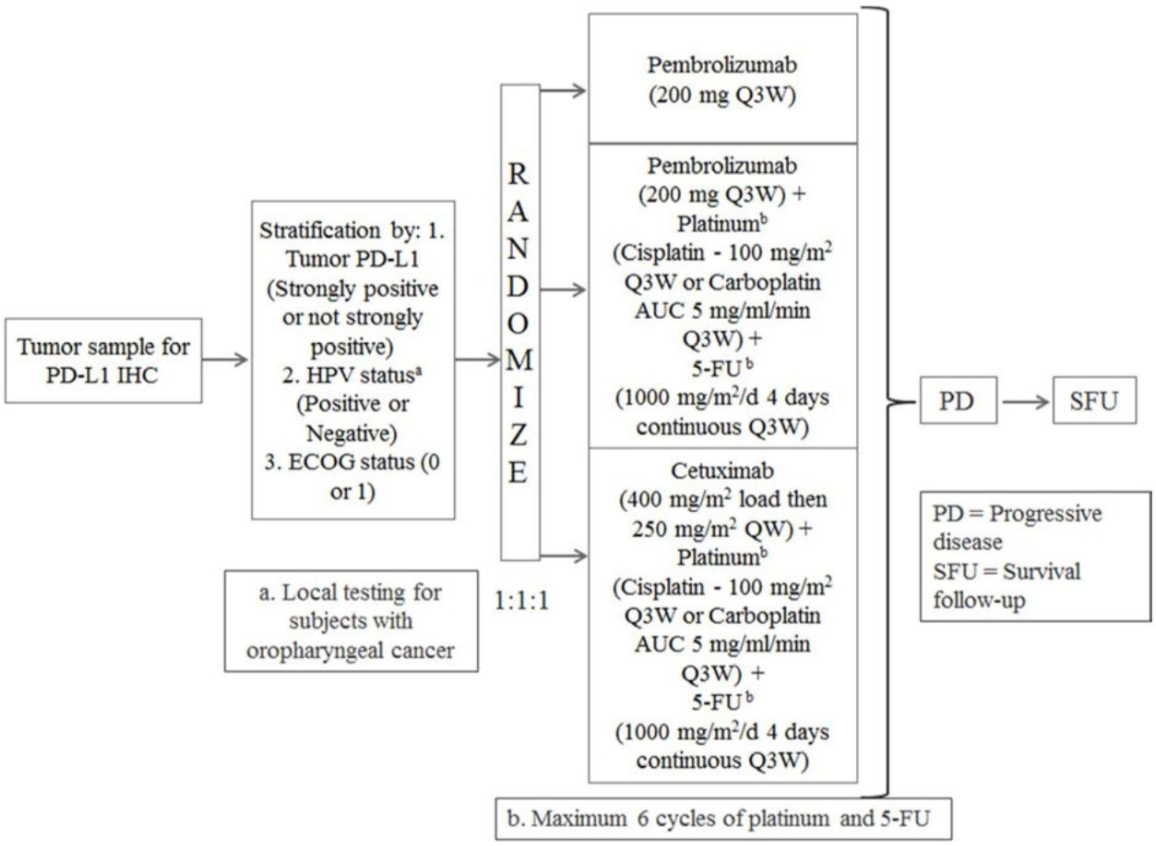
Data source: EPAR 2019,[26] Burtness 2019[1]

a) Trials

KEYNOTE-048 is an ongoing phase 3, open-label, three-group, international multicentre randomized clinical trial of the efficacy and safety of PEMB mono or PEMB-chemo with CET-chemo in patients with recurrent or metastatic HNSCC that was considered incurable by local therapies, and who had received no prior chemotherapy for metastatic disease. The trial was conducted at 200 sites in the US, Canada, Europe, South America, Russia, and Asia. The majority of subjects were from Europe or North America. Figure 2 shows a schematic of the trial, and characteristics of the trial are summarized in Table 5.

The primary objectives of the trial were to compare PEMB-mono with CET-chemo (EXTREME regimen) and PEMB-chemo with CET-chemo for OS and PFS in all patients. Additional primary objectives were to make the same comparisons for the subsets of patients with PD-L1 CPS ≥ 1 and CPS ≥ 20. Secondary objectives were to compare PEMB mono with CET-chemo and PEMB-chemo with CET-chemo for the proportion of patients with PFS at 6 and 12 months, ORR, and changes from baseline and TTD for global health-related quality of life.

Figure 2: Schematic of KEYNOTE-048 design



Abbreviations: 5-FU = 5-fluorouracil, AUC = area under the curve, ECOG = Eastern Cooperative Oncology Group, HPV = human papilloma virus, ICH = immunohistochemistry, Q3w = every 3 weeks, QW = every week, PD-L1 = programmed death ligand 1

Figure source: EPAR 2019,[26] Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Eligibility criteria

Patients were eligible for the KEYNOTE-048 trial if they were adults (18 years or older) with pathologically confirmed squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, or larynx that was recurrent or metastatic and was not considered curable by local therapies. Patients with primary tumours in the nasopharynx were not eligible. Patients could not have received prior systemic therapy for recurrent or metastatic disease, while systemic therapy for locally advanced disease was allowed if it had been completed >6 months prior to screening. Patients had to have at least one tumour that was evaluable for RECIST 1.1 and have tumour tissue available for PD-L1 testing. Eligibility did not depend on PD-L1 expression. Those with oropharyngeal cancers had to have results of testing for p16 expression available. Patients were to have an ECOG performance status score of 0 or 1.

Patients were excluded if they had progressive disease within six months of systemic treatment given with intent to cure locoregionally advanced disease, short life expectancy (<3 months), and/or rapidly progressing disease. Patients with active CNS metastases and/or carcinomatous meningitis were excluded. Patients with an active infection or active autoimmune disease were excluded, as were those with a history of non-infectious pneumonitis requiring steroids. Patients could not have previously been treated with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or have received radiotherapy within 2 weeks prior to randomization, or have not fully recovered from AEs occurring during radiotherapy.

Randomization and treatment phases

Patients were centrally randomized using an IVRS in a 1:1:1 ratio to the three treatment groups, PEMB-mono, PEMB-chemo, and CET-chemo. For patients randomized to PEMB-chemo or CET-chemo, platinum chemotherapy was either carboplatin or cisplatin as selected by the investigator prior to randomization. Randomization was stratified by the percentage of PD-L1 expressing tumour cells (tumour proportion score, TPS≥50% versus <50%); by p16 status (yes versus no for oropharyngeal cancers, while other cancers were assumed to be p16-negative; and by ECOG performance status (0 versus 1). A temporary safety hold was imposed on randomization to the PEMB plus chemotherapy arm between August 13, 2014 and October 2, 2014, for safety review of deaths in that arm early in the study; following this review, randomization to the three arms was resumed. Patient follow-up continued until a sufficient number of events had accrued for the planned analyses involving OS and PFS.

Treatment was continued until disease progression as evaluated by RECIST v 1.1, intolerable toxicity, physician or patient decision, or completion of treatment, whichever occurred first. Patients randomized to PEMB or PEMB-chemo could receive PEMB for up to 35 21-day cycles. No upper limit was imposed on number of cycles or duration of CET. Patients randomized to chemotherapy could receive up to six 21-day cycles.

Tumour assessment

Tumour imaging and measurement was conducted at baseline, week 9, and every 6 weeks through year 1, then every 9 weeks through year 2, until radiographic disease progression. Thereafter, patients were followed up every 12 weeks for survival. Computed tomography (CT) imaging was preferred, but magnetic resonance imaging (MRI) could also be used. Imaging included the patient's head, neck, chest, and abdomen, with optimal imaging of the pelvis. The imaging modality, protocol and views were to be kept consistent throughout the trial for image comparison.

Site reading and interpretation of images based on RECIST 1.1 was used to determine patient eligibility, with central blinded retrospective review. Radiologic progression, as used for determination of endpoints, was based on independent central assessment. The central imaging vendor verified progressive disease identified by the site radiologist.

Outcomes

The co-primary endpoints are OS, defined as time from randomization to death from any causes, and PFS, defined as time from randomization to radiographically confirmed disease progression or death from any cause. Secondary endpoints are: Proportion who are progression free 6 and 12 months and ORR (defined as proportion of patients with overall response, complete response (CR) or partial response (PR) according to RECIST 1.1 criteria). DOR, defined as duration of response following CR or PR, was defined as an exploratory endpoint. PRO secondary endpoints were time to deterioration (TTD) in EORTC QLQ-C30 global health status/QoL and TTD in pain and swallowing as measured by EORTC QLQ-H&N35. Pre-specified exploratory endpoints were additional analyses of the EORTC QLQ-C30 and EORTC QLQ-H&N35 domains, and health utilities as measured by EQ-5D.

The primary analysis used RECIST 1.1 as confirmed by blinded independent central review. For patients receiving PEMB mono or PEMB-chemo, RECIST 1.1 was adapted to allow for the tumour response characteristics of immunotherapeutic agents. Once central review verified an initial assessment of PD, imaging was repeated ≥4 weeks later to confirm progression. The protocol offered the option of continuing treatment while awaiting radiologic confirmation of progression. If, upon repeat imaging, there was a reduction in tumour burden compared to the initial scan, treatment continued or resumed. If repeat imaging confirmed PD, subjects were discontinued from treatment.

EORTC QLQ-C30 is a self-reported scale of 30 items measuring QoL in patients with cancer. It contains 5 functional dimensions (physical, role, emotional, cognitive, social), 3 symptom items (fatigue, nausea/vomiting, pain), and 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). Twenty-eight questions covering these domains are answered on a 4-point scale from 1 (not at all) to 4 (very much). Two questions rate overall health and overall quality of life from 1 (very poor) to 7 (excellent). Five questions cover present status and the remainder ask about the past week. The global health quality of life and the global function scales are scored from 0 to 100, with higher values indicating greater quality of life or better function. MID for deterioration was defined as a 10-point worsening for both scales. EORTC QLQ-C30 was measured at treatment cycles 1 through 4, 6 (15 weeks), and every 2 cycles thereafter until discontinuation.

EORTC QLQ-H&N35 is a standard instrument measuring QoL in patients with head and neck cancer. It contains seven multi-item scales (mouth pain, problems with swallowing, senses, speech, social eating, social contact) and 11 single-item scales (problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, analgesic use, use of nutritional supplements, use of feeding tube, weight gain, weight loss). Thirty items are scored from 1 (not at all) to 4 (very much), and five are answered 1 (no) and 2 (yes). All questions ask about the previous week. True deterioration is defined as 10 points or greater from baseline, confirmed by a second, adjacent measurement. Deterioration was defined as a 10-point worsening for both pain and swallowing. EORTC QLQ-C30 was measured at treatment cycles 1 through 4, 6 (15 weeks), and every 2 cycles thereafter until discontinuation.

EuroQoL-5D (EQ-5D) is a standard instrument collecting health utility. Data are collected on five health state dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each question is asked on a 3-point scale, with 1 = extreme problem, 3 = no problem. Overall health status is graded 0 to 100 on a visual analog scale (VAS). A MID/MCID was not defined, as an analysis of clinically significant change was not planned.

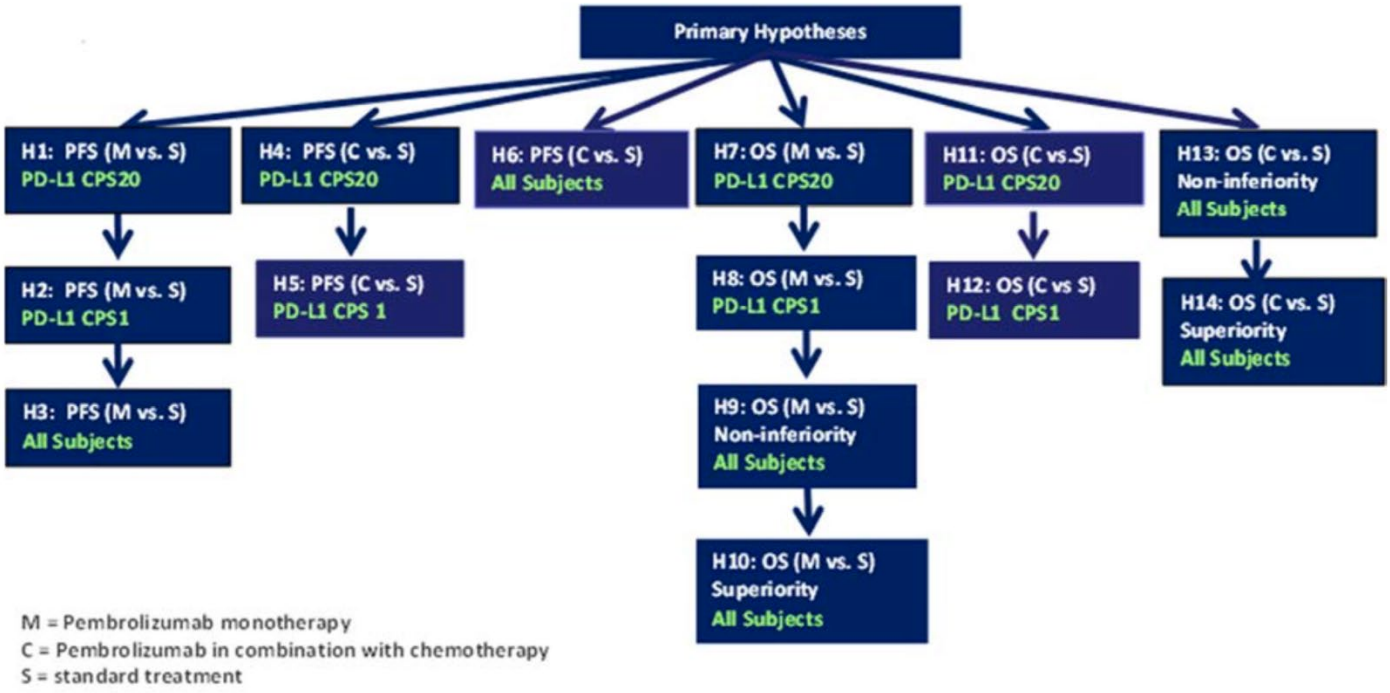
Statistical analysis

Hypotheses

The final protocol amendment declared four primary objectives which tested two comparisons (PEMB mono versus CET-chemo and PEMB-chemo versus CET chemo) for two outcomes (OS and PFS). Fourteen hypotheses (H1 to H14) were tested. Analyses could be conducted at three time points, two interim analyses (IA1 and IA2) and one final analysis. PFS hypotheses were tested at IA1, with a second test at IA2 (the final analysis for PFS) only if superiority was not declared at IA1 (as was the case for all hypotheses). OS hypotheses were tested at two interim analyses (IA1 and IA2), with the final analysis at FA. Figure 3 shows the scheme for testing of hypotheses derived from the primary objectives.

- **H1:** Superiority of PEMB mono versus CET-chemo for PFS in the CPS≥20 population (tested at IA1 and IA2)
  - **H2:** If superiority was shown for H1, testing of superiority of PEMB mono versus CET-chemo for PFS in the CPS≥1 population (could be tested at IA1 and IA2)
  - **H3:** If superiority was shown for H2, testing of superiority of PEBM mono versus CET-chemo for PFS in the ITT population (could be tested at IA1 and IA2)
- **H4:** Superiority of PEMB-chemo versus CET-chemo for PFS in the CPS≥20 population (tested at IA1 and IA2)
  - **H5:** If superiority was shown for H4, testing of superiority of PEMB-chemo versus CET-chemo for PFS in the CPS≥1 population (could be tested at IA1 and IA2)
- **H6:** Superiority of PEMB-chemo versus CET-chemo for PFS in the total population (tested at IA1 and IA2)
- **H7:** Superiority of PEMB mono versus CET-chemo for OS in the CPS≥20 population (tested at IA1, IA2 and FA)
  - **H8:** If superiority was shown for H7, testing of superiority of PEMB mono versus CET-chemo for OS CPS≥1 population (could be tested at IA1, IA2 and FA)
  - **H9:** If superiority was shown for H8, testing of noninferiority of PEMB mono versus CET-chemo for OS in the total population (could be tested at IA1, IA2 and FA)
  - **H10:** If noninferiority was shown for H9, testing of superiority of PEMB mono versus CET-chemo for OS in the total population (could be tested at IA1, IA2 and FA)
- **H11:** Superiority of PEMB-chemo versus CET-chemo for OS in the CPS≥20 population (tested at IA1, IA2 and FA)
  - **H12:** If superiority was shown for H11, testing of non-inferiority of PEMB-chemo versus CET-chemo for OS in the CPS≥1 population (could be tested at IA1, IA2 and FA)
- **H13:** Non-inferiority of PEMB-chemo versus CET-chemo for OS in the total population (tested at IA1, IA2 and FA)
  - **H14:** If non-inferiority was shown for H13, testing of superiority of PEMB-chemo versus CET-chemo for OS in the total population (could be tested at IA1, IA2 and FA)

Figure 3: Scheme for testing of hypotheses in KEYNOTE-048



Abbreviations: C = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, M = pembrolizumab monotherapy, PD-L1 = programmed death ligand 1, OS = overall survival, PFS = progression free survival, S = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil

Figure source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Sample size

The expected final sample size was approximately 882 patients. The sample size calculation for PFS assumed that: 1) PFS follows an exponential distribution with a median of 6 months in the CET-chemo treatment arm; 2) HRs for PFS are 0.58 for patients with PD-L1 CPS≥20, 0.59 for patients with PD-L1CPS≥1 and 0.6 for all patients; 3) the enrollment period would be 21 months; 4) there would be at least 9 months follow-up at IA1, and 17 months follow-up at IA2; and 5) the yearly dropout rate would be 5%. PFS hypotheses were tested at IA1, and only if superiority was not declared, at IA2 (final PFS analysis). At IA2 the expectations were:

- For patients with PD-L1 CPS≥20, approximately 237 PFS events observed across both arms would provide 90% power to detect a HR of 0.58 for PEMB mono versus CET-chemo (**H1**) and PEMB-chemo versus CET chemo (**H4**) at one-sided alpha = 0.0019.
- For patients with PD-L1 CPS≥1, approximately 378 PFS events observed across both arms would provide 98.6% power to detect a HR of 0.59 for PEMB mono versus CET-chemo (**H2**) and PEMB-chemo versus CET chemo (**H5**) at one-sided alpha = 0.0019. H2 and H5 would only be tested if H1 and H4, respectively, were rejected.
- For all patients, approximately 474 PFS events observed across both arms would provide 99.6% power to detect a HR of 0.60 for PEMB mono versus CET chemo (**H3**) at one-sided alpha = 0.0019. H3 would only be tested if H2 were rejected.
- For all patients, approximately 474 PFS events observed across both arms would provide 97.7% power to detect a HR of 0.6 for PEMB-chemo versus CET chemo (**H6**) at one-sided alpha = 0.002.

The sample size calculation for OS assumed that: 1) OS follows an exponential distribution with a median of 10 months in the CET-chemo treatment arm; 2) HRs for OS are 0.60 for patients with PD-L1 CPS≥20, 0.65 for patients with PD-L1CPS≥1 and 0.7 for superiority for all patients and 0.8 for non-inferiority for all patients; 3) the enrollment period would be 21 months; 4) there would be at least 23 months follow-up at FA; and 5) the yearly dropout rate would be 2%. OS was tested at two interim analyses and the final analysis. For the FA:

- For patients with PD-L1 CPS≥20, approximately 222 deaths observed across both arms would provide 90.5% power to detect a HR of 0.60 for PEMB mono versus CET-chemo (**H7**) and PEMB-chemo versus CET chemo (**H11**) at one-sided alpha = 0.007.
- For patients with PD-L1 CPS≥1, approximately 359 deaths observed across both arms would provide 94.3% power to detect a HR of 0.65 for PEMB mono versus CET-chemo (**H8**) and PEMB-chemo versus CET chemo (**H12**) at one-sided alpha = 0.007. H8 and H12 would only be tested if H7 and H11, respectively, were rejected.
- For all patients, approximately 455 deaths observed across both arms would provide 87.9% power to detect a HR of 0.85 for the non-inferiority comparison (NI margin = 1.2) for PEMB mono versus CET chemo (**H9**) and PEMB-chemo versus CET-chemo (**H13**) at one-sided alpha = 0.007. H9 would only be tested if H7 and H8 were rejected.
- For all patients, approximately 455 deaths observed across both arms would provide 90.4% power to detect a HR of 0.7 for the superiority comparison for PEMB mono versus CET chemo (**H10**) and PEMB-chemo versus CET-chemo (**H14**) at one-sided alpha = 0.007. H10 was only tested if H7, H8, and H9 were rejected, and H14 was only tested if H13 was rejected.

Hypothesis testing and control of multiplicity

Fourteen hypotheses (H1 to H14) were tested, covering the co-primary outcomes of OS and PFS for the three populations, ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20. Six hypotheses were tested in parallel with partitioning of the available alpha between them, followed by hierarchical testing of the remaining eight hypotheses. Alpha was also reallocated between selected hypotheses, depending upon results of testing. The overall hypothesis testing strategy is described above and depicted in Figure 3.

Figure 4 shows the strategy for controlling multiplicity, using the graphical method of Maurer and Bretz. Total alpha was (one sided) 0.025, allocated between the six initial hypotheses, H1 (0.0019), H4 (0.0019), H6 (0.0002), H7 (0.007), H11 (0.007), and H13 (0.007). In the diagram, these are identified in red text. Depending on the results of the testing, alpha was available to be passed between hypotheses. Thus:

- If superiority was shown for PEMB mono versus CET-chemo for PFS in the ITT population (**H3**), alpha could be passed to
  - Testing of superiority of PEMB mono versus CET-chemo for OS in the CPS≥20 population (**H7**)
- If superiority was shown for PEMB mono versus CET-chemo for OS in the ITT population (**H10**), alpha could be passed to
  - Testing of superiority of PEMB mono versus CET-chemo for PFS in the CPS≥20 population (**H1**)
  - Testing of superiority of PEMB-chemo versus CET-chemo for OS in the CPS≥20 population (**H11**)
  - Testing of noninferiority of PEMB-chemo versus CET-chemo for OS in the ITT population (**H13**)
- If superiority was shown for PEMB-chemo versus CET-chemo for OS in the ITT population (**H14**), alpha could be passed to
  - Testing of superiority of PEMB mono versus CET-chemo for OS in the CPS≥20 population (**H7**)
  - Testing of superiority of PEMB-chemo versus CET-chemo for PFS in the CPS≥20 population (**H4**)
- If superiority were shown for PEMB-chemo versus CET-chemo for PFS in the ITT population (**H6**), alpha could be passed to
  - Testing of superiority of PEMB-chemo versus CET-chemo for OS in the CPS≥20 population (**H11**)
  - Testing of noninferiority of PEMB-chemo versus CET-chemo for OS in the ITT population (**H13**).

Available alpha at IA2 and FA was determined using the spending fraction and the information fraction (ratio of the actual number of deaths or PFS events at the interim analysis to the targeted number of deaths or PFS events at the final analysis). The final analysis used the alpha unspent at IA2, regardless of the number of events. The calculation of the P-value test boundary took account of the correlation between test statistics as determined by the actual number of OS events at the previous and current analyses.

Figure 4: Strategy for controlling multiplicity for KEYNOTE-048

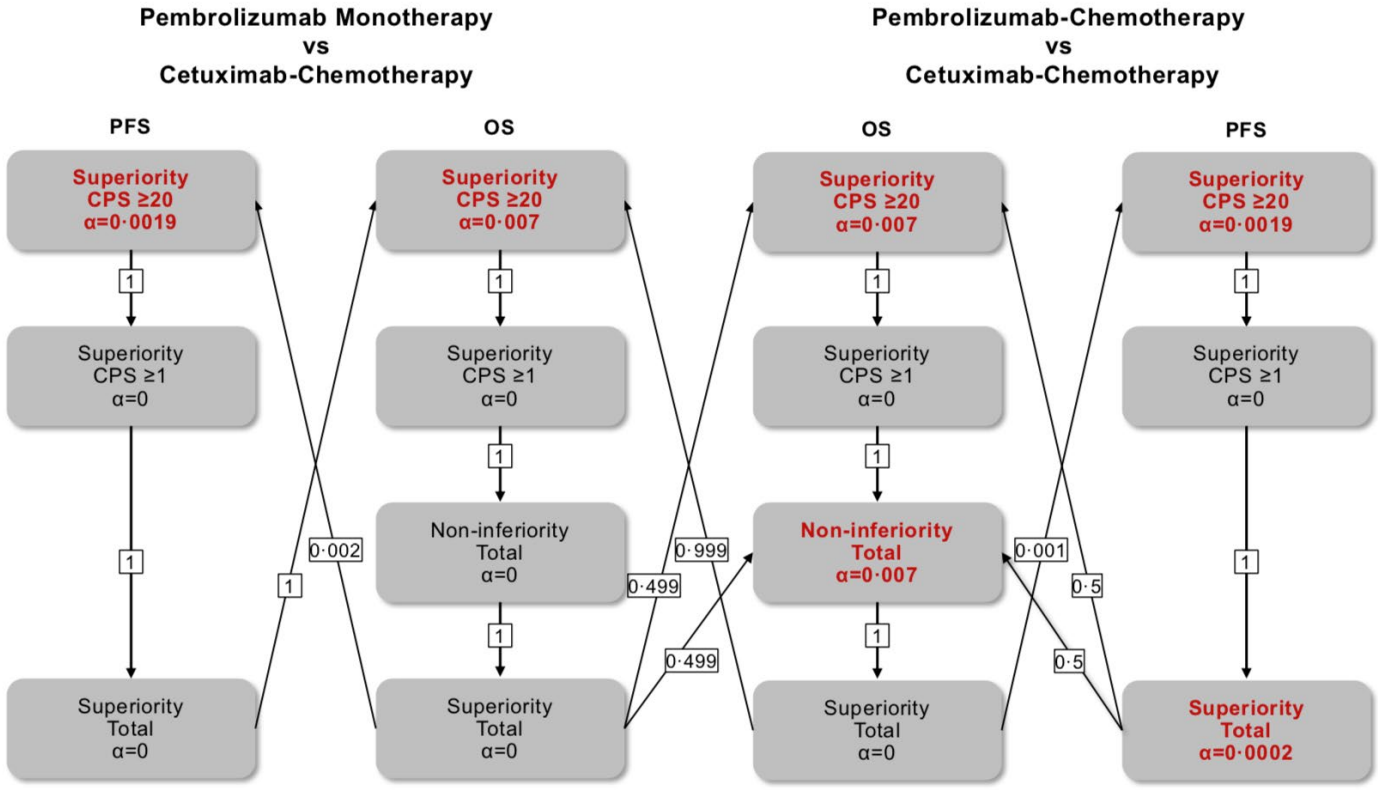


Figure source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Multiplicity was not controlled for the analyses of the secondary efficacy and HRQoL outcomes (proportion of PFS at 6 and 12 mos, ORR, DOR, and mean change from baseline in global health status/QoL and TTD in global health status/QoL, and pain and swallowing).

Analysis methods for individual endpoints

OS and PFS were both estimated using a non-parametric Kaplan-Meier method with testing for treatment difference using a stratified log-rank test. HRs were estimated using a stratified Cox proportional hazard model with Efron's method for tie-handling. The analyses used the same stratification factors as in randomization; for the ITT and PD-L1 CPS≥1 population these were PD-L1 TPS≥50%, HPV and ECOG status, and for the PD-L1 CPS≥20 population, HPV and ECOG status. If low events were found in one or more strata, then stratification factors were successively omitted from the model in the order ECOG, HPV, and all stratification factors.

The planned OS analyses could include explorations of the effects of cross-over to other anti PD-L1 treatments following disease progression. Previous experience with comparisons between immunotherapy and chemotherapy suggested that the proportional hazards assumption might not hold. This was assessed using graphical methods and a survival model that incorporated a treatment by time interaction. Planned sensitivity analyses involved tested for difference using a Fleming and Harrison weighted log-rank test with parameter (0,1), which weighted testing towards late differences between survival curves, and a restricted mean survival time (RMST) analysis from 3 to 24 months of follow-up.

In the PFS analyses, the date of disease progression was approximated by the date at which progression was documented by central imaging review, according to RECIST 1.1. Sensitivity analyses were conducted to assess the influence of missing assessments, to incorporate treatment discontinuation as an indicator of disease progression in patients without documented

progressive disease or death, to compare results for PFS by central review and investigator assessment, and to assess the effect of non-proportional hazards (RMST). The calculation of proportion of patients who survived or were progression free at various time-points was based on the KM analyses.

ORR comparisons between treatments used the stratified Miettinen and Nurminem's method with the same stratification factors as used for OS and PFS analyses, and the same strategy to address low events in one or more strata by combining strata. DOR was calculated for patients who had shown CR or PR as the time from the first documented event of CR or PR until disease progression or death from any cause. Patients who were known to be alive, without documented progression, loss to follow-up, or initiation of a new cancer treatment, and who had had a disease assessment within ~5 months for the data cut-off were assumed to have ongoing response.

For the analyses of patient reported outcomes, TTD in global health status/QoL, pain and swallowing, the KM method was used to estimate the TTD survival curve for selected endpoints. The difference in treatment groups was estimated using the stratified Cox proportional hazards model with Efron's method tie handling and the same stratification factors as were used for the PFS and OS analyses.

Subgroup analyses

Prespecified analyses were conducted for the following subgroups:

Randomization stratification factors
- ECOG (0 versus 1, stratification factor for randomization)
- PD-L1 TPS (≥50% versus <50%, stratification factor for randomization)
- HPV status (positive versus negative, stratification

Non-stratification factors
- Age category (< 65 years versus ≥ 65 years)
- Sex (female versus male)
- Race (White versus all others)
- Region (North America versus European Union versus Rest of the World)
- Smoking status (never versus former versus current)
- PD-L1 CPS (≥ 20 versus < 20; ≥ 1 versus < 1)
- Disease status (recurrent versus metastatic)

Subgroup analyses were descriptive and not adjusted for multiplicity, therefore were considered exploratory only.

Safety analysis

Interim safety analyses used the safety population (All Subjects as Treated, ASaT), which grouped patients according to the treatment they received, and were planned for the following time-points:

- A formal interim safety analysis after ten patients in the PEMB-chemo arm had completed 2 cycles of therapy. If more than 80% of patients required a dose modification of platinum and/or 5-FU by the end of 2 cycles, a protocol modification permanently reducing dosing was to be considered, while if more than 80% of patients required 2 dose modification of platinum and/or 5-FU by the end of 2 cycles, permanent discontinuation of the arm was to be considered.
- Interim safety analyses conducted approximately every quarter after completion of the formal interim safety analysis, in which dose modification and AE data were summarized for review.

Protocol amendments

There were 10 protocol amendments between the original protocol and January 11, 2019. Six were global amendments and four were country-specific amendments adding required assessments of benefit/risk for Norway, Sweden, or both countries. The global assessments made the following changes:

- *Changes to exclusion criteria.* Changes to exclusion criteria based on accumulating data on pembrolizumab safety profile, definitions of laboratory values, and clarifications of requirements for sample availability and testing (Amendment 1, June 26, 2015;

Amendment 5, August 5, 2016). Criteria were added that excluded patients with radiation therapy within 2 weeks prior to randomization or who had not recovered from adverse events of previous treatment (with exceptions of ≤Grade 2 neuropathy, ≤Grade 2 neuropathy, and laboratory abnormalities that did not meet the exclusion criteria for adequate organ function), life expectancy <3 months or rapidly progressive disease, history of allogenic tissue/solid organ transport.

- *Changes to dosing guidelines.* Dose modification guidelines were updated per health authority feedback (Amendment 9, November 9, 2017), adding specific management for Type 1 diabetes mellitus or hyperglycemia and myocarditis, and expanding guidance for management and monitoring of the other adverse events. Changes in guidelines for pembrolizumab dose withholding and discontinuation were minimal.
- *Changes to sample size.* The sample size was increased from 750 to 780 patients, based on the prevalence of strongly positive PD-L1 expression (by PD-L1 TPS) observed in HNSCC cohorts in KEYNOTE-048 (Amendment 1, June 26, 2015), and then to 825 patients, in response to OS being changed from a secondary to a primary objective and the biomarker populations being redefined (Amendment 5, August 5, 2016).
- *Changes to subpopulations.* The biomarker population was initially defined according to PD-L1 TPS but was redefined according to PD-L1 CPS (combined proportion score, incorporating PD-L1 expression on tumour and infiltrating immune cells). Data from KEYNOTE-012 suggested that CPS showed improved association with clinical outcome in patients treated with pembrolizumab, compared with TPS. The subgroups defined were PD-L1 CPS ≥ 20, CPS ≥ 10, and CPS ≥ 1, while the strongly positive PD-L1 (TPS ≥ 50%) enrichment population was removed (Amendment 5, August 5, 2015). The PD-L1 CPS ≥ 10 population was subsequently removed (Amendment 7, March 17, 2017), leaving CPS ≥ 20 and CPS ≥ 1 as the populations of interest.
- *Changes to follow-up time.* Follow-up time was increased at the interim and final analyses by 3 months to achieve data maturity at these timepoints (Amendment 8, August 24, 2017) and again for the second interim analysis and final analysis to allow adequate follow-up time to assess long-term effects of pembrolizumab (Amendment 9, November 9, 2017). The final amendment referred to expected events, rather than required events, removed references to “event-driven” timing, and enabled the timing of the final analysis to accommodate a scenario where the number of deaths for one hypothesis accumulates slower than expected to prevent the trial continuing for an unreasonable period for the final analysis (Amendment 10, January 11, 2019).
- *Changes to endpoints.* In the original protocol, the primary endpoint was PFS, with secondary endpoints including OS, proportion of patients progression free at 6 and 12 months, ORR, DUR, and safety and tolerability. OS was changed from a secondary endpoint to a primary endpoint on the basis of external evidence from trials of nivolumab in non-squamous non-small cell lung cancer (NSCLC) and recurrent or metastatic HNSCC and pembrolizumab in non-squamous NSCLC that PFS was a poor predictor of survival in patients receiving immunotherapy (Amendment 5, August 5, 2016). HRQoL secondary objectives were added (change from baseline in global health status and time to deterioration in global health status/QoL, swallowing, and pain) and ORR (Amendment 5, August 5, 2015). DOR and PFS per irRECIST were changed from secondary to exploratory objectives (Amendment 5, August 5, 2015). DOR was changed from a secondary to an exploratory endpoint (Amendment 7, March 17, 2017).
- *Changes to hypotheses and statistical testing strategy.* The original protocol included three primary hypotheses, superiority of PEMB mono versus CET-chemo for PFS in the ITT and PD-L1 strongly positive (PD-L1 TPS ≥ 50%) populations, and superiority of PEMB-chemo versus CET-chemo for PFS in the ITT population. A hypothesis was added concerning PFS for PEMB-chemo compared with standard treatment in subjects with strongly positive PD-L1 expression (Amendment 1, June 26, 2015).

  When OS was changed to a primary endpoint, the analysis plan was amended to include 12 primary hypotheses: superiority of PEMB mono versus CET-chemo for OS and PFS in the ITT, PD-L1 CPS ≥ 1, CPS ≥ 10, and CPS ≥ 20 populations; superiority of PEMB-chemo versus CET-chemo for OS and PFS in the ITT population; non-inferiority of PEMB versus CET-chemo and PEMB-chemo versus CET-chemo for OS in the ITT population. Hypotheses for PFS and OS superiority in the biomarker positive subpopulation were added (Amendment 9, November 9, 2017). Two of these hypotheses were removed when the PD-L1 CPS≥10 population was removed (Amendment 7, March 17, 2017), and four hypotheses were added: superiority of PEMB-chemo versus CET-chemo for OS and PFS in the PD-L1 CPS ≥ 1 and CPS ≥ 20 populations.

b) Populations

The analysis populations for efficacy and safety analysis are shown in Table 7. A total of 882 participants were randomized, 301 to PEMB mono, 281 to PEMB-chemo, and 300 to CET-chemo. Twenty-two patients were randomized to CET-chemo during the pause in enrollment between August 13, 2015, and October 2, 2015. These patients were excluded from the comparison of PEMB-chemo versus CET-chemo, as randomization for PEMB-chemo versus CET-chemo during that time period was not preserved. The patients were included in the comparison of PEMB mono versus CET-chemo.

Efficacy endpoints were analyzed for three populations:

- ITT population (all participants regardless of PD-L1 status), consisting of 601 patients for the comparison of PEMB mono versus CET-chemo and 559 patients for the comparison of PEMB-chemo versus CET chemo.
- PD-L1 CPS ≥1 population (ITT patients with PD-L1 CPS ≥1), consisting of 512 patients for the comparison of PEMB mono versus CET-chemo and 477 patients for the comparison of PEMB-chemo versus CET-chemo.
- PD-L1 CPS ≥20 population (ITT patients with PD-L1 CPS ≥20), consisting of 255 patients for the comparison of PEMB mono versus CET-chemo and 236 patients for the comparison of PEMB-chemo versus CET-chemo.

Safety data were analyzed for the All Subjects as Treated population (ASaT), which analyzed patients according to the treatment they received.

Quality-of-life endpoints were analyzed for three populations:

- PRO FAS population, consisting of all participants who were randomized and treated and had at least one PRO assessment, regardless of PD-L1 status.
- PRO FAS CPS ≥1 population (PRO FAS patients with PD-L1 CPS ≥1)
- PRO FAS CPS ≥20 population (PRO FAS patients with PD-L1 CPS ≥20)

Table 7: Analysis populations for KEYNOTE-048

	PEMB mono versus CET-chemo		PEMB-chemo versus CET-chemo	
	PEMB	CET-chemo	PEMB-chemo	CET-chemo
Subjects Randomized, n	301	300	281	300
ITT, n (%)	301 (100.0)	300 (100.0)	281 (100.0)	278 (92.7)
PD-L1 CPS ≥ 1, n (%)	257 (85.4)	255 (85.0)	242 (86.1)	235 (78.3)
PD-L1 CPS ≥ 20, n (%)	133 (44.2)	122 (40.7)	126 (44.8)	110 (36.7)
All-Subjects-as-Treated (ASaT), n (%)	300 (99.7)	287 (95.7)	276 (98.2)	287 (95.7)
PRO FAS, n (%)	294 (97.6)	279 (93.0)	268 (95.4)	259 (86.3)

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, ITT = intention to treat, PD-L1 = programmed death ligand 1, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Database cut-off: June 13, 2018

Source: EPAR 2019[26]

PEMB mono versus CET-chemo comparison

Table 8 shows baseline patient characteristics for the three populations for the comparison between PEMB mono and CET chemo. Table 9 shows a summary of prior lines of therapy for the ITT population.

In the ITT population the majority of patients were male (85.0%), White or Asian (73.7% and 18.6%, respectively), and not Hispanic or Latino (77.2%). The median age was 61 years, range 22 to 94 years. Most patients were current or former smokers (15.6% and 63.1%, respectively), and had an ECOG performance score of 1 (60.9%). Most patients had metastatic disease (69.7%). The primary tumour site was the oropharynx for 37.8%, the oral cavity for 28.8%, the larynx for 22.5%, and the hypopharynx for 12.8%. Most patients had tumours with PD-L1 expression, with PD-L1 TPS strongly positive (≥50%) in 22.1%, PD-L1 CPS ≥ 1 in 85.2% and PD-L1 CPS ≥ 20 in 42.2%. HPV status was negative in 78.4%. Around half had received prior systemic therapy, with most receiving platinum and a small proportion receiving cetuximab (around 7%; Table 9) Their median time from the latest platinum therapy was 553 days (range 119 to 6817 years, reported for 269 patients), and the time from prior systemic therapy was 530 days (35 to 9264

days, reported for 297 patients). Selection of platinum was done prior to randomization, and for those patients randomized to CET-chemo, 130 (43%) patients were to receive cisplatin at baseline and 170 (57%) to receive carboplatin.

The balance at baseline for the ITT population was generally good. PEMB mono had a lower proportion of males (83.1% versus 87.0%), a higher proportion of patients with PD-L1 CPS ≥ 20 (44.2% versus 40.7%) and metastatic disease (71.8% versus 67.7%), and a shorter time since previous therapy: median time from latest platinum therapy 518 days versus 596 days and median time from prior systemic therapy 511.0 to 571.5 days. These differences are unlikely to have an impact on the treatment difference observed.

The PD-L1 CPS≥1 group (512 patients total) had similar characteristics to the ITT population. PEMB mono had a lower proportion of males (83.1% versus 86.3%), a higher proportion of patients with PD-L1 CPS ≥ 20 (51.8% versus 47.8%) and metastatic disease (69.6% versus 65.9%), and a shorter time since previous therapy: median time from latest platinum therapy 510 days versus 585.5 days and median time from prior systemic therapy 507.5 to 627.0 days. These differences are unlikely to have an impact on the treatment difference observed.

In the smaller PD-L1 CPS≥20 group (255 patients total), the difference in proportion of males between groups was greater (78.2% for PEMB mono versus 88.5% for CET chemo). In the PEMB mono group, the patients were younger (<65 years, 60.2% versus 69.7%), and a lower proportion are HPV positive (18.0% versus 23.0%). The proportion with metastatic disease was similar (66.2% versus 64.8%), as was the time from latest platinum therapy 512.5 days versus 529.5 days. There was still a difference in time from prior systemic therapy, median 509 days versus 582.5 days. Since males tended to have a poorer outcome, the baseline imbalance has the potential to create a bias favouring PEMB mono. Sensitivity analyses reported by the manufacturer suggest that the impact was minimal.

The most commonly used concomitant medication was [redacted] randomized to PEMB mono and [redacted] randomized to CET-chemo.[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 8: Baseline patient characteristics for PEMB mono versus CET-chemo in KEYNOTE-048 (ITT, CPS ≥ 1, and CPS ≥ 20 populations)

	ITT		PD-L1 CPS ≥ 1		PD-L1 CPS ≥20	
	PEMB mono	CET-chemo	PEMB mono	CET-chemo	PEMB mono	CET-chemo
Subjects in population	301	300	257	255	133	122
Gender						
Male	250 (83.1)	261 (87.0)	209 (81.3)	220 (86.3)	104 (78.2)	108 (88.5)
Female	51 (16.9)	39 (13.0)	48 (18.7)	35 (13.7)	29 (21.8)	14 (11.5)
Age (Years)						
<65	190 (63.1)	195 (65.0)	163 (63.4)	166 (65.1)	80 (60.2)	85 (69.7)
≥65	111 (36.9)	105 (35.0)	94 (36.6)	89 (34.9)	53 (39.8)	37 (30.3)
Mean	61.2	61	60.8	60.8	60.5	59.8
SD	9.4	10	9.7	10.2	10.2	10.2
Median	62	61	62	61	62	60
Range	22 to 94	24 to 84	22 to 94	24 to 84	22 to 83	24 to 81
Race						

	ITT		PD-L1 CPS ≥ 1		PD-L1 CPS ≥20	
	PEMB mono	CET-chemo	PEMB mono	CET-chemo	PEMB mono	CET-chemo
American Indian Or Alaska Native	5 (1.7)	6 (2.0)	4 (1.6)	6 (2.4)	2 (1.5)	3 (2.5)
Asian	58 (19.3)	54 (18.0)	50 (19.5)	47 (18.4)	24 (18.0)	22 (18.0)
Black or African American	4 (1.3)	6 (2.0)	3 (1.2)	3 (1.2)	2 (1.5)	1 (0.8)
Multi-Racial	12 (4.0)	9 (3.0)	10 (3.9)	9 (3.5)	7 (5.3)	4 (3.3)
White	219 (72.8)	224 (74.7)	188 (73.2)	189 (74.1)	98 (73.7)	92 (75.4)
Missing	3 (1.0)	1 (0.3)	2 (0.8)	1 (0.4)	0	0
Ethnicity						
Hispanic of Latino	46 (15.3)	44 (14.7)	35 (13.6)	34 (13.3)	22 (16.5)	15 (12.3)
Not Hispanic or Latino	233 (77.4)	231 (77.0)	204 (79.4)	199 (78.0)	101 (75.9)	93 (76.2)
Not Reported	19 (6.3)	16 (5.3)	16 (6.2)	15 (5.9)	10 (7.5)	9 (7.4)
Unknown	3 (1.0)	9 (3.0)	2 (0.8)	7 (2.7)	0 (0.0)	5 (4.1)
Region group						
North America	75 (24.9)	62 (20.7)	68 (26.5)	54 (21.2)	32 (24.1)	31 (25.4)
Europe	87 (28.9)	105 (35.0)	74 (28.8)	92 (36.1)	44 (33.1)	42 (34.4)
Rest of world	139 (46.2)	133 (44.3)	115 (44.7)	109 (42.7)	57 (42.9)	49 (40.2)
Smoking Status						
Never Smoker	62 (20.6)	64 (21.3)	59 (23.0)	61 (23.9)	34 (25.6)	30 (24.6)
Ex Smoker	186 (61.8)	193 (64.3)	154 (59.9)	156 (61.2)	82 (61.7)	71 (58.2)
Current Smoker	53 (17.6)	41 (13.7)	44 (17.1)	36 (14.1)	17 (12.8)	20 (16.4)
Missing	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.8)
ECOG†						
0	118 (39.2)	117 (39.0)	104 (40.5)	101 (39.6)	58 (43.6)	52 (42.6)
1	183 (60.8)	183 (61.0)	153 (59.5)	154 (60.4)	75 (56.4)	70 (57.4)
HPV p16 Status†						
Positive	63 (20.9)	67 (22.3)	54 (21.0)	55 (21.6)	24 (18.0)	28 (23.0)
Negative	238 (79.1)	233 (77.7)	203 (79.0)	200 (78.4)	109 (82.0)	94 (77.0)
PD-L1 TPS Status†						
Strongly Positive	67 (22.3)	66 (22.0)	67 (26.1)	66 (25.9)	66 (49.6)	62 (50.8)
Not Strongly Positive	234 (77.7)	234 (78.0)	190 (73.9)	189 (74.1)	67 (50.4)	60 (49.2)
PD-L1 CPS status (CPS≥1)						
CPS≥1	257 (85.4)	225 (85)	NA	NA	NR	NR
CPS <1	44 (14.6)	45 (15)	NA	NA	NR	NR
PD-L1 CPS status (CPS≥20)						
CPS ≥20	133 (44.2)	122 (40.7)	133 (51.8)	122 (47.8)	NA	NA
CPS < 20	167 (55.5)	175 (58.3)	123 (47.9)	131 (51.4)	NA	NA
Missing	1 (0.3)	3 (1)	1 (0.4)	2 (0.8)	NA	NA
PD-L1 CPS status						

	ITT		PD-L1 CPS ≥ 1		PD-L1 CPS ≥20	
	PEMB mono	CET-chemo	PEMB mono	CET-chemo	PEMB mono	CET-chemo
CPS < 1	44 (14.6)	45 (15)	NA	NA	NA	NA
1 ≤ CPS < 20	124 (41.2)	133 (44.3)	NA	NA	NA	NA
CPS ≥ 20	133 (44.2)	122 (40.7)	NA	NA	NA	NA
Disease Status						
Metastatic	216 (71.8)	203 (67.7)	179 (69.6)	168 (65.9)	88 (66.2)	79 (64.8)
Recurrent	82 (27.2)	94 (31.3)	75 (29.2)	84 (32.9)	42 (31.6)	42 (34.4)
Neither	3 (1)	3 (1)	3 (1.2)	3 (1.2)	3 (2.3)	1 (0.8)
Primary Tumour Location						
Oral cavity	82 (27.2)	91 (30.3)	75 (29.2)	80 (31.4)	49 (36.8)	49 (40.2)
Larynx	74 (24.6)	61 (20.3)	57 (22.2)	53 (20.8)	25 (18.8)	19 (15.6)
Hypopharynx	38 (12.6)	39 (13.0)	34 (13.2)	32 (12.5)	16 (12.0)	8 (6.6)
Oropharynx	113 (37.5)	114 (38.0)	97 (37.7)	94 (36.9)	46 (34.6)	46 (37.7)
Time from Latest Platinum Therapy (days)						
Subjects with data	132	137	112	120	56	56
Mean	766.3	887	754.6	860.9	840.1	940.4
SD	666	902.7	676.3	864.3	803.3	1102.8
Median	518.5	596	510.0	585.5	512.5	529.5
Range	193 to 4620	119 to 6817	193 to 4620	201 to 6817	193 to 4620	224 to 6817
Time from Prior Systemic Therapy (days)						
Subjects with data	151	146	130	125	63	58
Mean	809.8	862.7	810.8	847	971.1	925.4
SD	980.9	877	1029.7	846.5	1373.3	1084.3
Median	511	571.5	507.5	627	509	582.5
Range	35 to 9264	119 to 6817	35 to 9264	201 to 6817	35 to 9264	224 to 6817

† Randomization stratification variables

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, ECOG = Eastern Cooperative Oncology Group, HPV = human papilloma virus, NA = not applicable, NR = not reported, PEMB = pembrolizumab, TPS = Tumour Proportion Score

Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

Table 9: Prior therapy for PEMB mono versus CET-chemo, ITT population

	PEMB mono	CET-chemo
	n(%)	n(%)
Subjects in population	301	300
Subjects with no prior systemic therapy	150 (49.8)	154 (51.3)
Primary/Locally Advanced/With Curative Intent	143 (47.5)	143 (47.7)
Cetuximab	20 (6.6)	18 (6.0)

	PEMB mono	CET-chemo
	n(%)	n(%)
Platinum	125 (41.5)	134 (44.7)
Recurrent/With Curative Intent	11 (3.7)	5 (1.7)
Cetuximab	3 (1.0)	0 (0.0)
Platinum	9 (3.0)	4 (1.3)

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB mono = pembrolizumab monotherapy

Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

PEMB-chemo versus CET chemo comparison;

Table 10 shows baseline patient characteristics for the three populations (ITT, PD-L1 CPS ≥ 1, and PD-L1 CPS ≥ 20) for the comparison between PEMB-chemo and CET-chemo. Table 11 shows a summary of prior lines of therapy for the ITT population.

In the ITT population the majority of patients were male (83.4%), White or Asian (73.3% and 19.5%, respectively), and not Hispanic or Latino (75.8%). The median age was 61 years, range 20 to 85 years. Most patients were current or former smokers (16.5% and 62.1%, respectively), and had an ECOG performance score of 1 (61.0%). Most patients had metastatic disease (69.4%). The primary tumour site was the oropharynx for 39.4%, the oral cavity for 29.7%, the larynx for 18.2%, and the hypopharynx for 14.3%. Most had tumours with PD-L1 expression, with PD-L1 TPS strongly positive (≥50%) in 22.9%, PD-L1 CPS ≥ 1 in 83.5% and PD-L1 CPS ≥ 20 in 42.4%. HPV status was negative in 78.4%. Around half had received prior systemic therapy, with most receiving platinum and a small proportion receiving cetuximab (around 6%; Table 11). Their median time from the latest platinum therapy was 513 days (range 119 to 6817 days, reported for 260 patients), and the time from prior systemic therapy was 449 days (range 119 to 6817 days, reported for 279 patients; Table 10). Selection of platinum therapy was made prior to randomization. For patients randomized to PEMB-chemo, 121 (43%) were to receive cisplatin at baseline, and 160 (57%) were to receive carboplatin. For patients randomized to CET-chemo, 122 (44%) patients were to receive cisplatin at baseline and 156 (56%) were to receive carboplatin.

The balance at baseline for the ITT population was generally good. PEMB-chemo had a lower proportion of males (79.7% versus 87.1%), a higher proportion of patients with PD-L1 CPS ≥ 20 (44.8% versus 39.6%) and metastatic disease (71.8% versus 67.3%), and a shorter time since previous therapy: median time from latest platinum therapy 457.5 days versus 585.5 days and median time from prior systemic therapy 449 to 571.5 days. These differences are unlikely to have an impact on the treatment difference observed.

The PD-L1 CPS≥1 group (477 patients total) has similar characteristics to the ITT population. PEMB-chemo had a lower proportion of males (77.7% versus 86.4%), a higher proportion of patients with PD-L1 CPS ≥ 20 (52.1% versus 46.8%) and metastatic disease (71.5% versus 65.5%), and a shorter time since previous therapy: median time from latest platinum therapy 441.0 days versus 575.0 days and median time from prior systemic therapy 440.0 to 601.0 days. These differences are unlikely to have an impact on the treatment difference observed.

In the smaller PD-L1 CPS≥20 group (236 patients total), the difference in proportion of males between groups was greater (71.4% for PEMB-chemo versus 87.3% for CET chemo). In the PEMB-chemo group, the patients were younger (<65 years, 61.1% versus 70.0%). The proportion with metastatic disease was higher (69.0% versus 62.7%). The time from previous therapy is shorter: time from latest platinum therapy median 430.0 days versus 502.0 days, and prior systemic therapy, median 421.0 days versus 512.5 days. Since males tended to have a poorer outcome, the baseline imbalance had the potential to create a bias favouring PEMB-chemo. Sensitivity analyses reported by the manufacturer suggest that the impact was minimal.

The most commonly used concomitant medication was [redacted] randomized to PEMB-chemo and [redacted] randomized to CET-chemo.[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 10: Baseline patient characteristics PEMB-chemo versus CET-chemo in KEYNOTE-048 (ITT, CPS ≥ 1, and CPS ≥ 20 populations)

	ITT		CPS ≥ 1		CPS ≥ 20	
	PEMB chemo	CET chemo	PEMB chemo	CET chemo	PEMB chemo	CET chemo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects in population	281	278	242	235	126	110
Gender						
Male	224 (79.7)	242 (87.1)	188 (77.7)	203 (86.4)	90 (71.4)	96 (87.3)
Female	57 (20.3)	36 (12.9)	54 (22.3)	32(13.6)	36 (28.6)	14 (12.7)
Age (Years)						
<65	180 (64.1)	181 (65.1)	153 (63.2)	152 (64.7)	77 (61.1)	77 (70.0)
≥65	101 (35.9)	97 (34.9)	89 (36.8)	83 (35.3)	49 (38.9)	33 (30.0)
Mean	60.7	60.9	60.6	60.8	61.1	59.8
SD	9.8	10	9.9	10.3	9.6	10.2
Median	61	61	61	61	62	60
Range	20 to 85	24 to 84	20 to 85	24 to 84	28 to 85	24 to 80
Race						
American Indian Or Alaska Native	3 (1.1)	6 (2.2)	2 (0.8)	6 (2.6)	1 (0.8)	3 (2.7)
Asian	60 (21.4)	49 (17.6)	48 (19.8)	43 (18.3)	24 (19.0)	20 (18.2)
Black or African American	11 (3.9)	6 (2.2)	10 (4.1)	3 (1.3)	3 (2.4)	1 (0.9)
Multi-Racial	4 (1.4)	9 (3.2)	4 (1.7)	9 (3.8)	3 (2.4)	4 (3.6)
White	203 (72.2)	207 (74.5)	178 (73.6)	173 (73.6)	95 (75.4)	82
Missing	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0	0
Ethnicity						
Hispanic of Latino	45 (16.0)	44 (15.8)	39 (16.1)	34 (14.5)	24 (19.0)	15 (13.6)
Not Hispanic or Latino	213 (75.8)	211 (75.9)	185 (76.4)	181 (77.0)	96 (76.2)	82 (74.5)
Not Reported	18 (6.4)	14 (5.0)	14 (5.8)	13 (5.5)	4 (3.2)	8 (7.3)
Unknown	5 (1.8)	9 (3.2)	4 (1.7)	7 (3.0)	2 (1.6)	5 (4.5)
Region group						
North America	60 (21.4)	59 (21.2)	53 (21.9)	51 (21.7)	30 (23.8)	30 (27.3)
Europe	88 (31.3)	94 (33.8)	76 (31.4)	82 (34.9)	39 (31.0)	35 (31.8)
Rest of world	133 (47.3)	125 (45.0)	113 (46.7)	102 (43.4)	57 (45.2)	45 (40.9)
Smoking Status						
Never Smoker	57 (20.3)	61 (21.9)	50 (20.7)	58 (24.7)	30 (23.8)	28 (25.5)
Ex Smoker	168 (59.8)	179 (64.4)	143 (59.1)	142 (60.4)	75 (59.5)	63 (57.3)
Current Smoker	56 (19.9)	36 (12.9)	49 (20.2)	33 (14.0)	21 (16.7)	18 (16.4)
Missing	0	2 (0.7)	0	2 (0.9)	0	1 (0.9)
ECOG†						
0	110 (39.1)	108 (38.8)	92 (38.0)	94 (40.0)	47 (37.7)	47 (42.7)
1	171 (60.9)	170 (61.2)	150 (62.0)	141 (60)	79 (62.7)	63 (57.3)
HPV Status†						
Positive	60 (21.4)	61 (21.9)	53 (21.9)	50 (21.3)	27 (21.4)	25 (22.7)
Negative	221 (78.6)	217 (78.1)	189 (78.1)	185 (78.7)	99 (78.6)	85 (77.3)

	ITT		CPS ≥ 1		CPS ≥ 20	
	PEMB chemo	CET chemo	PEMB chemo	CET chemo	PEMB chemo	CET chemo
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PD-L1 TPS Status†						
Strongly Positive	66 (23.5)	62 (22.3)	66 (27.3)	62 (26.4)	65 (51.6)	58 (52.7)
Not Strongly Positive	215 (76.5)	216 (77.7)	176 (72.7)	173 (73.6)	61 (48.4)	52 (47.3)
PD-L1 CPS status (CPS≥1)						
CPS≥1	242 (86.1)	235 (84.5)	NA	NA	NR	NR
CPS <1	39 (13.9)	43 (15.5)	NA	NA	NR	NR
PD-L1 CPS status (CPS≥20)						
CPS ≥20	126 (44.8)	110 (39.6)	126 (52.1)	110 (46.8)	NA	NA
CPS < 20	154 (54.8)	165 (59.4)	115 (47.5)	123 (52.3)	NA	NA
Missing	1 (0.4)	3 (1.1)	1 (0.4)	2 (0.9)	NA	NA
PD-L1 CPS status						
CPS < 1	39 (13.9)	43 (15.5)	NA	NA	NA	NA
1 ≤ CPS < 20	116 (41.3)	125 (45)	NA	NA	NA	NA
CPS ≥ 20	126 (44.8)	110 (39.6)	NA	NA	NA	NA
Disease Status						
Metastatic	201 (71.5)	187 (67.3)	173 (71.5)	154 (65.5)	87 (69.0)	69 (62.7)
Recurrent	76 (27)	88 (31.7)	65 (26.5)	78 (33.2)	38 (30.2)	40 (36.4)
Neither	4 (1.4)	3 (1.1)	4 (1.7)	3 (1.3)	1 (0.8)	1 (0.9)
Primary Tumour Location						
Oral cavity	82 (29.2)	84 (30.2)	77 (31.8)	73 (31.1)	51 (40.5)	44 (40.0)
Larynx	46 (16.4)	56 (20.1)	37 (15.3)	48 (20.4)	14 (11.1)	16 (14.5)
Hypopharynx	44 (15.7)	36 (12.9)	33 (13.6)	30 (12.8)	17 (13.5)	7 (6.4)
Oropharynx	113 (40.2)	107 (38.5)	98 (40.5)	88 (37.4)	45 (35.7)	43 (39.1)
Time from Latest Platinum Therapy (days)						
Subjects with data	130	130	109	113	53	50
Mean	795	893.5	734.4	866.8	813.7	951
SD	954.8	920.1	939.9	883	1137.9	1157.3
Median	457.5	585.5	441.0	575	430	502
Range	146 to 6278	119 to 6817	146 to 6278	201 to 6817	146 to 6278	224 to 6817
Time from Prior Systemic Therapy (days)						
Subjects with data	141	138	118	118	57	52
Mean	760	871.3	705.3	851.8	764.6	933.9
SD	922.1	894.8	905.8	863.8	1100.4	1135.7
Median	449	571.5	440.0	601	421	521.5
Range	146 to 6278	119 to 6817	146 to 6278	201 to 6817	146 to 6278	224 to 6817

† Stratification variables

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, ECOG = Eastern Cooperative Oncology Group, HPV = human papilloma virus, NA = not applicable, NR = not reported, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, TPS = Tumour Proportion Score

Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

Table 11: Prior therapy for PEMB-chemo versus CET-chemo ITT population

	PEMB-chemo	CET-chemo
	n(%)	n(%)
Subjects in population	281	278
Subjects with no prior systemic therapy	140 (49.8)	140 (50.4)
Primary/Locally Advanced/With Curative Intent	136 (48.4)	136 (48.9)
Cetuximab	19 (6.8)	16 (5.8)
Platinum	125 (44.5)	128 (46.0)
Recurrent/With Curative Intent	10 (3.6)	4 (1.4)
Cetuximab	0 (0.0)	0 (0.0)
Platinum	9 (3.2)	3 (1.1)

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

c) Interventions

KEYNOTE-048

The three treatment groups were PEMB mono, PEMB-chemo (cisplatin or carboplatin), and CET-chemo (cisplatin or carboplatin). Patients receiving PEMB-chemo and CET-chemo continued on PEMB and CET, respectively, following completion of chemotherapy. Doses, duration, and permitted dose adjustments are summarized in Table 12 and detailed below.

- Patients who were randomized to PEMB mono or PEMB-chemo received pembrolizumab 200 mg IV every three weeks until disease progression, intolerable toxicity, physician or patient decision, or completion of 35 cycles (24 months), whichever occurred first. Clinically stable patients with unconfirmed disease status could remain on PEMB until disease status was ascertained. Patients were allowed to discontinue PEMB per protocol if they experienced a CR and had completed at least 24 weeks of treatment, including two PEMB treatments after the CR. No cross-overs were permitted between PEMB mono and PEMB chemo, or between either and CET-chemo. Patients who had completed 24 months of PEMB treatment without disease progression or intolerability or who had discontinued PEMB after experiencing a CR were eligible for up to one year of retreatment after experiencing disease progression that was verified by central review (Second Course Phase).

  Dose reduction of PEMB was not allowed. Immune-related adverse events were treated according to adverse event and grade by a prespecified algorithm, which, depending on the adverse event and its grade, involved dose interruption or dose discontinuation. Corticosteroid administration with taper was allowed for treatment of immune-related adverse events. Withholding or permanent discontinuation was at the discretion of the treating investigator, but PEMB was to be permanently discontinued if an AE did not resolve or corticosteroid dose could not be reduced to 10 mg or below within 12 weeks.
- Patients who were randomized to chemotherapy (PEMB-chemo and CET-chemo) received carboplatin (AUC 5 mg/m^2) or cisplatin (100 mg/m^2) every three weeks for six cycles. Carboplatin dosing was adjusted for renal function. Investigators determined whether patients received carboplatin or cisplatin. The initial determination preceded randomization, but patients who had started the study on cisplatin were allowed to cross over to carboplatin.

  There were two levels of allowed dose reduction for toxicity for cisplatin: to 80 mg/m^2 (20%), then to 64 mg/m^2 (20%). There were two levels of allowed dose reduction for carboplatin: to AUC 4 (20%), then AUC 3. Patients who had dose modification to cisplatin prior to crossing over to carboplatin could start at a carboplatin dose of AUC 5 (no reduction), with two allowed levels of dose reduction. Need for further reduction led to discontinuation of chemotherapy.
- Patients who were randomized to chemotherapy (PEMB-chemo or CET-chemo) received 5-FU 1000 mg/m^2/day IV every day for four successive days every three weeks for six cycles.

  There were two levels of allowed dose reduction for 5FU: to 800 mg/m^2/day (20%), then to 64 mg/m^2/day (20%). Need for further reduction led to discontinuation of 5-FU.

- Patients randomized to CET-chemo received CET as a loading dose (400 mg/m^2) followed by 250 mg/m^2 every week until disease progression, intolerable toxicity, or physician or patient decision, whichever occurred first. No upper limit was imposed on number of cycles or duration of treatment. No cross-overs were permitted between CET-chemo and either of the PEMB groups.

  There were two levels of dose reduction for CET: to 200 mg/m^2 (20%), then to 150 mg/m^2 (20%). Need for further reduction led to discontinuation of 5-FU.

d) Patient Disposition

A total of 1,228 patients were screened, 346 were excluded, and 882 patients were randomized (Table 12). Three hundred and one patients were randomized to PEMB mono, 281 patients to PEMB-chemo, and 300 patients to CET-chemo. The first patient first visit was April 1, 2015, and the last patient was randomized on January 17, 2015. A temporary safety hold was imposed by the DMC on randomization to the PEMB-chemo group between August 13, 2014 and October 2, 2014; following safety review, randomization to the three arms was resumed. The twenty-two patients randomized to the CET-chemo arm during that time were excluded from the analyses of PEMB-chemo versus CET-chemo, as randomization had not been preserved for these patients for that comparison.

Following randomization, one (0.3%) patient randomized to PEMB, five (1.8%) patients randomized to PEMB-chemo, and 13 (4.3%) patients randomized to CET-chemo did not receive study medication. The principal reason given was patient decision. These patients were included in the ITT analyses and excluded from the safety analyses.

Data cut-off for the second interim analysis (IA2) was June 13, 2018, at which time the final analysis for PFS occurred and other outcomes were analyzed. The median duration of follow-up for all patients was 11.7 months (range, 0.2 to 37.3 months) in the PEMB mono group (301 patients) and 10.7 months (range, 0.1 to 35.3 months) in the CET-chemo group (300 patients). The median duration of follow-up was 13.0 months (range, 0.1 to 36.6 months) in the PEMB-chemo group (281 patients) and 10.7 months (range, 0.1 to 35.3 months) in the CET-chemo group (287 patients).

Data cut-off for the final analysis (FA) was February 25, 2019, at which time the final analysis for OS was conducted and confirmatory analyses were done on PFS and other outcomes. The median duration of follow-up for patients was 11.5 months (range, 0.2 to 45.7 months) in the PEMB mono group (301 patients) and 10.7 months (range, 0.1 to 41.8 months) in the CET-chemo group (300 patients). The median duration of follow-up was 13.0 months (range, 0.1 to 43.4 months) in the PEMB-chemo group (281 patients) and 10.7 months (range, 0.1 to 40.7 months) in the CET-chemo group (287 patients).

As of February 25, 2019, 31 (10.3%) patients randomized to PEMB mono, 27 (9.6%) patients randomized to PEMB-chemo, and no patients randomized to CET-chemo had completed treatment (CET treatment was not limited in the number of cycles), while 269 (89.4%) patients randomized to PEMB mono, 249 (88.6%) patients randomized to PEMB-chemo, and 278 (92.7%) patients randomized to CET-chemo had discontinued treatment. The most common reason for treatment discontinuation was disease progression, whether identified as progressive disease on imaging or as clinical progression, followed by discontinuation due to an adverse event.

Table 12: Summary of patient disposition for KEYNOTE-048, ITT population

	PEMB mono	PEMB-chemo	CET-chemo
Assessed for eligibility		1228	
Did not meet eligibility criteria		346	
Randomized	301	281	300
Received allocated treatment	300 (99.7)	276 (98.2)	287 (95.7)
Did not receive allocated treatment	1 (0.3)	5 (1.8)	13 (4.3)
Initial treatment phase			
Completed treatment	31 (10.3)	27 (9.6)	0
Ongoing treatment	0	0	9 (3.0)
Discontinued treatment	269 (89.4)	249 (88.6)	278 (92.7)
Progressive disease	186 (61.8)	157 (55.9)	185 (61.7)
Adverse event	34 (11.3)	44 (15.7)	45 (15.0)
Clinical progression*	26 (8.6)	21 (7.5)	16 (5.3)
Withdrawal by participant	10 (3.3)	13 (4.6)	18 (6.0)
Complete response	6 (2.0)	9 (3.2)	3 (1.0)
Death	3 (1.0)	2 (0.7)	2 (0.7)
Physician decision	3 (1.0)	2 (0.7)	8 (2.7)
Loss to follow-up	1 (0.3)	0	1 (0.3)
Excluded medication	0	1 (0.3)	0
Second course phase			
Ongoing treatment	3 (1.0)	1 (0.3)	0
Discontinued	0	3 (1.1)	0

* Clinical progression of disease without confirmed radiographic progression.

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB mono = pembrolizumab mono therapy, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

e) Limitations/Sources of Bias

KEYNOTE-048 was an open label study, due to the expectation that adverse events would enable patients and physicians to infer treatment assignment. The study employed various strategies to reduce the potential for bias arising from knowledge of treatments. The study team, including statisticians, were kept blinded to treatment assignment, and independent statisticians conducted analyses for DMC and safety review. Objective and standardized endpoints were used (OS, PFS by RECIST v1.1, ORR). Decision-making and endpoints based on radiological progression (PFS, ORR, DOR) required confirmation of investigators' interpretation by independent central review by radiologists blinded to treatment assignments. RECIST v1.1 was modified to allow a second scan for confirmation of progression in the PEMB and PEMB-chemo groups prior to discontinuation of therapy, with the option to continue treatment in the interim. This modification was made as a result of previous experience with tumour behaviour in response to pembrolizumab. If progression was confirmed, the date of the first scan was used as the date of progression. Dose modification, dose interruption, treatment withdrawal, and treatment for adverse events that might influence efficacy (e.g., treatment with systemic steroids) was done according to pre-specified protocols.

Randomization was stratified according to PD-L1 TPS (≥50% versus <50%), HPV (positive versus negative), and ECOG (0 versus 1), and appears to have been effective (the change from PD-L1 TPS used in stratification to CPS used to define subgroups is discussed below). Observed baseline characteristics were balanced for the two comparisons and two of the three populations. In the smallest population, PD-L1 CPS≥20, there was an observed imbalance in the proportion of males and patients with metastatic

disease, potentially favouring the PEMB containing groups. A sensitivity analysis conducted by the manufacturer suggested the effect was minimal.

Longer term survival is influenced by all treatment received, and treatment following discontinuation of randomized therapy differed among groups. Patients assigned to PEMB, whether as monotherapy or in combination with chemotherapy who had progression following complete response had the option of restarting PEMB for up at a year. As of the most recent report[4], this represented a small number of patients (<5). About half of the patients in each treatment group received subsequent cancer therapies after discontinuation, with comparatively more patients who had received PEMB mono subsequently receiving chemotherapy, more patients who had received CET-chemo receiving an immune checkpoint inhibitor, and more patients who had received PEMB receiving an EGFR inhibitor. The CGP considered this reflected available treatment options.

Biomarker-defined subgroups were redefined to be based on PD-L1 CPS rather than PD-L1 TPS, based on external information from other pembrolizumab trials that suggested that CPS was a better predictor of outcome. This meant the variable used to stratify randomization (TPS≥50% and <50%) was no longer identical to that used to specify biomarker-specified populations of interest (CPS≥1 and CPS≥20); for example, in the CPS≥20 population, about 50% of patients in each treatment group were assessed as strongly positive (TPS≥50%). The proportion of patients with TPS≥50% (strongly positive) appeared balanced in the ITT, CPS≥1, and CPS≥20 populations. Some minor imbalances were observed in baseline biomarkers and biomarker specified populations. Most of these were probably insignificant, but in the comparisons involving the PD-L1 CPS≥20 population, which was the smallest, there was an imbalance in the proportion of males that potentially favoured the pembrolizumab-containing therapies.

In protocol amendments the number of hypotheses for the primary efficacy analyses was increased from the original three to fourteen hypotheses, with the alpha spending strictly controlled by a testing scheme that involved parallel testing of six hypotheses and hierarchical testing of the remainder. Alpha was redistributed following rejection of hypotheses by a pre-specified scheme based on the graphical method of Maurer and Bretz. An alpha-spending algorithm controlled multiplicity for testing at multiple endpoints. There was no control of multiplicity for the secondary efficacy or patient reported outcomes, or the exploratory efficacy outcomes.

Inspection of the survival curves indicated deviation from the proportional hazards assumption that underlies standard methods for survival comparisons, by which the hazard ratio between treatments is assumed to be unchanged over the duration of the comparison. For comparisons of OS and PFS for PEMB mono with CET-chemo, the Kaplan-Meier survival curves crossed over, inverting the hazard ratios. For comparisons of OS and PFS for PEMB-chemo the Kaplan-Meier survival curves initially lay close to each other, and then diverged. Particularly if follow-up is short, and only a portion of the curve captured, standard methods could over or underestimate the treatment difference. As violations of the proportional hazards assumption had been observed elsewhere for comparisons of targeted therapies (pembrolizumab in other tumour types and nivolumab) and chemotherapy, sensitivity analyses were prespecified that tested for and attempted to adjust for nonproportional hazards. Results of these analyses were consistent with the results of the proportional hazards analysis. The median follow-up at final analysis was 10.7 to 13.0 months, depending on the group, reflecting the limited survival for this patient population. The extensive censoring and small number of patients results in high uncertainty around the latter part of the curve.

Pre-specified subgroup analyses were conducted for age (<65 years versus ≥65 years), sex, face (white versus all others), ECOG (0 versus 1), region (North America, Europe, rest of world), smoking status (never, positive, and current), PD-L1 TPS (≥50% versus <50%), PD-L1 CPS (≥1 versus <1, and ≥20 versus <20), and disease status (metastatic versus recurrent). Subgroups were consistent with those identified by the CGP and PAG, although limited in their potential to detect differences by size, and to examine effects in smaller subgroups (e.g., Asian patients) by pooling. There was no adjustment for multiplicity in these subgroup analyses, and they should be regarded as exploratory.

Important protocol deviations were reported for 308 (34.9%) of 882 randomized patients, 85 (28.2%) randomized to PEMB mono, 116 (41.3%) randomized to PEMB-chemo, and 107 (35.7%) randomized to CET-chemo. Important protocol deviations were defined as those that may significantly affect quality or integrity of key study data, or significantly affect participant's rights, safety, or wellbeing. EPAR[26] does not note an imbalance between arms or an overall concern with study conduct.

Following unblinding of the study team and program statisticians on July 26, 2018, one patient was found to have been excluded from the analysis in error. The analyses were repeated to include this patient. On independent data review, sixteen patients were

identified as having measurement discrepancies, leading to a change of status for four patients. Sensitivity analysis with the new assessments showed minimal impact on PFS analyses at IA2, and none on the OS analyses.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

In the following sections, results for the comparison of PEMB mono versus CET-chemo are presented first, followed by the results for the comparison of PEMB-chemo versus CET-chemo. Results for efficacy and patient reported outcomes will be presented. Safety outcomes for PEMB mono, PEMB-chemo and CET-chemo are reported together in the subsequent section.

Table 13 shows a summary of the results of testing of each of the hypotheses, including the p-value boundary against which the test was conducted (including the pre-planned transfer of alpha from rejected hypotheses). All comparisons were made between PEMB mono and CET-chemo or PEMB-chemo and CET-chemo; there were no planned comparisons of PEMB mono with PEMB-chemo. Successful testing (rejection of the hypothesis) is indicated in bold.

Table 13: Summary of results of statistical testing, KEYNOTE-048

Hypothesis	Outcome	Intervention	Population	Test	Overall alpha	Nominal P-value	P-value*† boundary	Result
Tested at IA2								
H1	PFS	PEMB mono	CPS≥20	Superiority	0.0019	0.45625	0.0016	Not rejected
H2	PFS	PEMB mono	CPS≥1	Superiority	NA	0.93303	NA	Not tested
H3	PFS	PEMB mono	ITT	Superiority	NA	0.99951	NA	Not tested
H4	PFS	PEMB-chemo	CPS≥20	Superiority	0.0019	0.01622	0.0017	Not rejected
H5	PFS	PEMB-chemo	CPS≥1	Superiority	NA	0.02286	NA	Not tested
H6	PFS	PEMB-chemo	ITT	Superiority	0.0002	0.16971	0.0002	Not rejected
H7	**OS**	**PEMB mono**	**CPS≥20**	**Superiority**	**0.007**	**0.00074**	**0.0024**	**Rejected with initial alpha**
H8	**OS**	**PEMB mono**	**CPS≥1**	**Superiority**	**0.01399***	**0.00855**	**0.0109**	**Rejected with alpha from H7 and H14**
H9	**OS**	**PEMB mono**	**ITT**	**Noninferiority**	**0.01399***	**0.0001399**	**0.0117**	**Rejected with alpha from H8**
H10	OS	PEMB mono	ITT	Superiority	0.01399	0.04563	0.0117	Not rejected
H11	OS	PEMB-chemo	CPS≥20	Superiority	0.007	0.00984	0.0018	Not rejected
H12	OS	PEMB-chemo	CPS≥1	Superiority	NA	0.00072	NA	Not tested
H13	**OS**	**PEMB-chemo**	**ITT**	**Noninferiority**	**0.007**	**0.0000040**	**0.0041**	**Rejected with initial alpha**
H14	**OS**	**PEMB-chemo**	**ITT**	**Superiority**	**0.007***	**0.00335**	**0.0041**	**Rejected with alpha shifted from H13**
Tested at FA								
H10	OS	PEMB mono	ITT	Superiority	0.020986	0.0059	0.01985	Not rejected
H11	**OS**	**PEMB-chemo**	**CPS≥20**	**Superiority**	**0.007**	**0.0023**	**0.00044**	**Rejected**
H12	**OS**	**PEMB-chemo**	**CPS≥1**	**Superiority**	**0.007**	**0.0026**	**0.00002**	**Rejected**

Abbreviations: CPS = Combined Proportion Score, FA = final analysis, IA2 = second interim analysis, ITT = intention to treat, PEMB mono = pembrolizumab monotherapy, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PFS = progression-free survival, OS = overall survival.

† Alpha spending and IA2 was determined using the spending fraction and the information fraction (ratio of the actual number of events at the interim analysis to the targeted number of events at the final analysis)

† The final analysis used the alpha unspent in earlier analyses, regardless of the number of events observed.

** Alpha for the final analysis was transferred from other hypotheses that were rejected at IA2. 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 analyses.

Data source: EPAR 2019[26]

a) Efficacy outcomes for PEMB mono versus CET-chemo

Overall survival

Table 14 provides a summary of results for the OS comparisons for PEMB mono versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA (February 25, 2019). Figure 5, Figure 6, and Figure 7 show the KM survival curves for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA, respectively.

Median OS in the ITT population at the final analysis (February 25, 2019) was 11.5 months (95% CI 10.3 to 13.4 months) for PEMB mono and 10.7 months (95% CI 9.3 to 11.7 months) for CET chemo, with median follow-up of 11.5 months (range: 0.2 to 45.7 months) and 10.7 months (range 0.1 to 41.8 months) for PEMB mono and CET-chemo, respectively. The HR for the comparison was 0.83 (95% CI 0.70 to 0.99), which was non-significant (did not show superiority) with a P-value 0.01985 (P-value boundary 0.0059; **H10**). At 12 months, the percentage of patients surviving was 48.7% for PEMB mono versus 44.4% for CET-chemo. At 24 months, the percentage of patients surviving was 27.0% for PEMB mono versus 18.8% for CET-chemo.

For the comparison of PEMB mono versus CET chemo for the PD-L1 CPS≥1 population the difference in OS was statistically significant at IA2, HR 0.78 (95% CI 0.64 to 0.96), P-value = 0.00855 (P-value boundary 0.0109; **H8**), favouring PEMB mono. The median OS was 12.3 months (95% CI 10.8 to 14.9 months) for PEMB mono, compared with 10.3 months (95% CI 9.0 to 11.5 months) for CET-chemo, and at the time of the analysis 383 (75%) of 512 patients had died. The confirmatory analysis at FA supported this finding. The median OS was 12.3 months (95% CI 10.8 to 14.3 months) for the PEMB mono group and 10.3 months (95% CI 9.0 to 11.5 months), with a HR for the comparison of 0.74 (95% CI 0.61 to 0.90). At 12 months, the percentage of patients surviving was 50.4% for PEMB mono versus 43.6% for CET-chemo. At 24 months, the percentage of patients surviving is 28.9% for PEMB mono versus 17.4% for CET-chemo.

For the comparison of PEMB mono versus CET-chemo for the PD-L1 CPS≥20 population the difference in survival was statistically significant at IA2, HR 0.61 (95% CI 0.45 to 0.83) P-value = 0.00074 (P-value boundary 0.0024; **H7**), favouring PEMB mono. Median OS was 14.9 months (95% CI 11.6 to 21.5 months) for PEMB mono, compared with 10.7 months (95% CI 8.8 to 12.8 months) for CET-chemo, and at the time of the analysis, 177 of 255 patients had died. The confirmatory analysis at FA supported this finding. The median OS was 14.8 months (95% CI 11.5 to 20.6 months) for the PEMB mono group and 10.7 months (95% CI 8.8 to 12.8 months), with a HR for the comparison of 0.58 (95 CI 0.44 to 0.78). At 12 months, the percentage of patients surviving was 56.4% for PEMB mono versus 44.9% for CET-chemo. At 24 months, the percentage of patients surviving was 35.3% for PEMB mono versus 19.1% for CET-chemo.

Table 14: Summary of results for OS for PEMB mono versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

	PEMB mono	CET chemo
Data cut-off date	February 25, 2019	
Median follow-up time (months)	11.5 (range 0.2, 45.7)	10.7 (range: 0.1, 41.8)
ITT		
N	301	300
Number of events (%)	237 (78.7)	264 (88.0)
Median OS in months (95% CI)	11.5 (10.3, 13.4)	10.7 (9.3, 11.7)
HR (95% CI)	0.83 (0.70, 0.99)	
P-value (superiority statistic)	0.01985*	
OS at 12 months, % (95% CI)	48.7 (42.9, 54.2)	44.4 (38.7, 49.9)
OS at 18 months, % (95% CI)	35.7 (30.3, 41.1)	27.2 (22.3, 32.4)
OS at 24 months, % (95% CI)	27.0 (22.1, 32.1)	18.8 (14.6, 23.5)
PD-L1 CPS≥1		
N	257	255
Number of events (%)	197 (76.7)	229 (89.8)

	PEMB mono	CET chemo
Median OS in months (95% CI)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)
HR (95% CI)	0.74 (0.61, 0.90)	
P-value (superiority statistic)	0.00133†	
OS at 12 months, % (95% CI)	50.4 (44.1, 56.4)	43.6 (37.4, 49.6)
OS at 18 months, % (95% CI)	38.7 (32.7, 44.6)	26.6 (21.3, 32.1)
OS at 24 months, % (95% CI)	28.9 (23.5, 34.5)	17.4 (13.0, 22.4)
PD-L1 CPS≥20		
N	133	122
Number of events (%)	94 (70.7)	108 (88.5)
Median OS in months (95% CI)	14.8 (11.5, 20.6)	10.7 (8.8, 12.8)
HR (95% CI)	0.58 (0.44, 0.78)	
P-value (superiority statistic)	0.0001†	
OS at 12 months, % (95% CI)	56.4 (47.5, 64.3)	44.9 (35.9, 53.4)
OS at 18 months, % (95% CI)	45.1 (36.5, 53.3)	26.6 (19.1, 34.7)
OS at 24 months, % (95% CI)	35.3 (27.3, 43.4)	19.1 (12.7, 26.6)

* Formally tested at FA under pre-planned hierarchical testing strategy

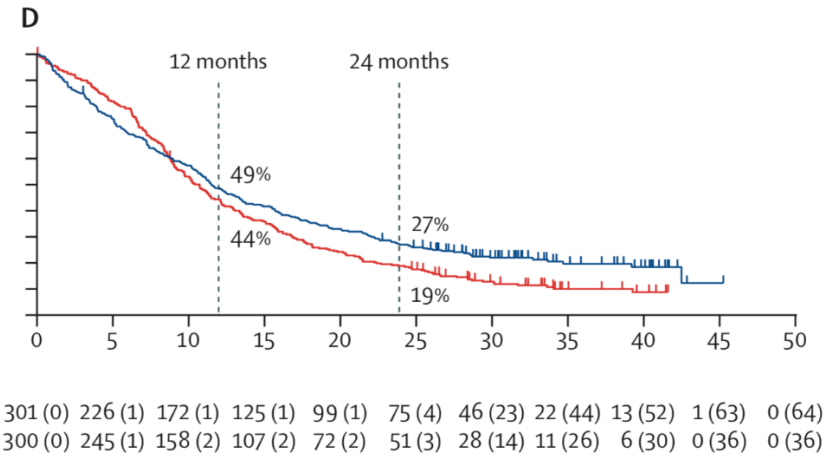
† Confirmatory analysis at FA. P-values nominal only. Tested at IA2 (where indicated under formal hierarchy), and results are reported in text.

CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, HR = hazard ratio, OS = overall survival, PEMB mono = pembrolizumab monotherapy

Data cut-off: February 25, 2019 (FA)

Data source: EPAR 2019[26]

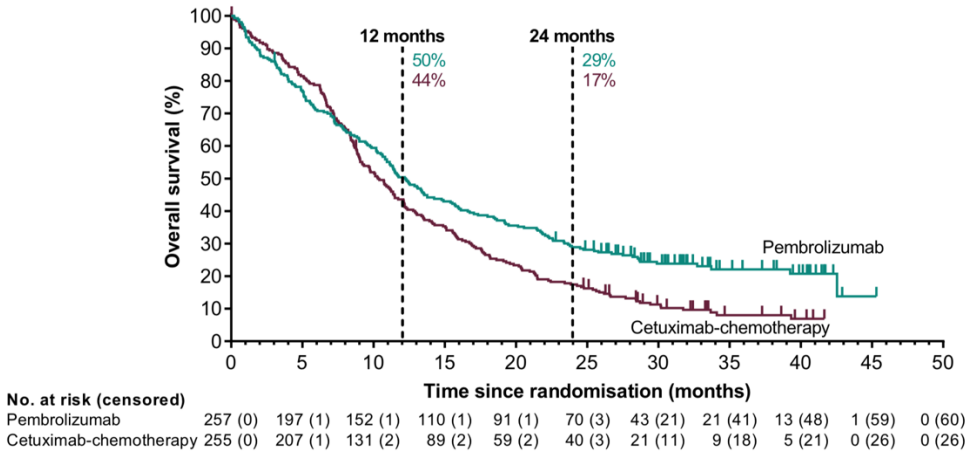
Figure 5: Kaplan-Meier estimates for OS for PEMB mono versus CET-chemo, ITT population, FA



Data cut-off: February 25, 2019

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

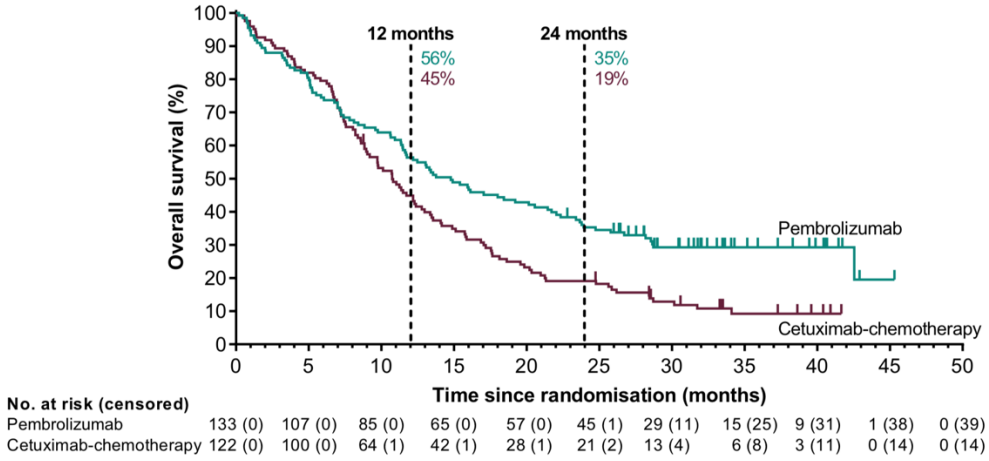
Figure 6: Kaplan-Meier estimates for OS for PEMB mono versus CET-chemo, CPS≥1 population, FA



Data cut-off: February 25, 2019

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 7: Kaplan-Meier estimates for OS for PEMB mono versus CET-chemo, CPS≥20 population, FA



Data cut-off: February 25, 2019

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

As seen above, the survival curves for OS for the two treatments cross for all three populations. Graphical assessment and testing of treatment-by-time interactions in the overall Cox proportional hazards model suggested deviation from the proportional hazards assumption. The results from the weighted log-rank test, weighting towards later values, support those of the Cox proportional hazards model (Table 15). The restricted mean survival time (RSMT) differences for overall survival for all three populations show point estimates increasing over time, although confidence intervals overlap the null at all time points, except for PD-L1 CPS≥20 at 24 months, difference 2.34 (95% CI 0.29 to 4.39).

Table 15:Analysis of OS for PEMB mono versus CET chemo by log-rank and weighted log-rank tests, IA2

	Population	Test	P-value (one-sided)*
PEMB mono versus CET-chemo	ITT	Log-rank	0.04563
		Weighted log-rank (0, 1)	0.00130
	CPS≥1	Log-rank	0.00855
		Weighted log-rank (0, 1)	0.00015
	CPS≥20	Log-rank	0.00074
		Weighted log-rank (0, 1)	<0.00001

* Stratified by factors used for randomization

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

An exploratory analysis of KEYNOTE-048 OS data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 46.2 months for patients in the PEMB mono versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the median OS for patients receiving PEMB mono was 11.5 months, compared with 10.7 months for those receiving CET-chemo, HR 0.81 (0.68 to 0.97). Four year OS was 15.4% versus 6.6% for PEMB mono versus CET chemo. For the PD-L1 CPS≥1 population, the median OS for patients receiving PEMB mono was 12.3 months, compared with 10.4 for those receiving CET-chemo, HR 0.74 (0.61 to 0.89). Four year OS was 16.7% versus 5.9% for PEMB mono versus CET-chemo, respectively. For the PD-L1 CPS≥20 population, the median OS for patients receiving PEMB mono was 14.9 months, compared with 10.8 for those receiving CET-chemo, HR 0.61 (0.46 to 0.81). Four year OS was 21.6% versus 8.0% for PEMB mono versus CET-chemo, respectively.

Progression free survival

Table 16 provides a summary of results for the PFS comparisons for PEMB mono versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA. Figure 8 shows the KM estimates for PFS for the three populations at the FA. No significant differences were found at IA1 (interim analysis for PFS) for any PFS hypothesis, and these results are not shown. IA2 was the final analysis for PFS endpoints, and the results are described in the text.

The comparison between PEMB mono and CET-chemo for the ITT population (**H3**) was not tested at IA2 because H1 was not statistically significant at IA2. Median PFS was 2.3 months (95% CI 2.2 to 3.3 months) for PEMB mono and 5.2 months (4.9 to 6.0 months) for CET-chemo, HR 1.35 (95% CI 1.13 to 1.59). At FA, median PFS was 2.3 months (95% CI 2.2 to 3.3 months) for PEMB mono and 5.2 months (95% CI 4.9 to 6.1 months) for CET-chemo. The PFS curves crossed. Exploratory analyses at the FA gave an HR for the comparison of 1.29 (1.09, 1.53). At 6 months, the percentage of patients with PFS for PEMB mono was 26.2%, compared with 45.7% for CET chemo. At 12 months, the percentage of patients with PFS for PEMB mono was 17.6%, compared with 15.0% for CET chemo.

The comparison between PEMB mono and CET-chemo for the PD-L1 CPS≥1 population (H2) was not tested at IA2 because H1 was not statistically significant at IA2. Median PFS was 3.2 months (95% CI 2.2 to 3.4 months) for PEMB mono and 5.0 months (95% CI 4.8 to 4.8 months) for CET-chemo, HR 1.16 (95% CI 0.96 to 1.39). At FA, the median PFS is 3.2 months (95% CI 2.2 to 3.4 months) for the PEMB mono group and 5.0 months (95% CI 4.8 to 6.0 months) for CET chemo. The PFS curves crossed. Exploratory analyses at FA gave an HR for the comparison of 1.13 (95% 0.94 to 1.36). At 6 months, the percentage of patients with PFS for PEMB mono is 28.7%, compared with 43.9% for CET chemo. At 12 months, the percentage of patients with PFS for PEMB mono is 20.6%, compared with 13.6% for CET chemo.

The comparison between PEMB mono and PEMB-chemo in the PD-L1 CPS≥20 population (H1) was not statistically significant at IA2 P-value = 0.46791 (P-value boundary = 0.0016; **H1**). IA2. Median PFS was 3.4 months (95% CI 3.2 to 3.8 months) for PEMB mono and 5.0 months (95% CI 4.8 to 6.2 months) for CET-chemo, HR 0.99 (95% CI 0.75 to 1.29). At FA, the median PFS was 3.4 months (95% CI 3.2 to 3.8 months) for the PEMB mono group and 5.3 months (95% CI 4.8 to 6.3 months). The PFS curves crossed.

Exploratory analyses at FA gave a HR for the comparison of 0.99 (95% CI 0.76, 1.29). At 6 months, the percentage of patients with PFS for PEMB mono is 33.0%, compared with 46.6% for CET chemo. At 12 months, the percentage of patients with PFS for PEMB mono is 23.5%, compared with 15.1% for CET chemo.

Table 16: Summary of results for PFS for PEMB mono versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

	PEMB mono	CET chemo
Data cut-off date	February 25, 2019	
ITT		
N	301	300
Number of events (%)	272 (90.4)	277 (92.3)
Median in months (95% CI)	2.3 (2.2, 3.3)	5.2 (4.9, 6.1)
HR (95% CI)	1.29 (1.09, 1.53)	
P-value (superiority statistic)	0.9983†	
PFS at 6 months (95% CI)	26.2 (21.4, 31.3)	45.7 (39.9, 51.3)
PFS at 9 months (95% CI)	20.0 (15.7, 24.7)	21.4 (16.9, 26.3)
PFS at 12 months (95% CI)	17.6 (13.5, 22.1)	15.0 (11.2, 19.4)
PD-L1 CPS≥1		
N	257	255
Number of events (%)	228 (88.7)	237 (92.9)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)
HR (95% CI)	1.13 (0.94, 1.36)	
P-value (superiority statistic)	0.8958†	
PFS at 6 months (95% CI)	28.7 (23.3, 34.4)	43.9 (37.6, 49.9)
PFS at 9 months (95% CI)	23.5 (18.5, 28.9)	19.8 (15.1, 25.0)
PFS at 12 months (95% CI)	20.6 (15.9, 25.8)	13.6 (9.6, 18.2)
PD-L1 CPS≥20		
N	133	122
Number of events (%)	115 (86.5)	114 (93.4)
Median in months (95% CI)	3.4 (3.2, 3.8)	5.3 (4.8, 6.3)
HR (95% CI)	0.99 (0.76, 1.29)	
P-value (superiority statistic)	0.46791†	
PFS at 6 months (95% CI)	33.0 (25.2, 41.0)	46.6 (37.5, 55.2)
PFS at 9 months (95% CI)	26.8 (19.5, 34.5)	22.0 (15.1, 29.8)
PFS at 12 months (95% CI)	23.5 (16.6, 31.1)	15.1 (9.3, 22.2)

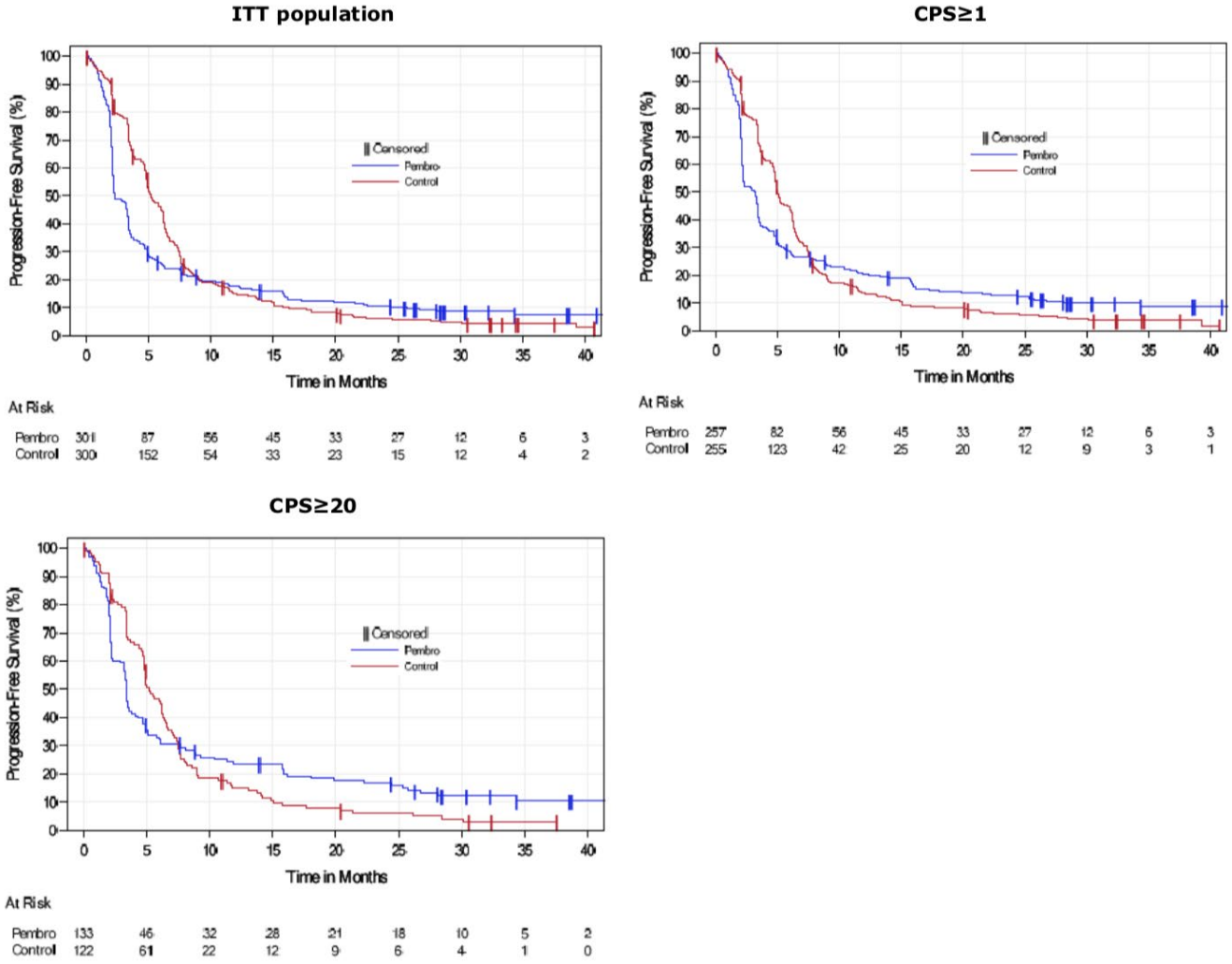
† Confirmatory analysis at FA. P-values nominal only. Tested (where indicated under formal hierarchy) at IA2, and results are reported in text.

CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, HR = hazard ratio, PEMB mono = pembrolizumab monotherapy, PFS = progression free survival

Data cut-off: February 25, 2019 (FA)

Data source: EPAR 2019[26]

Figure 8: Kaplan-Meier estimates for PFS for PEMB mono versus CET-chemo, ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, IA2



Abbreviations: Pembro = PEMB monotherapy, Control = CET-chemo

Data cut-off: June 13, 2018

Source: EPAR 2019[26]

An exploratory analysis of KEYNOTE-048 PFS data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 46.2 months for patients in the PEMB mono versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the median PFS for patients receiving PEMB mono was 2.3 months, compared with 5.8 months for those receiving CET-chemo. The PD-L1 CPS≥1 population, the median PFS was 3.2 months versus 5.0 months, and for the PD-L1 CPS≥20 population, the median PFS was 3.4 months versus 5.3 months, for PEMB mono and CET-chemo, respectively.

Overall response rate

Table 17 provides a summary of results for the ORR comparisons for PEMB mono versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA.

ORR in the ITT population at IA2 is 16.9% (95% CI 12.9% to 21.7%) for PEMB mono compared with 36.0% (95% CI 30.6% to 41.7%) for CET-chemo (IA2), with a difference in percentages -19.0% (95% CI -25.8% to -12.1%). This endpoint was not hypothesis tested or adjusted for multiplicity. Fourteen (4.7%) of patients who received PEMB mono had a CR, compared with 8 (2.7%) of those who received CET-chemo. Thirty-seven (12.3%) of patients who received PEMB mono had a PR, compared with 100 (33.3%) who received CET-chemo. Results at FA were consistent with those at IA2, with the number of patients with ORR unchanged.

ORR in the PD-L1 CPS≥1 population at IA2 was 19.1% (95% CI) for PEMB mono compared with 34.9% for CET-chemo (IA2). Fourteen (5.4%) of patients who received PEMB mono had a CR, compared with 7 (2.7%) of those who received CET-chemo. Thirty-five (13.6%) of patients who received PEMB mono had a PR, compared with 82 (34.9%) who received CET-chemo. Results at FA were consistent with those at IA2, with the number of patients with ORR unchanged.

ORR in the PD-L1 CPS≥20 at IA2 is 23.3% (95% CI) for PEMB mono compared with 36.1% for CET-chemo. Ten (7.5%) of patients who received PEMB mono had a CR, compared with 4 (3.3%) of those who received CET-chemo. Twenty-one (15.8%) of patients who received PEMB mono had a PR, compared with 40 (32.8%) who received CET-chemo. Results at FA were consistent with those at IA2, with the number of patients with ORR unchanged.

Table 17: Summary of results for ORR for PEMB mono versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

Table S5: Summary of confirmed objective response at final analysis for the comparison of pembrolizumab vs cetuximab-chemotherapy

Best Response	PD-L1 CPS ≥20 Population		PD-L1 CPS ≥1 Population		Total Population	
	Pembrolizumab N=133	Cetuximab-Chemotherapy N=122	Pembrolizumab N=257	Cetuximab-Chemotherapy N=255	Pembrolizumab N=301	Cetuximab-Chemotherapy N=300
Objective response	31 (23%)	44 (36%)	49 (19%)	89 (35%)	51 (17%)	108 (36%)
Complete response	10 (8%)	4 (3%)	14 (5%)	7 (3%)	14 (5%)	8 (3%)
Partial response	21 (16%)	40 (33%)	35 (14%)	82 (32%)	37 (12%)	100 (33%)
Stable disease	40 (30%)	43 (35%)	72 (28%)	84 (33%)	82 (27%)	102 (34%)
Progressive disease	42 (32%)	12 (10%)	100 (39%)	33 (13%)	122 (41%)	37 (12%)
Non-CR/non-PD*	8 (6%)	6 (5%)	11 (4%)	11 (4%)	14 (5%)	11 (4%)
Not evaluable or assessed†	12 (9%)	17 (14%)	25 (10%)	38 (15%)	32 (11%)	42 (14%)

CPS=combined positive score. Non-CR=non-complete response. Non-PD=non-progressive disease. PD-L1=programmed death ligand 1.

* Non-CR/non-PD includes participants without disease measurable per RECIST, version 1.1, by blinded, independent central review at baseline who did not have complete response or progressive disease.

† Not evaluable or assessed includes participants who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging.

* Not evaluable or assessed included patients who did not have both baseline and post-baseline imaging available for assessment

Abbreviations: CPS = Combined Proportion Score, ITT = intention to treat, ORR = objective response rate

Data cut-off: February 25, 2019

Source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

An exploratory analysis of KEYNOTE-048 ORR data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 46.2 months for patients in the PEMB mono versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the ORR for patients receiving PEMB mono was 16.9%, compared with 36.0% for those receiving CET-chemo. The PD-L1 CPS≥1 population, the ORR was 19.1% versus 34.9%, and for the PD-L1 CPS≥20 population, the ORR was 23.3% versus 36.1%, for PEMB mono and CET-chemo, respectively.

Duration of response

Table 18 provides a summary of results for DOR for PEMB-mono versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA. Results were consistent between IA2 and FA.

Median duration of response at FA in patients in the ITT population who received PEMB-mono and had CR or PR (51 patients) is 22.6 months (range, 1.5+ to 43.0+ months, the + indicating patients who had response ongoing at the end of follow-up), compared with 4.5 months (range, 1.2+ to 38.7+ months) in those who received CET-mono (108 patients). Thirty-seven (77.8%) and 32 (38.8%) patients who received PEMB-mono and CET-chemo, respectively, had response duration ≥ 6 months.

Median duration of response at FA in patients in the PD-L1 CPS≥1 population who received PEMB-mono and had CR or PR (49 patients) is 23.4 months (range, 1.5+ to 43.0+ months), compared with 4.5 months (range, 1.2+ to 38.7+ months) in those who received CET-chemo (89 patients). Thirty-seven (81.1%) and 24 (36.0%) patients who received PEMB-mono and CET-chemo, respectively, had response duration ≥ 6 months.

Median duration of response at FA in patients in the PD-L1 CPS≥20 population who received PEMB-mono and had CR or PR (31 patients) is 22.6 months (range, 2.7+ to 43.0+ months), compared with 4.2 months (range, 1.2+ to 31.5+ months) in those who received CET-chemo (44 patients). Twenty-four (83.5%) and 12 (34.8%) patients who received PEMB-mono and CET-chemo, respectively, had response duration ≥ 6 months.

Table 18: Summary of results for time to response and duration of response for PEMB mono versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

	PEMB	CET-chemo
Data cut-off date	February 25, 2019	
ITT		
N	301	300
Number with ORR	51	108
Median in months (range)	22.6 (1.5+ – 43.0+)	4.5 (1.2+ – 38.7+)
Median time to response (range)	2.1 (1.5 – 9.1)	2.1 (1.3 – 10.4)
Number (KM%) with response duration ≥ 6 months	37 (77.8)	32 (38.8)
PD-L1 CPS≥1		
N	242	235
Number with ORR	49	89
Median in months (range)	23.4 (1.5+ – 43.0+)	4.5 (1.2+ – 38.7+)
Median time to response (range)	2.1 (1.5 – 9.1)	2.1 (1.3 – 10.4)
Number (KM%) with response duration ≥ 6 months	37 (81.1)	24 (36.0)
PD-L1 CPS≥20		
N	126	110
Number with ORR	31	44
Median in months (range)	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 (1.9 – 6.0)
Number (KM%) with response duration ≥ 6 months	24 (83.5)	12 (34.8)

Abbreviations: CPS = Combined Proportion Score,KM = Kaplan-Meier, PD-L1 = programmed death ligand 1

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

An exploratory analysis of KEYNOTE-048 DOR data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 46.2 months for patients in the PEMB mono versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the median DOR for patients receiving PEMB-mono was 23.4 months, compared with 4.5 months for those receiving CET-chemo. The PD-L1 CPS≥1 population, the median DOR was 24.8 months versus 4.5 months, and for the PD-L1 CPS≥20 population, the median DOR was 23.4 months versus 4.2 months, for PEMB mono and CET-chemo, respectively.

Analyses of outcomes (OS, PFS, ORR, DOR) for subgroups of interest

Figure 9 shows the results of clinical exploratory subgroup analyses of OS for PEMB-mono versus CET-chemo in the ITT population at the time of FA (February 25, 2019) and Figure 10 shows the corresponding subgroup results for the PD-L1 CPS≥1 population. Figure 11 and Figure 12 show the results of the subgroup analyses for PFS, for the ITT and PD-L1 CPS≥1 populations, respectively,

at the FA. The subgroups were age, sex, ECOG performance status score, region of enrollment, smoking status, p16 status, PD-L1 CPS expression (for ITT population), and disease status (metastatic versus recurrent disease, where patients with both logoregional recurrence and metastases disease were classified as metastatic). Table 19 shows a summary of OS, PFS, ORR, and DOR for additional PD-L1 CPS subgroups (CPS<1, CPS≥1 and <20, and CPS<20) at the FA, and Table 20 shows a summary of OS, PFS, ORR, and DOR for the PD-L1 TPS subgroups, according to which randomization was stratified (TPS <50% and TPS≥50%) at the IA2.

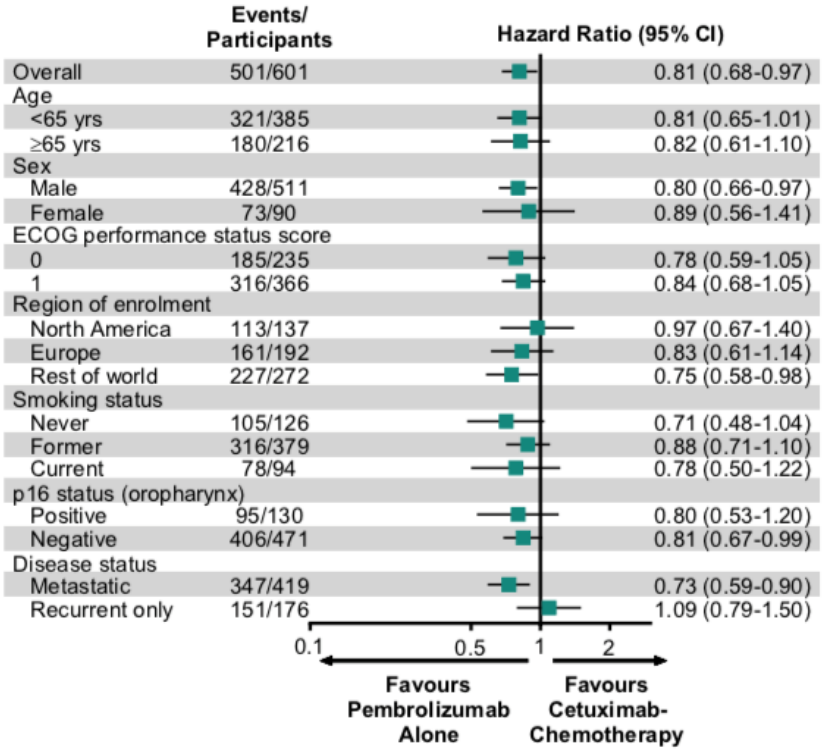
Estimated differences in OS between clinical subgroups were minimal for the ITT and PD-L1 CPS≥1 populations, with the greatest difference in point estimates seen for disease status (metastatic/recurrent). Patients in the ITT population with metastatic disease had HR for OS 0.73 (95% CI 0.59 to 0.90) compared with HR 1.09 (95% CI 0.79 to 1.50) for recurrent disease. Patients in the PD-L1 CPS≥1 population with metastatic disease had HR for OS 0.62 (95% CI 0.49 to 0.79 compared with HR 1.03 (95% CI 0.74 to 1.44) for recurrent disease.

A similar pattern for the clinical subgroups was seen for PFS. Patients in the ITT population with metastatic disease had HR for PFS 1.09 (95% CI 0.89 to 1.34), compared with HR 1.79 (95% CI 1.31 to 2.44). Patients in the PD-L1 CPS≥1 population with metastatic disease had HR for PFS 0.91 (95% CI 0.72 to 1.14), compared with HR 1.67 (95% CI 1.21 to 2.32).

Results for additional PD-L1 CPS subgroups (CPS<1, CPS≥1 and <20, and CPS<20) are suggestive of poorer results for patients without PD-L1 expression, with HR for OS for PD-L1 CPS<1 1.51 (95% CI 0.96 to 2.37) for PEMB-mono versus CET-combo, median survival 7.9 months versus 11.3 months, and ORR 4.5% versus 42.2% (Table 19). The difference is more marked for PFS, with HR for PD-L1 CPS<1 4.31 (95% CI 2.63 to 7.08), for PEMB-mono versus CET-combo and median survival 2.1 months versus 6.2 months (Table 19). However, the patient numbers for the PD-L1 CPS≥1 subgroup are small (89 patients total) and the estimates uncertain.

Similar estimates of treatment difference for OS were obtained for the two subgroups based on TPS, TPS <50%, HR 0.84 (95% CI 0.68 to 1.03), and TPS ≥50%, HR 0.91 (95% CI 0.60 to 1.37; Table 20). There was little difference in between treatment groups and subgroups in median survival or the proportion surviving at 12 months. PFS estimates were more divergent, with HR 1.45 (95% CI 1.19 to 1.76) and HR 0.95 (95% CI 0.65 to 1.38), for TPS <50% and TPS ≥50%, respectively.

Figure 9: Results of subgroup analyses for OS, PEMB mono versus CET-chemo, ITT population, FA

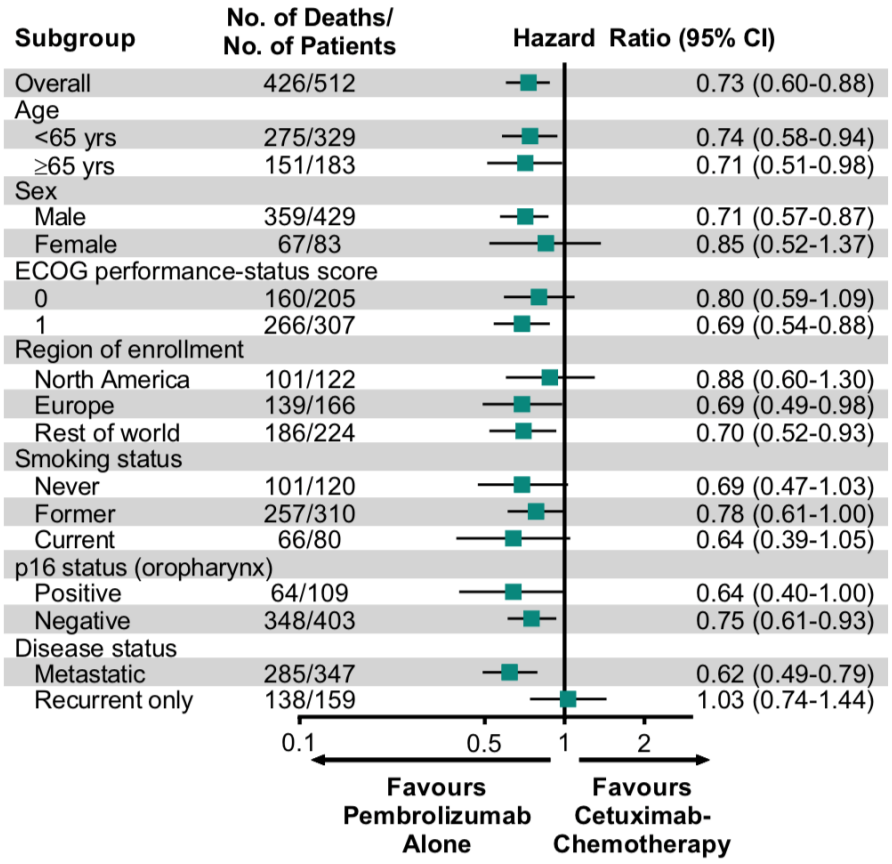


Abbreviations: ECOG = Eastern Cooperative Oncology Group

Data cut-off: February 25, 2019

Figure source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 10: Results of subgroup analyses for OS, PEMB mono versus CET-chemo, PD-L1 CPS≥1 population, FA



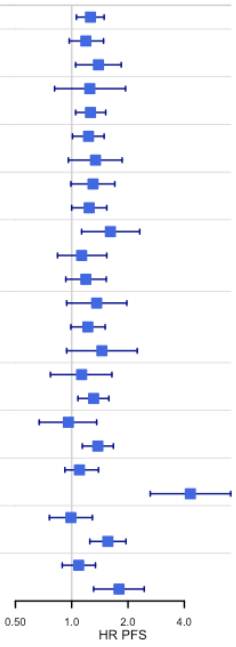
Abbreviations: ECOG = Eastern Cooperative Oncology Group

Data cut-off: February 25, 2019

Figure source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 11: Results of subgroup analyses for PFS, PEMB mono versus CET-chemo, ITT population, FA

Factor	Subgroup	N/Events	HR (95% CI)
Overall		601/549	1.26 (1.06, 1.49)
Age	<65 years	385/350	1.19 (0.97, 1.48)
	>= 65 years	216/199	1.39 (1.05, 1.84)
Sex	Female	90/82	1.25 (0.81, 1.94)
	Male	511/467	1.26 (1.05, 1.52)
Race	White	443/400	1.23 (1.01, 1.49)
	All others	154/145	1.34 (0.96, 1.86)
ECOG	0	235/210	1.3 (0.99, 1.7)
	1	366/339	1.24 (1, 1.54)
Region	North America	137/123	1.61 (1.13, 2.31)
	EU	192/173	1.13 (0.84, 1.54)
	ROW	272/253	1.19 (0.93, 1.53)
Smoking status	Never	126/116	1.36 (0.94, 1.97)
	Former	379/347	1.22 (0.99, 1.51)
	Current	94/84	1.45 (0.94, 2.24)
HPV status	Positive	130/114	1.13 (0.77, 1.64)
	Negative	471/435	1.31 (1.08, 1.58)
PD-L1 TPS	Strongly positive	133/119	0.96 (0.67, 1.36)
	Not strongly positive	468/430	1.38 (1.14, 1.67)
PD L1 CPS1	CPS>=1	512/465	1.1 (0.92, 1.39)
	CPS<1	89/84	4.31 (2.63, 7.08)
PD L1 CPS20	CPS>=20	255/229	0.99 (0.76, 1.29)
	CPS<20	342/316	1.56 (1.25, 1.95)
Disease status	Metastatic	419/380	1.09 (0.89, 1.34)
	Recurrent	176/164	1.79 (1.31, 2.44)



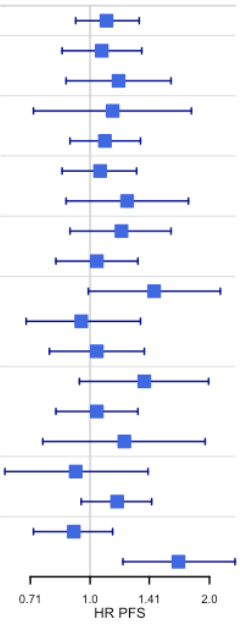
Abbreviations: CPS = Combined Proportion Score, HR = hazard ratio, PD-L1 = programmed death ligand 1

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Figure 12: Results of subgroup analyses for PFS, PEMB mono versus CET-chemo, PD-L1 CPS≥1 population, FA

Factor	Subgroup	N/Events	HR (95% CI)
Overall		512/465	1.1 (0.92, 1.33)
Age	<65 years	329/297	1.07 (0.85, 1.35)
	>= 65 years	183/168	1.18 (0.87, 1.6)
Sex	Female	83/75	1.14 (0.72, 1.8)
	Male	429/390	1.09 (0.89, 1.34)
Race	White	377/339	1.06 (0.85, 1.31)
	All others	132/123	1.24 (0.87, 1.77)
ECOG	0	206/182	1.2 (0.89, 1.6)
	1	307/283	1.04 (0.82, 1.32)
Region	North America	122/109	1.45 (0.99, 2.13)
	EU	166/149	0.95 (0.69, 1.34)
	ROW	224/207	1.04 (0.79, 1.37)
Smoking status	Never	120/111	1.37 (0.94, 1.99)
	Former	310/280	1.04 (0.82, 1.32)
	Current	80/72	1.22 (0.76, 1.95)
HPV status	Positive	109/95	0.92 (0.61, 1.4)
	Negative	403/370	1.17 (0.95, 1.43)
Disease status	Metastatic	347/312	0.91 (0.72, 1.14)
	Recurrent	159/148	1.67 (1.21, 2.32)



Abbreviations: CPS = Combined Proportion Score, HR = hazard ratio, PD-L1 = programmed death ligand 1

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Table 19: Summary of results for OS, PFS, ORR, and DOR for PEMB mono versus CET-chemo PD-L1 CPS <1, PD-L1 CPS <20, and PD-L1 CPS ≥ 1 to CPS <20 subgroups from KEYNOTE-48, FA

	PD-L1 CPS <1		PD-L1 CPS <20		PD-L1 CPS≥1 to CPS <20	
	PEMB mono N=44	CET-mono N=45	PEMB mono N=167	CET-mono N=175	PEMB mono N=124	CET-mono 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)	
OS 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 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)

	PD-L1 CPS <1		PD-L1 CPS <20		PD-L1 CPS≥1 to CPS <20	
	PEMB mono N=44	CET-mono N=45	PEMB mono N=167	CET-mono N=175	PEMB mono N=124	CET-mono N=133
OS 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)	4.31 (2.63, 7.08)		1.56 (1.25, 1.95)		1.25 (0.96, 1.61)	
PFS 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 DOR 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 TTR in months (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 (KM%) with response duration ≥6 months	0	8 (52.7)	13 (68.4)	20 (41.2)	13 (76.5)	12 (36.6)

Abbreviations: BICR = blind independent central review, CR = complete response, DOR = duration of response, KM = Kaplan-Meier, ORR = objective response rate, OS = overall survival, PFS = progression free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumours, TTR = time to response

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Table 20: Summary of results for OS, PFS, ORR, and DOR for PEMB mono versus CET-chemo D-L1 TPS < 50% and TPS ≥ 50% from KEYNOTE-48, IA2

	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	PEMB mono N=234	CET-chemo N=234	PEMB mono N=67	CET-chemo 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)	
OS 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)	
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)

	PD-L1 TPS <50%		PD-L1 TPS ≥50%	
	PEMB mono N=234	CET-chemo N=234	PEMB mono N=67	CET-chemo N=66
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 DOR in months (range)	15.2 (1.5+ - 30.6+)	4.5 (1.4+ - 30.6+)	33.4 (2.7 - 34.8+)	4.4 (1.2+ - 22.3+)
Median TTR in months (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 (KM%) with response duration ≥6 months	22 (71.7)	26 (41.1)	14 (83.0)	6 (30.0)

+ indicates ongoing response at data-cut off.

Abbreviations: BICR = blind independent central review, CR = complete response, DOR = duration of response, ORR = objective response rate, OS = overall survival, PFS = progression free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumours, TPS = Tumour Proportion Score

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

Quality of Life Outcomes

Table 21 presents a summary of HRQoL outcomes for PEMB-mono compared with CET-chemo for the FAS population (all patients who were randomized, received treatment, and had at least one PRO assessment). The EORTC scales were collected at treatment cycles 1 through 4, 6 (week 15), and every 2 cycles until 30 days post-treatment. Results were summarized for baseline and Week 15, the expected final cycle of chemotherapy. Figure 13 shows change from baseline in EORTC global health status, Figure 14 shows time to deterioration in EORTC global health status, Figure 15 shows time to deterioration in EORTC H&N35 pain subscale, and Figure 16 shows time to deterioration in EORTC H&N35 swallowing subscale. A decline of 10 points or greater on a 100-point scale represented clinically significant deterioration.

At Week 15, 191 patients (65%) randomized to PEMB-mono and 168 (65.4%) randomized to CET-chemo completed the EORTC QLQ-30 questionnaire. Compliance rates at baseline (the percentage of patients completing the questionnaire compared with those expected to complete per protocol) for the EORTC QLQ-30 were 94.9% for PEMB mono and 92% for CET-chemo, and at week 15 were 92.4% for PEMB-mono and 83% for CET-chemo. Similar compliance rates were seen for EORTC-QLQ H&N35 and EQ-5D. The number of patients available for assessment declined gradually ([redacted]).[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Measured quality of life and symptoms did not notably differ between groups over time and remained relatively stable. The mean EOTRC QLQ-30 Global health status at baseline was 61.3 (SD 21.60) on a 100-point scale for patients who received PEMB-mono and 59.7 (SD 21.48) for those who received CET-chemo. At Week 15, the means were 64.7 (SD 20.55) and 62.6 (SD 18.80), and the LS mean changes from baseline to Week 15 were 0.85 (95% CI -1.90 to 3.59) and 0.60 (95% CI -2.19 to 3.40), for PEMB-mono and CET-chemo, respectively.

HR for time to deterioration in the EORTC QLQ-C30 global health status (GHS)/QoL was 1.38 (95% CI 0.95 to 2.00) for the comparison of PEMB-mono with CET-chemo. HR for time to deterioration in EORTC H&N35 pain subscale was 0.80 (95% CI: 0.53, 1.21) and for EORTC H&N35 swallowing subscale was 1.26 (95% CI 0.85 to 1.88).

[redacted]

[redacted].[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 21: Summary of quality of life outcomes for PEMB mono versus CET chemo, FAS population, IA2

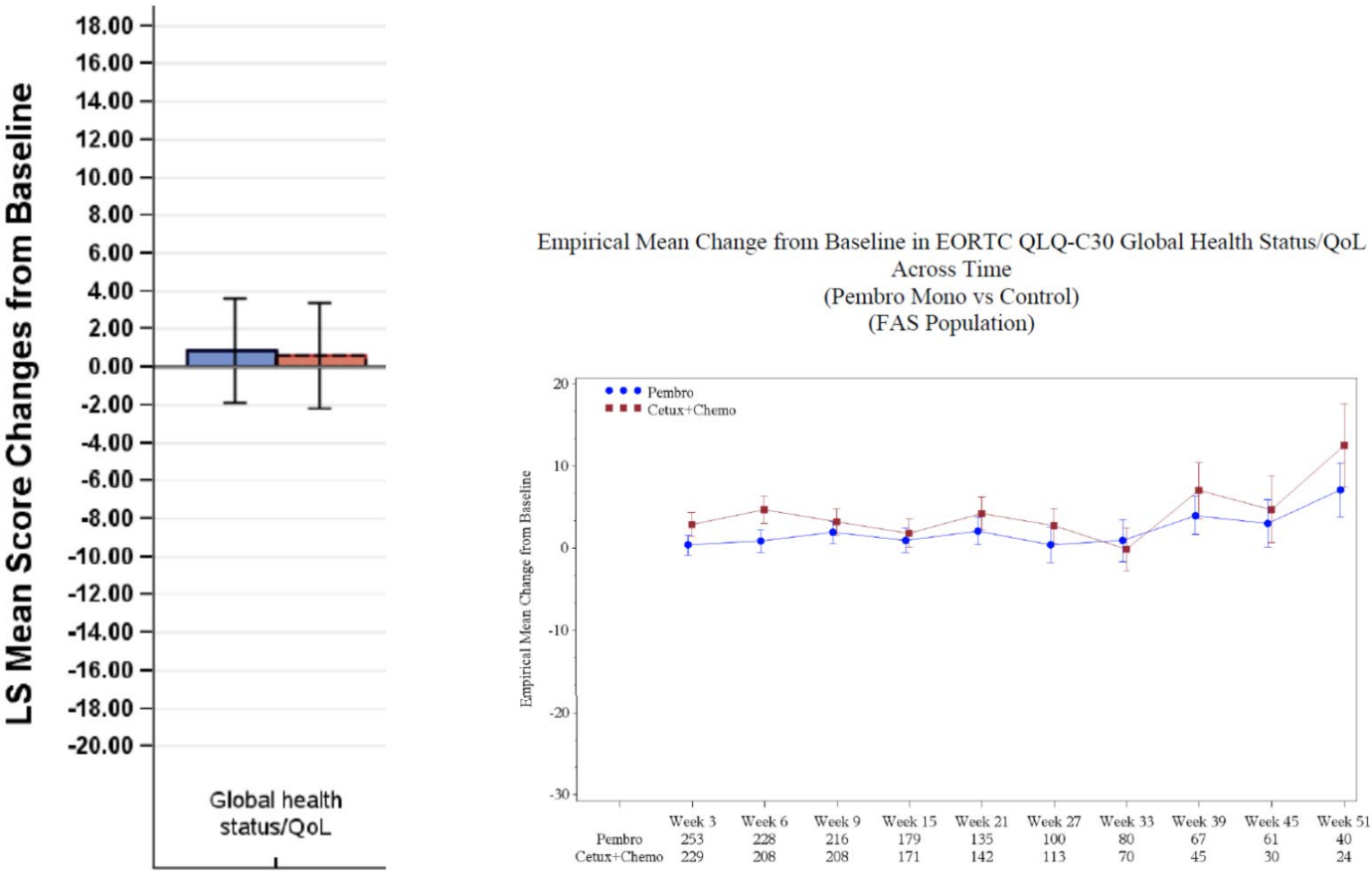
Variable	Time point		PEMB mono	CET chemo
EORCT QLQ-30 Global health status	Baseline	N	280	262
		Mean (SD)	61.3 (21.60)	59.7 (21.48)
	Week 15	N	191	182
		Mean (SD)	64.7 (20.55)	62.6 (18.80)
	Change from baseline to Week 15 (95% CI)	N	294	279
		LS Mean	0.85 (-1.90, 3.59)	0.60 (-2.19, 3.40)
		Difference in LS Mean (95% CI)	0.24 (-3.34, 3.40)	
Time to deterioration EORTC QLQ-30 Global Health Status		HR (95% CI)	1.38 (0.95, 2.00)	
Time to deterioration EORTC QLQ-H&N35 Pain		HR (95% CI)	0.80 (0.53, 1.21)	
Time to deterioration EORTC QLQ-H&N35 Swallowing		HR (95% CI)	1.26 (0.85, 1.88)	

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, PEMB mono = pembrolizumab monotherapy, QLQ = Quality of Life Questionnaire, SD = standard deviation

Data cut-off: June 13, 2018

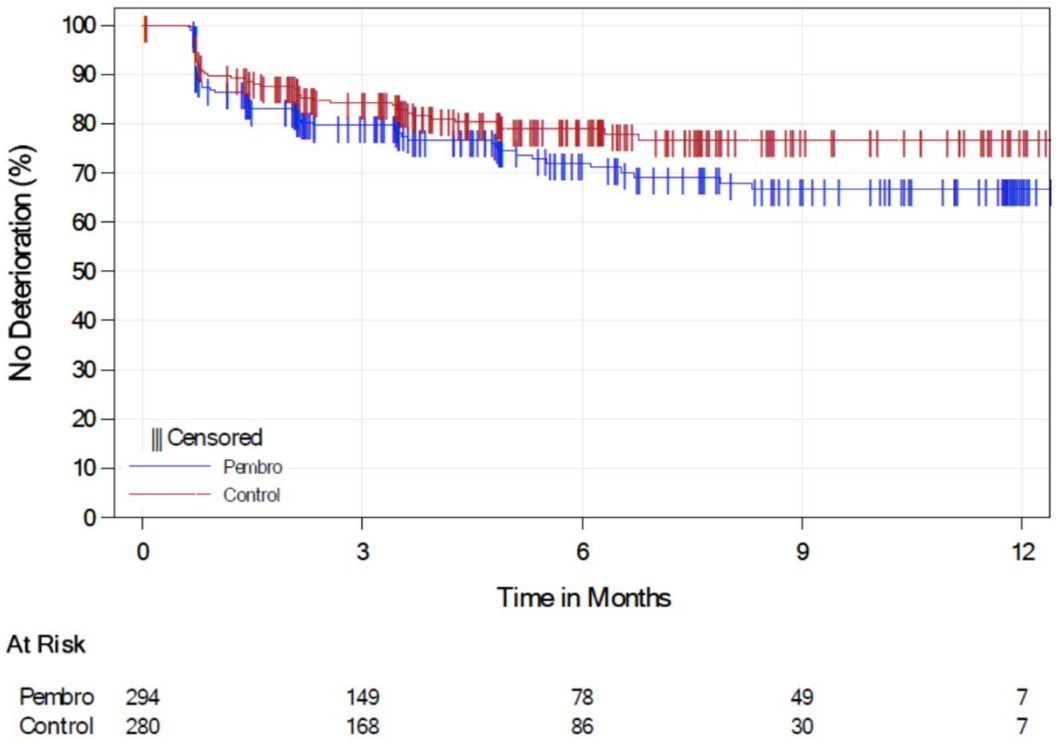
Data source: EPAR 2019[26]

Figure 13: Change from baseline in EORTC-QLQ global health status for PEMB mono versus CET-chemo in KEYNOTE-048, FAS population, IA2



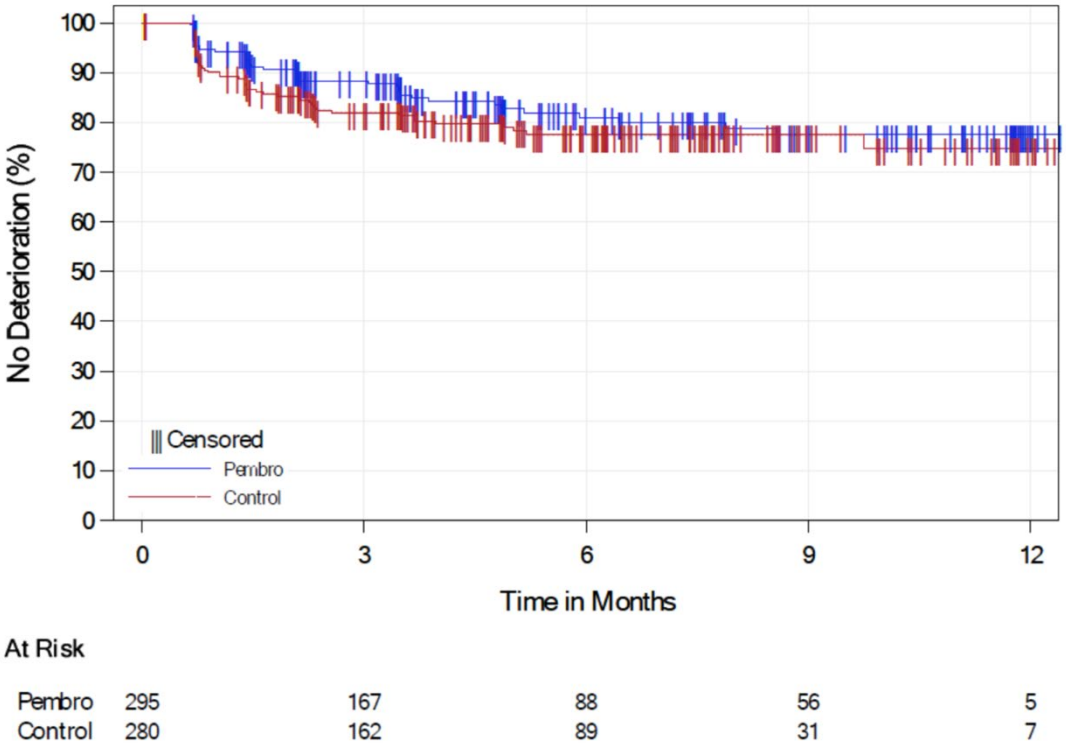
Abbreviations: Control = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, LS = least squares, QLQ = Quality of Life Questionnaire, QoL = quality of life, Pembro or PEMB mono = pembrolizumab monotherapy
Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

Figure 14: Time to true deterioration in EORTC-QLQ global health status for PEMB mono versus CET-chemo in KEYNOTE-048, FAS population, IA2



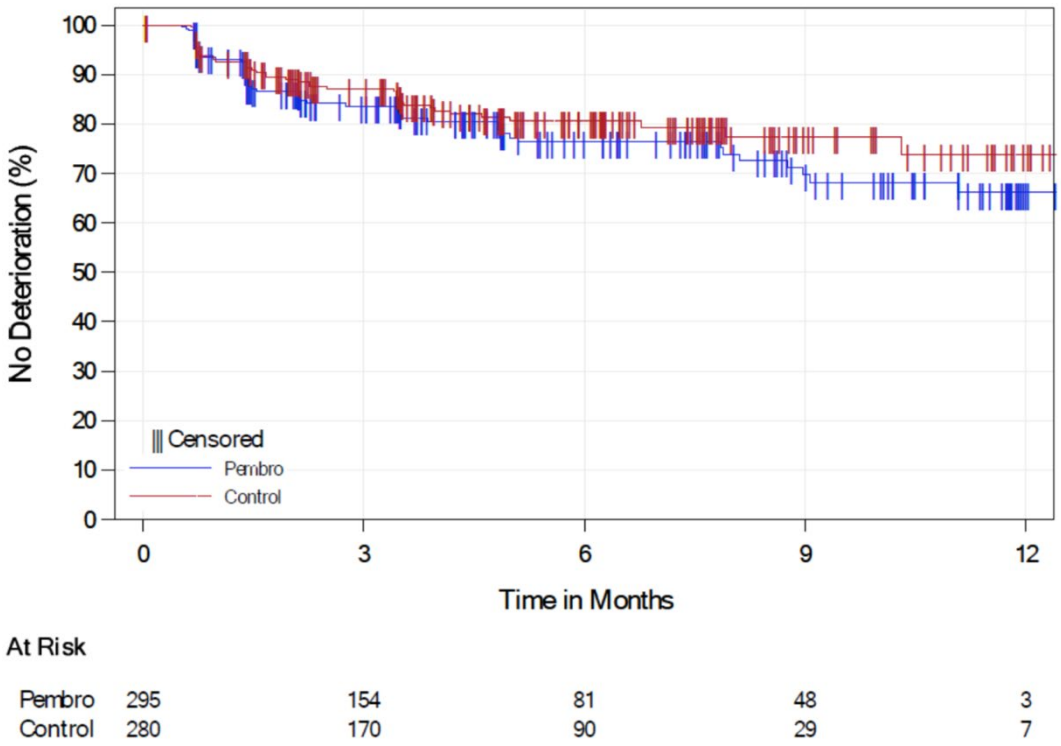
Abbreviations: Control or CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, Pembro or PEMB mono = pembrolizumab monotherapy, QLQ = Quality of Life Questionnaire
Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

Figure 15: Time to deterioration in EORTC-H&N35 pain for PEMB mono versus CET-chemo in KEYNOTE-048, FAS population, IA2



Abbreviations: Control = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, Pembro = pembrolizumab monotherapy
Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

Figure 16: Time to deterioration in EORTC-H&N35 swallowing for PEMB mono versus CET-chemo in KEYNOTE-048, FAS population, IA2



Abbreviations: Control = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, Pembro = pembrolizumab monotherapy
Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

Patients receiving a second course of pembrolizumab

The protocol allowed patients who discontinued pembrolizumab (whether as PEMB-mono or PEMB-chemo) following CR to receive a second course for up to a year. In an exploratory analysis of KEYNOTE-048 data with four-year follow-up reported in abstract form (data cut-off March 25, 2020),[4] a total of 11 patients (6 randomized to PEMB-mono) received second course pembrolizumab, with overall ORR 36.4%.

Treatment after discontinuation of study therapy

Table 22 summarizes the subsequent cancer therapies (second-line treatment as determined by investigators' choice) received by patients who discontinued the study treatments PEMB-mono and CET-chemo.

A similar proportion of patients received subsequent cancer therapy in PEMB-mono and CET-chemo, with a higher proportion of those who received PEMB-mono subsequently receiving chemotherapy (44.9% versus 34.0%, for PEMB-mono and CET-chemo respectively) and EGFR inhibitor (19.6% versus 6.3%), while a higher proportion of those who received CET-chemo subsequently receiving immune checkpoint inhibitor (2.0% versus 16.7%, for PEMB-mono and CET-chemo, respectively).

Table 22: Treatment after discontinuation for PEMB monotherapy versus CET-chemo in KEYNOTE-048, ITT population, FA

	PEMB mono N = 301	CET chemo N = 300
Number (%) who received subsequent cancer therapy	148 (49.2)	159 (53.0)
Chemotherapy	135 (44.9)	102 (34.0)
EGFR inhibitor	59 (19.6)	19 (6.3)
Immune checkpoint inhibitor	6 (2.0)	50 (16.7)
Other immunotherapy	1 (0.3)	6 (2.0)
Kinase inhibitor	1 (0.3)	1 (0.3)
Other	2 (0.7)	2 (0.7)
Individual therapies and combinations received by ≥5 patients		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB mono = pembrolizumab monotherapy

Data cut-off: February 25, 2019

Data source: Harrington ASCO 2020,[25] Checkpoint responses[29]

b) Efficacy outcomes for PEMB-chemo versus CET-chemo

Overall survival

Table 23 provides a summary of results for the OS analyses for PEMB-chemo versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA (February 25, 2019). Figure 17, Figure 18, and Figure 19 show the KM survival curves for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA, respectively.

For the comparison of PEMB-chemo versus CET-chemo for the ITT population, the difference in OS was statistically significant at IA2, HR 0.77 (95% CI 0.63 to 0.93), P-value = 0.0034 (P-value boundary 0.0041; **H14**), favouring PEMB-chemo. Median OS was 13.0 months (95% CI 10.9 to 14.7 months) for PEMB-chemo, compared with 10.7 months (95% CI 9.3 to 11.7 months) for CET-chemo, and at the time of the analysis 420 (75%) of 559 patients had died. The confirmatory analysis at FA supported this finding. Median OS in the ITT population at FA was 13.0 months (95% CI 10.9 to 14.7 months) for PEMB-chemo and 10.7 months (95% CI 9.3 to 11.7 months) for CET chemo, with median follow-up of 13.0 months (range 0.1 to 43.4 months) and 10.7 months (range 0.1 to 40.7 months). The HR for the comparison was 0.72 (95% CI 0.60 to 0.87). At 12 months, the percentage of patients surviving was 53.0% for PEMB-chemo versus 43.9% for CET-chemo. At 24 months, the percentage of patients surviving was 29.4% for PEMB-chemo versus 18.2% for CET-chemo.

Median OS in the PD-L1 CPS≥1 population at FA was 13.6 months (95% CI 10.7 to 15.5 months) for PEMB-chemo and 10.4 months (95% CI 9.1 to 11.7 months) for CET-chemo. The HR for the comparison was 0.65 (95% CI 0.53 to 0.80) statistically significant in favour of PEMB-chemo, P-value = 0.0002 (P-value boundary 0.0026; **H12**). At 12 months, the percentage of patients surviving was 55.0% for PEMB-chemo versus 43.5% for CET-chemo. At 24 months, the percentage of patients surviving is 30.8% for PEMB-chemo versus 16.8% for CET-chemo.

Median OS in the PD-L1 CPS≥20 population at FA was 14.7 months (95% CI 10.3 to 19.3 months) for PEMB-chemo and 11.0 months (95% CI 9.2 to 13.0 months) for CET-chemo. The HR for the comparison was 0.60 (95% CI 0.45 to 0.82) statistically significant in favour of PEMB-chemo, P-value 0.00044 (P-value boundary 0.0023; **H11**). At 12 months, the percentage of patients surviving was 57.1% for PEMB-chemo versus 46.1% for CET-chemo. At 24 months, the percentage of patients surviving was 35.4% for PEMB-chemo versus 19.4% for CET-chemo.

Table 23: Summary of results for OS for PEMB-chemo versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

	PEMB-chemo	CET-chemo
Data cut-off date	February 25, 2019	
Median follow-up time	13.0 (range 0.1, 43.4)	10.7 (0.1, 40.7)
ITT		
N	281	278
Number of events (%)	213 (75.8)	247 (88.8)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
HR (95% CI)	0.72 (0.60, 0.87)	
P-value (superiority statistic)	0.00025†	
OS at 12 months, % (95% CI)	53.0 (47.0, 58.7)	43.9 (38.0, 49.7)
OS at 18 months, % (95% CI)	37.6 (32.0, 43.3)	27.2 (22.1, 32.6)
OS at 24 months, % (95% CI)	29.4 (24.2, 34.8)	18.2 (13.9, 22.9)
PD-L1 CPS≥1		
N	242	235
Number of events (%)	177 (73.1)	213 (90.6)

	PEMB-chemo	CET-chemo
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
HR (95% CI)	0.65 (0.53, 0.80)	
P-value (superiority statistic)	0.00002*	
OS at 12 months, % (95% CI)	55.0 (48.5, 61.0)	43.5 (37.0, 49.7)
OS at 18 months, % (95% CI)	39.1 (33.0, 45.2)	26.7 (21.2, 32.5)
OS at 24 months, % (95% CI)	30.8 (25.1, 36.7)	16.8 (12.3, 21.9)
PD-L1 CPS≥20		
N	126	110
Number of events (%)	84 (66.7)	98 (89.1)
Median in months (95% CI)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)
HR (95% CI)	0.60 (0.45, 0.82)	
P-value (superiority statistic)	0.00044*	
OS rate at 12 months (95% CI)	57.1 (48.0, 65.2)	46.1 (36.6, 55.1)
OS rate at 18 months (95% CI)	43.5 (34.7, 51.9)	27.7 (19.6, 36.3)
OS rate at 24 months (95% CI)	35.4 (27.2, 43.8)	19.4 (12.6, 27.3)

* Formally tested at FA under pre-planned hierarchical testing strategy

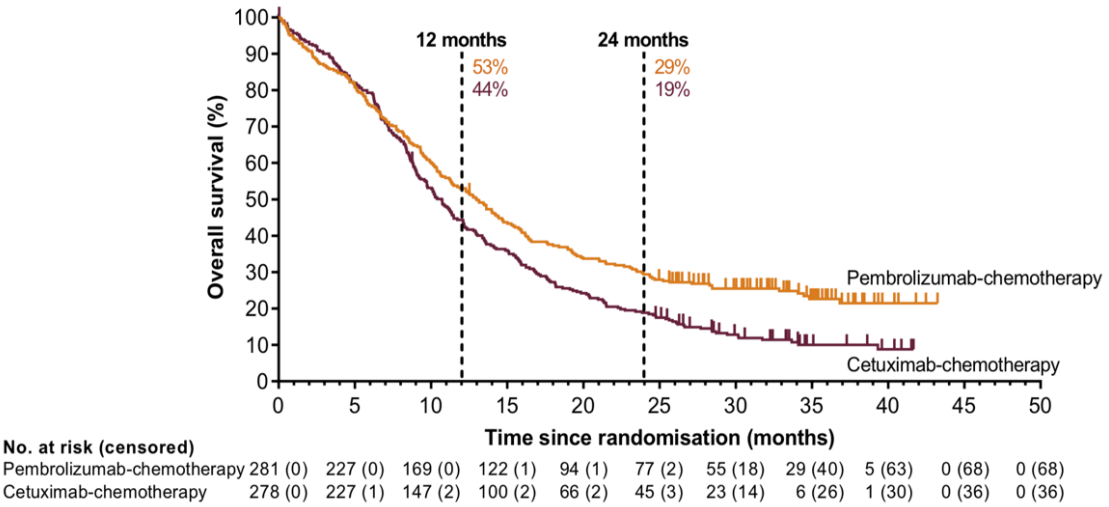
† Confirmatory analysis at FA. P-values nominal only. Tested at IA2, and results are reported in text.

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, HR = hazard ratio, OS = overall survival, PD-L1 = programmed death ligand 1, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Figure 17: Kaplan-Meier estimates for OS for PEMB-chemo versus CET-chemo, ITT population, FA

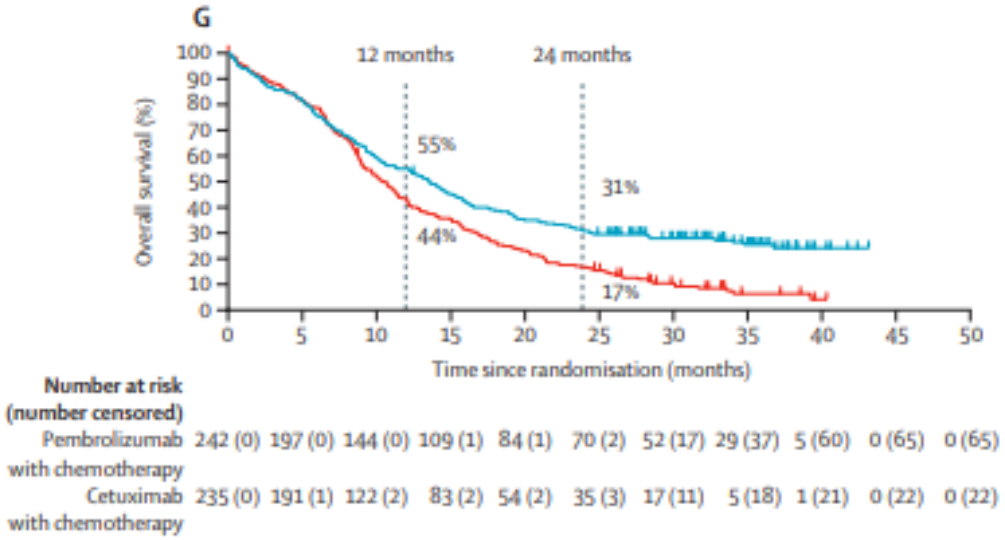


Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, FA = final analysis, ITT = intention to treat, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 18: Kaplan-Meier estimates for OS for PEMB-chemo versus CET-chemo, CPS≥1 population, FA

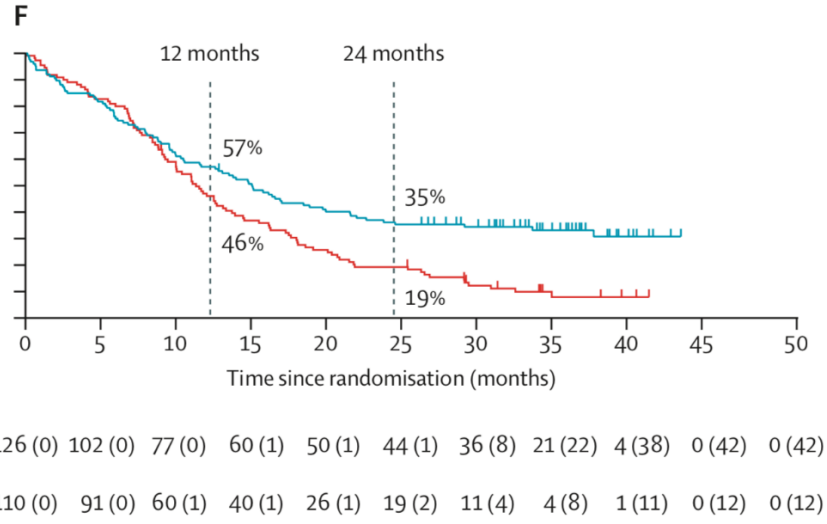


Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, FA = final analysis, OS = overall survival, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 19: Kaplan-Meier estimates for OS for PEMB-chemo versus CET-chemo, CPS≥20 population, FA



Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, FA = final analysis, OS = overall survival, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

As seen above, the survival curves for OS for the two treatments cross for all three populations. Graphical assessment and testing of treatment-by-time interactions in the overall Cox proportional hazards model suggested deviation from the proportional hazards assumption. The results from the weighted log-rank test, weighting towards later values, support those of the Cox proportional hazards model. For the ITT population, the log-rank p-value was 0.00335 and the weighted log-rank p-value was 0.00130. The RSMT differences for overall survival show point estimates increasing over time, although confidence intervals overlapping the null at all time points with the exception of 24-month follow-up, survival difference 1.38 (95% CI 0.05 to 2.72). This is also consistent with the interpretation of the primary analysis.

An exploratory analysis of KEYNOTE-048 data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 45.6 months for patients in the PEMB-chemo versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the median OS for patients receiving PEMB-chemo was 13.0 months, compared with 10.7 months for those receiving CET-chemo, HR 0.71 (0.59 to 0.85). Four year OS was 19.4% versus 4.5% for PEMB-chemo versus CET-chemo. For the PD-L1 CPS≥1 population, the median OS for patients receiving PEMB-chemo was 13.6 months, compared with 10.6 for those receiving CET-chemo, HR 0.64 (0.53 to 0.78). Four year OS was 21.0% versus 4.1% for PEMB-chemo versus CET-chemo, respectively. For the PD-L1 CPS≥20 population, the median OS for patients receiving PEMB-chemo was 14.7 months, compared with 11.1 for those receiving CET-chemo, HR 0.62 (0.46 to 0.84). Four year OS was 28.6% versus 6.6% for PEMB-chemo versus CET-chemo, respectively.

Progression free survival

Table 24 provides a summary of results for the PFS comparisons for PEMB-chemo versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the FA. Figure 20 shows the KM estimates for PFS for the three populations at the FA. No significant differences were found at IA1 (interim analysis for PFS) for any PFS hypothesis, and these results are not shown. IA2 was the final analysis for PFS endpoints, and the results are described in the text.

The comparison between PEMB-chemo and CET-chemo for the ITT population (H6) was not statistically significant at IA2, P-value 0.1697 (P-value boundary 0.0002). Median PFS was 4.9 months (95% CI 4.7 to 6.0 months) for PEMB-mono and 5.1 months (4.9 to 6.0 months) for CET-chemo, HR 0.92 (95% CI 0.77 to 1.10). At FA, PFS is 4.9 months (95% CI 4.7 to 6.1 months) for PEMB-chemo and 5.1 months (95% CI 4.9 to 6.1 months) for CET-chemo. Exploratory analyses at the FA gave an HR for the comparison of 0.93 (95% CI 0.78 to 1.11). At 6 months, the percentage of patients with PFS for PEMB-chemo was 44.7%, compared with 44.9% for CET chemo. At 12 months, the percentage of patients with PFS for PEMB-chemo was 17.2%, compared with 13.6% for CET-chemo.

The comparison between PEMB-chemo and CET-chemo for the PD-L1 CPS≥1 population (**H5**) was not tested at IA2 because H4 was not statistically significant. Median PFS was 5.0 months (95% CI 4.7 to 6.2 months) for PEMB-mono and 5.0 months (4.8 to 5.8 months) for CET-chemo, 0.82 (95% CI 0.67 to 1.00). At FA, the median PFS was 5.1 months (95% CI 4.7 to 6.2 months) for the PEMB-chemo group and 5.0 months (95% CI 4.8 to 6.0 months) for CET-chemo. Exploratory analyses at the FA gave an HR for the comparison of 0.84 (95% CI 0.69 to 1.02). At 6 months, the percentage of patients with PFS for PEMB-chemo is 44.9%, compared with 43.3% for CET-chemo. At 12 months, the percentage of patients with PFS for PEMB-chemo is 19.7%, compared with 12.5% for CET-chemo.

The comparison between PEMB-chemo and PEMB-chemo in the PD-L1 CPS≥20 population (**H4**) was not statistically significant at IA2, P-value = 0.1697 (P-value boundary = 0.0002). Median PFS was 5.8 months (95% CI 4.7 to 7.6 months) for PEMB-mono and 5.2 months (4.8 to 6.2 months) for CET-chemo, HR 0.73 (95% CI 0.55 to 0.97). At FA, the median PFS was 5.8 months (95% CI 4.7 to 7.6 months) for the PEMB-chemo group and 5.3 months (95% CI 4.9 to 6.3 months). Exploratory analyses at the FA gave an HR for the comparison of 0.76 (0.58, 1.01). At 6 months, the percentage of patients with PFS for PEMB-chemo is 49.9%, compared with 47.2% for CET-chemo. At 12 months, the percentage of patients with PFS for PEMB-chemo is 23.9%, compared with 14.0% for CET chemo.

Table 24: Summary of results for PFS for PEMB-chemo versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

	PEMB-chemo	CET-chemo
Data cut-off date	February 25, 2019	
ITT		
N	281	278
Number of events (%)	250 (89.0)	260 (93.5)
Median in months (95% CI)	4.9 (4.7, 6.1)	5.1 (4.9, 6.1)
HR (95% CI)	0.93 (0.78, 1.11)	
P-value (superiority statistic)	0.21211†	
PFS at 6 months (95% CI)	44.7 (38.8, 50.5)	44.9 (38.9, 50.8)
PFS at 9 months (95% CI)	26.9 (21.8, 32.3)	20.5 (15.9, 25.6)
PFS at 12 months (95% CI)	17.2 (13.0, 21.9)	13.6 (9.8, 18.1)
PD-L1 CPS≥1		
N	242	235
Number of events (%)	212 (87.6)	221 (94.0)
Median in months (95% CI)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
HR (95% CI)	0.84 (0.69, 1.02)	
P-value (superiority statistic)	0.03697†	
PFS at 6 months (95% CI)	44.9 (38.5, 51.1)	43.3 (36.9, 49.6)
PFS at 9 months (95% CI)	28.0 (22.4, 33.9)	19.4 (14.5, 24.8)
PFS at 12 months (95% CI)	19.7 (14.8, 25.0)	12.5 (8.6, 17.3)
PD-L1 CPS≥20		
N	126	110
Number of events (%)	106 (84.1)	104 (94.5)
Median in months (95% CI)	5.8 (4.7, 7.6)	5.3 (4.9, 6.3)
HR (95% CI)	0.76 (0.58, 1.01)	
P-value (superiority statistic)	0.02951†	
PFS at 6 months (95% CI)	49.4 (40.3, 57.9)	47.2 (37.5, 56.2)
PFS at 9 months (95% CI)	35.4 (27.0, 43.8)	21.7 (14.4, 29.9)
PFS at 12 months (95% CI)	23.9 (16.7, 31.7)	14.0 (8.2, 21.3)

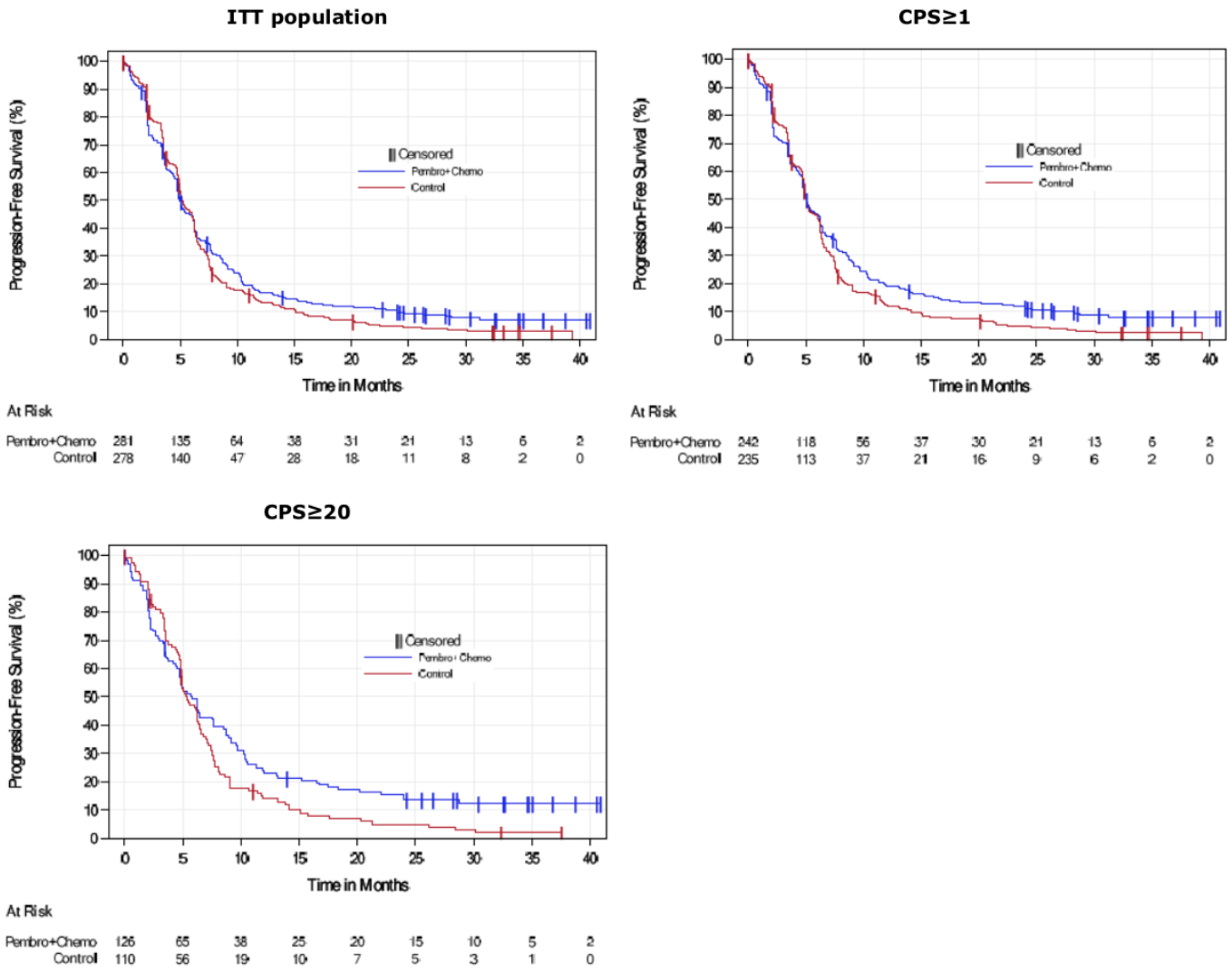
† Confirmatory testing at FA. P-values nominal only. Tested (where indicated under formal hierarchy) at IA, and results are reported in text.

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, HR = hazard ratio, PD-L1 = programmed death ligand 1, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PFS = progression free survival

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Figure 20: Kaplan-Meier estimates for PFS for PEMB-chemo versus CET-chemo, ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, IA2



Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, HR = hazard ratio, PD-L1 = programmed death ligand 1, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PFS = progression free survival

Data cut-off: June 13, 2018

Figure source: EPAR 2019[26]

An exploratory analysis of KEYNOTE-048 PFS data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 45.6 months for patients in the PEMB-chemo versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the median PFS for patients receiving PEMB-chemo was 4.9 months, compared with 5.3 months for those receiving CET-chemo. The PD-L1 CPS≥1 population, the median PFS was 5.1 months versus 5.0 months, and for the PD-L1 CPS≥20 population, the median PFS was 5.8 months versus 5.3 months, for PEMB-chemo and CET-chemo, respectively.

Overall response rate

Table 25 provides a summary of results for the ORR comparisons for PEMB-chemo versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at the IA2 analysis.

ORR in the ITT population at IA2 was 35.6% (95% CI 30.0% to 41.5%) for PEMB-chemo compared with 36.3% (95% CI 30.7% to 42.3%) for CET-chemo (IA2), with a difference in percentages -0.8% (95% CI -8.7% to 7.2%). This endpoint was not hypothesis tested. Seventeen (6.0%) of patients who received PEMB-chemo had a CR, compared with 8 (2.9%) of those who received CET-chemo. Eighty-three (29.5%) of patients who received PEMB-chemo had a PR, compared with 93 (33.5%) who received CET-chemo.

ORR in the PD-L1 CPS≥1 population at IA2 was 36.4% for PEMB-chemo compared with 35.7% for CET-chemo (IA2). Sixteen (6.6%) patients who received PEMB-chemo had a CR, compared with 7 (3.0%) of those who received CET-chemo. Seventy-two (29.8%) patients who received PEMB-chemo had a PR, compared with 77 (32.8%) of those who received CET-chemo.

ORR in the PD-L1 CPS≥20 population at IA2 was 42.9% for PEMB-chemo compared with 38.2% for CET-chemo. Twelve (9.5%) of patients who received PEMB-chemo had a CR, compared with 4 (3.6%) of those who received CET-chemo. Forty-two (33.3%) of patients who received PEMB-chemo had a PR, compared with 38 (34.5%) who received CET-chemo.

Table 25: Summary of results for ORR for PEMB-chemo versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, IA2

	PEMB-chemo	CET-chemo
Data cut-off date	June 13, 2018	
ITT		
N	281	278
ORR n, % (95% CI)	100, 35.6 (30.0, 41.5)	101, 36.3 (30.7, 42.3)
Difference in % versus control (95% CI)	-0.8 (-8.7, 7.2)	
Complete responses (CR), n (%)	17 (6.0)	8 (2.9)
Partial responses (PR), n (%)	83 (29.5)	93 (33.5)
Stable disease (SD), n (%)	78 (27.8)	95 (34.2)
Progressive disease (PD), n (%)	48 (17.1)	33 (11.9)
Non-CR/Non-PD, n (%)	13 (4.6)	9 (3.2)
Not evaluable (NE), n (%)	5 (1.8)	2 (0.7)
No assessment, n (%)	37 (13.2)	38 (13.7)
PD-L1 CPS≥1		
N	242	235
ORR n, % (95% CI)	88, 36.4 (30.3, 42.8)	84, 35.7 (29.6, 42.2)
Complete responses (CR), n (%)	16 (6.6)	7 (3.0)
Partial responses (PR), n (%)	72 (29.8)	77 (32.8)
Stable disease (SD), n (%)	64 (26.4)	77 (32.8)
Progressive disease (PD), n (%)	42 (17.4)	29 (12.3)
Non-CR/Non-PD, n (%)	11 (4.5)	9 (3.8)
Not evaluable (NE), n (%)	4 (1.7)	2 (0.9)
No assessment, n (%)	33 (13.6)	34 (14.5)

	PEMB-chemo	CET-chemo
PD-L1 CPS≥20		
N	126	110
ORR n % (95% CI)	54, 42.9 (34.1, 52.0)	42, 38.2 (29.1, 47.9)
Complete responses (CR), n (%)	12 (9.5)	4 (3.6)
Partial responses (PR), n (%)	42 (33.3)	38 (34.5)
Stable disease (SD), n (%)	29 (23.0)	37 (33.6)
Progressive disease (PD), n (%)	19 (15.1)	10 (9.1)
Non-CR/Non-PD, n (%)	4 (3.2)	5 (4.5)
Not evaluable (NE), n (%)	2 (1.6)	0
No assessment, n (%)	18 (14.3)	16 (14.5)

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, FA = final analysis, ORR = objective response rate, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PD-L1 = programmed death ligand 1

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

An exploratory analysis of KEYNOTE-048 ORR data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 45.6 months for patients in the PEMB-chemo versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the ORR for patients receiving PEMB-chemo was 36.3%, compared with 36.3% for those receiving CET-chemo. The PD-L1 CPS≥1 population, the ORR was 37.2% versus 35.7%, and for the PD-L1 CPS≥20 population, the ORR was 43.7% versus 38.2%, for PEMB-mono and CET-chemo, respectively.

Duration of response

Table 26 provides a summary of results for DOR for PEMB-chemo versus CET-chemo for the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations at FA. Results were consistent between IA2 and FA.

Median DOR in patients in the ITT population who received PEMB-chemo and had CR or PR (100 patients) is 6.7 months (range, 1.6+ to 39.0+ months, the + indicating patients who had response ongoing at the end of follow-up), compared with 4.3 months (range, 1.2+ to 31.5+ months) in those who received CET-chemo (101 patients). Forty-nine (53.5%) and 28 (36.8%) patients who received PEMB-chemo and CET-chemo, respectively, had response duration ≥ 6 months.

Median DOR in patients in the PD-L1 CPS≥1 population who received PEMB-chemo and had CR or PR (88 patients) is 6.7 months (range, 1.6+ to 39.0+ months), compared with 4.3 months (range, 1.2+ to 31.5+ months) in those who received CET-mono (84 patients). Forty-four (54.3%) and 21 (34.3%) patients who received PEMB-chemo and CET-chemo, respectively, had response duration ≥ 6 months.

Median DOR in patients in the PD-L1 CPS≥20 population who received PEMB-chemo and had CR or PR (54 patients) is 7.1 months (range, 2.1+ to 39.0+ months), compared with 4.2 months (range, 1.2+ to 31.5+ months) in those who received CET-mono (42 patients). Thirty-one (60.2%) and 11 (34.0%) patients who received PEMB-chemo and CET-chemo, respectively, had response duration ≥ 6 months.

Table 26: Summary of results for DOR for PEMB-chemo versus CET-chemo in the ITT, PD-L1 CPS≥1, and PD-L1 CPS≥20 populations in KEYNOTE-048, FA

	PEMB-chemo	CET-chemo
Data cut-off date	February 25, 2019	
ITT		
N	281	278
Number with response	100	101
Median in months (range)	6.7 (1.6+ - 39.0+)	4.3 (1.2+ - 31.5+)
Median time to response (range)	2.1 (1.4 – 13.7)	2.1 (1.3 – 10.4)
Number (KM%) with response duration ≥ 6 months	49 (53.5)	28 (36.8)
PD-L1 CPS≥1		
N	242	235
Number with response	88	84
Median in months (range)	6.7 (1.6+ - 39.0+)	4.3 (1.2+ - 31.5+)
Median time to response (range)	2.1 (1.4 – 13.7)	2.1 (1.3 – 10.4)
Number (KM%) with response duration ≥ 6 months	44 (54.3)	21 (34.3)
PD-L1 CPS≥20		
N	126	110
Number with response	54	42
Median in months (range)	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 (1.9 - 6.0)
Number (KM%) with response duration ≥ 6 months	31 (60.2)	11 (34.0)

+ indicates that patients had ongoing response at time of last follow-up.

Abbreviations: CPS = Combined Proportion Score, DOR = duration of response, ITT = intention to treat, KM = Kaplan-Meier, PD-L1 = programmed death ligand 1

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

An exploratory analysis of KEYNOTE-048 DOR data with four-year follow-up has been reported in abstract form (data cut-off March 25, 2020).[4] Median study follow-up was 45.6 months for patients in the PEMB-chemo versus CET-chemo comparison. Results were consistent with those from earlier analyses. For the ITT population, the ORR for patients receiving PEMB-chemo was 6.7 months, compared with 4.3 months for those receiving CET-chemo. The PD-L1 CPS≥1 population, the ORR was 6.7 months versus 4.3 months, and for the PD-L1 CPS≥20 population, the ORR was 7.0 months versus 4.2 months, for PEMB-mono and CET-chemo, respectively.

Analyses of subgroups (OS, PFS, ORR, DOR) for subgroups of interest

Figure 21 shows the results of clinical exploratory subgroup analyses of OS for PEMB-chemo versus CET-chemo in the ITT population at the time of FA (February 25, 2019), and Figure 22 shows the corresponding subgroup results for the PD-L1 CPS≥1 population. Figure 23 and Figure 24 show the results of the subgroup analysis for PFS for the ITT and PD-L1 CPS≥1 populations, respectively at the FA. The subgroups were age, sex, ECOG performance status score, region of enrollment, smoking status, p16 status, PD-L1 CPS expression (for ITT population), and disease status (metastatic versus recurrent, where patients with both logoregional recurrence and metastases were classified as metastatic). Table 27 shows a summary of OS, PFS, ORR, and DOR results for additional PD-L1 CPS subgroups, and Table 28 shows a summary of OS, PFS, ORR, and DOR results for the PD-L1 TPS subgroups, on which randomization was originally stratified.

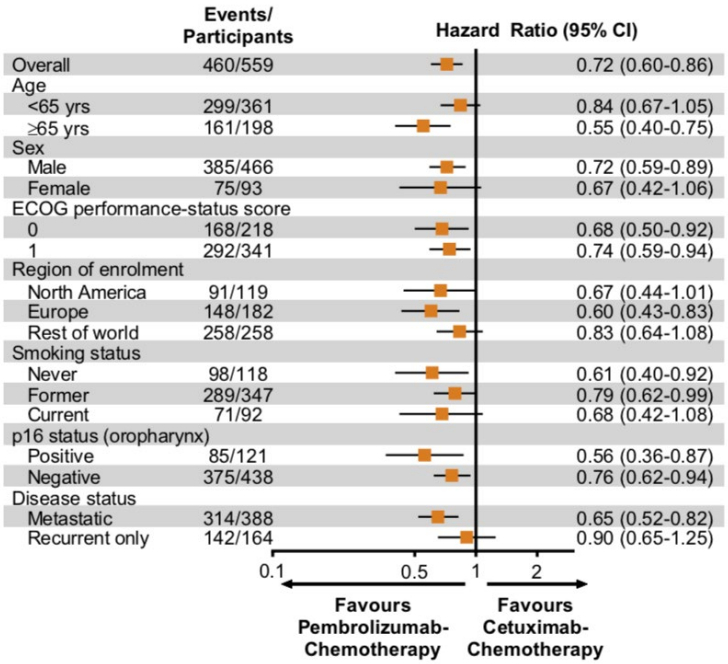
Estimated differences in OS between clinical subgroups were minimal for the ITT and PD-L1 CPS≥1 populations, with the exception of age (dichotomized) and disease status (recurrent/metastatic). Patients in the ITT populations aged < 65 years had HR for OS 0.84 (95% CI 0.67 to 1.05), while those aged ≥ 65 had HR 0.55 (95% CI 0.40 to 0.75). Patients with metastatic disease had HR for OS 0.65 (95% CI 0.52 to 0.82) compared with HR 0.90 (95% CI 0.65 to 1.25) for recurrent disease. Patients in the PD-L1 CPS≥1 populations aged < 65 years had HR for OS 0.74 (95% CI 0.57 to 0.94), while those aged ≥ 65 had HR 0.54 (95% CI 0.39 to 0.76. Patients with metastatic disease had HR for OS 0.60 (95% CI 0.47 to 0.77) compared with HR 0.80 (95% CI 0.56 to 1.14) for recurrent disease.

Similar results were seen for PFS. Patients in the ITT population aged ≥65 years had HR 0.72 (95% CI 0.54 to 0.96), compared with HR 1.0 (95% 0.8 to 1.24) for patients aged < 65 years. Patients in the ITT population with metastatic disease had HR for PFS 0.78 (95% CI 0.63 to 0.96), compared with HR 1.18 (95% CI 0.86 to 1.62).

Results for additional PD-L1 CPS subgroups (CPS<1, CPS≥1 and <20, and CPS<20), do not suggest a difference in OS or PFS between levels of PD-L1 expression, including for the CPS<1 subgroup. HR for OS for PD-L1 CPS<1 was 1.21 (95% CI 0.76 to 1.94) and for PD-L1 CPS<20 HR is 0.83 (95% CI 0.65 to 1.05; Table 27). HR for PFS for PD-L1 CPS<1 is 1.46 (0.93 to 2.30) and for PD-L1 CPS<20 HR is 1.05 (95% CI 0.84 to 1.32). However, particularly for the PD-L1 CPS<1 group, the numbers are small (82 patients total), leading to uncertainty of the estimate and potentially obscuring a difference.

A slight difference was seen for OS between subgroups with TPS <50%, HR 0.74 (95% CI 0.59 to 0.92), and TPS ≥50%, HR 0.88 95% CI 0.58 to 1.35; Table 28). At 12 months, the proportion of patients with TPS <50% surviving was 52.1% for PEMB-chemo versus 41.9% with PEMB-chemo, while the proportions with TPS ≥50% were 56.1% and 51.3%. For PFS, there was little difference between treatment groups and subgroups in HR or the proportion with PFS at 6 months.

Figure 21: Results of subgroup analyses for OS, PEMB-chemo versus CET-chemo, ITT population, FA

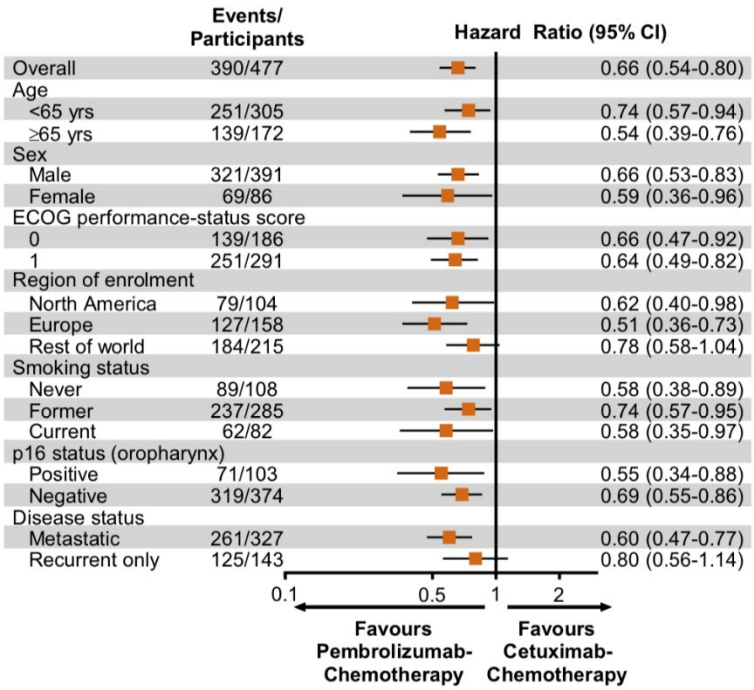


Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Figure source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 22: Results of subgroup analyses for OS, PEMB-chemo versus CET-chemo, PD-L1 CPS≥1 population, FA



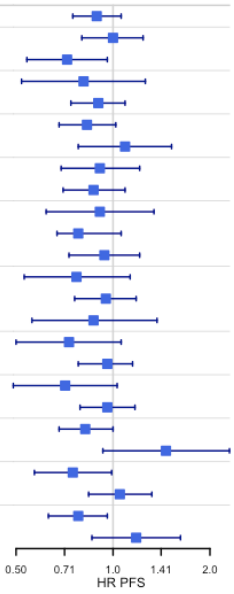
Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Figure source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

Figure 23: Results of subgroup analyses for PFS, PEMB-chemo versus CET-chemo, ITT population, FA

Factor	Subgroup	N/Events	HR (95% CI)
Overall		559/510	0.89 (0.75, 1.06)
Age	<65 years	361/326	1 (0.8, 1.24)
	>= 65 years	198/184	0.72 (0.54, 0.96)
Sex	Female	93/83	0.81 (0.52, 1.26)
	Male	466/427	0.9 (0.74, 1.09)
Race	White	410/369	0.83 (0.68, 1.02)
	All others	148/140	1.09 (0.78, 1.52)
ECOG	0	216/192	0.91 (0.69, 1.21)
	1	341/318	0.87 (0.7, 1.09)
Region	North America	119/106	0.91 (0.62, 1.34)
	EU	182/163	0.78 (0.67, 1.06)
	ROW	258/241	0.94 (0.73, 1.21)
Smoking status	Never	118/108	0.77 (0.53, 1.13)
	Former	347/319	0.95 (0.76, 1.18)
	Current	92/81	0.87 (0.56, 1.37)
HPV status	Positive	121/107	0.73 (0.5, 1.06)
	Negative	438/403	0.96 (0.78, 1.15)
PD-L1 TPS	Strongly positive	128/112	0.71 (0.49, 1.03)
	Not strongly positive	431/398	0.96 (0.79, 1.17)
PD L1 CPS1	CPS>=1	477/433	0.82 (0.68, 1)
	CPS<1	82/77	1.46 (0.93, 2.3)
PD L1 CPS20	CPS>=20	236/210	0.75 (0.57, 0.99)
	CPS<20	319/296	1.05 (0.84, 1.32)
Disease status	Metastatic	388/301	0.78 (0.63, 0.96)
	Recurrent	164/155	1.18 (0.86, 1.62)

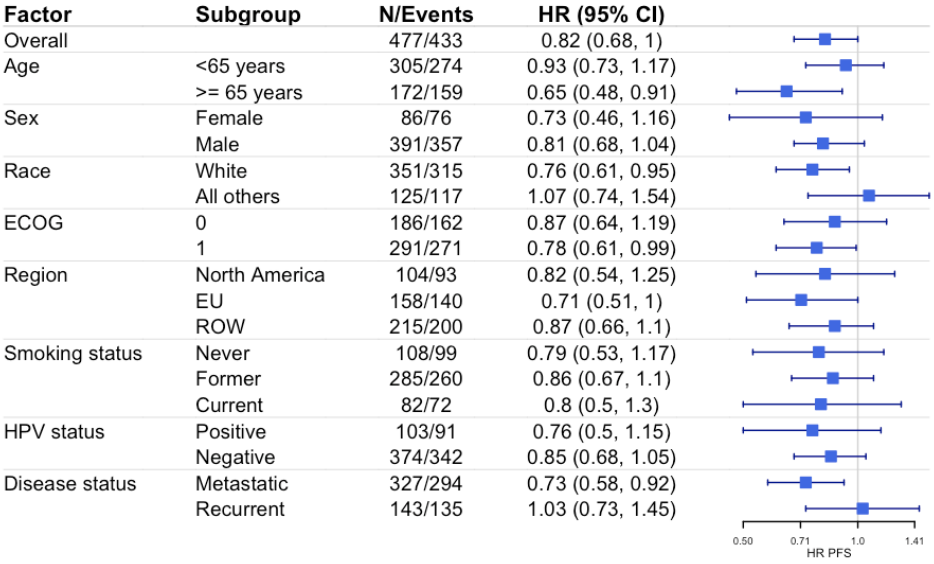


Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, PD-L1 = programmed death ligand 1, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Figure source: EPAR 2019[26]

Figure 24: Results of subgroup analyses for PFS, PEMB-chemo versus CET-chemo, PD-L1 CPS≥1 population, FA



Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, PD-L1 = programmed death ligand 1, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Figure source: EPAR 2019[26]

Table 27: Summary of results for OS, PFS, ORR, and DOR for PEMB-chemo versus CET-chemo PD-L1 CPS <1, PD-L1 CPS <20, and PD-L1 CPS ≥ 1 to CPS <20 subgroups from KEYNOTE-48, FA

	PD-L1 CPS <1		PD-L1 CPS <20		PD-L1 CPS ≥ 1 to CPS <20	
	PEMB-chemo N=39	CET-chemo N=43	PEMB-chemo N=154	CET-chemo N=165	PEMB-chemo N=116	CET-chemo 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, 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)	
OS 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 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 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)						

	PD-L1 CPS <1		PD-L1 CPS <20		PD-L1 CPS ≥ 1 to CPS <20	
	PEMB-chemo N=39	CET-chemo N=43	PEMB-chemo N=154	CET-chemo N=165	PEMB-chemo N=116	CET-chemo N=125
Number of events (%)	38 (97.4)	39 (90.7)	143 (92.9)	153 (92.7)	106 (91.4)	117 (93.6)
Median, 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)	1.46 (0.93, 2.30)		1.05 (0.84, 1.32)		0.93 (0.71, 1.21)	
PFS at 6 months (95% CI)	43.6 (27.9)	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)						
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 Response Duration ≥ 6 months	5 (46.9)	7 (49.0)	18 (45.1)	17 (38.5)	13 (44.3)	10 (34.0)

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, CR = complete response, DOR = duration of response, KM = Kaplan-Meier, OS = overall survival, PD-L1 = programmed death ligand 1, PFS = progression free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumours

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Table 28: Summary of results for OS, PFS, ORR, and DOR for PEMB-chemo versus CET-chemo PD-L1 TPS < 50% and TPS ≥ 50% from KEYNOTE-48, IA2

	PD-L1 TPS <50%		PD-L1 TPS ≥ 50%	
	PEMB-chemo N=215	CET-chemo N=216	PEMB-chemo N=66	CET-chemo 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)	1 2.2 (8.9, 15.9)
HR (95% CI)	0.74 (0.59, 0.92)		0.88 (0.58,1.35)	
OS 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)
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)	
PFS 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+)

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, CPS = Combined Proportion Score, CR = complete response, DOR = duration of response, KM = Kaplan-Meier, OS = overall survival, PD-L1 = programmed death ligand 1, PFS = progression free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumours, TPS = Tumour Proportion Score

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

Quality of Life Outcomes

Table 29 presents a summary of HRQoL outcomes for PEMB-chemo compared with CET-chemo. The EORTC scales were collected at treatment cycles 1 through 4, 6 (week 15), and every 2 cycles until 30 days post-treatment.

Results were summarized for baseline and Week 15, the expected final cycle of chemotherapy. Figure 25 shows change from baseline in EORTC global health status, Figure 26 shows time to deterioration in EORTC global health status, Figure 27 shows time to deterioration in EORTC H&N35 pain subscale, and Figure 28 shows time to deterioration in EORTC H&N35 swallowing subscale. A decline of 10 points or greater on a 100-point scale represented clinically significant deterioration.

At Week 15, 173 patients (64.1%) randomized to PEMB-chemo and 168 (64.6%) completed the EORTC QLQ-30 questionnaire. Compliance rates (the percentage of patients completing the questionnaire compared with those expected to complete per protocol) at baseline for the EORTC QLQ-30 were 94.4% for PEMB-chemo and 93.8% for CET-chemo, and at week 15 were 82% for PEMB-chemo and 78.9% for CET-chemo. Similar compliance rates were seen for EORTC-QLQ H&N35 and EQ-5D. The number of patients available for assessment declined gradually ([redacted]).[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Quality of life and symptoms did not notably differ between groups over time and remained relatively stable. At baseline, the mean EOTRC QLQ-30 Global health status was 62.2 (SD 21.18) on a 100-point scale for patients who received PEMB-chemo and 60.0

(21.86) for those who received CET-chemo. At Week 15, the means were 64.6 (21.10) and 63.3 (18.27), and the LS mean changes from baseline to Week 15 are 1.17 (95% CI -1.79 to 4.12) and 0.77 (95% CI -2.22 to 3.76), for PEMB-chemo and CET-chemo, respectively.

HR for time to deterioration in the EORTC QLQ-C30 GHS/QoL was 1.37 (95% CI 0.94 to 2.00) for the comparison of PEMB-chemo with CET-chemo. HR for time to deterioration in EORTC H&N35 pain subscale was 1.37 (95% CI: 0.93, 2.02) and for EORTC H&N35 swallowing subscale was 1.05 (95% CI 0.69 to 1.59).

[redacted].[28] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 29: Summary of quality of life outcomes for PEMB-chemo versus CET chemo, FAS population, IA2

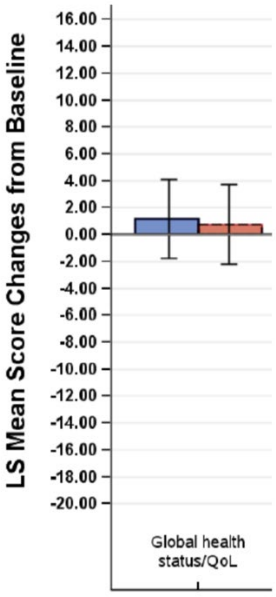
Variable	Time point		PEMB-chemo	CET-chemo
EOTRC QLQ-30 Global health status	Baseline	N	255	244
		Mean (SD)	62.2 (21.18)	60.0 (21.86)
	Week 15	N	173	167
		Mean (SD)	64.6 (21.1)	63.3 (18.27)
	Change from baseline to Week 15 (95% CI)	N	268	259
		LS Mean	1.17 (-1.79, 4.12)	0.77 (-2.22, 3.76)
		Difference in LS Mean (95% CI)	0.40 (-3.46, 4.26)	
Time to deterioration EORTC QLQ-30 Global Health Status		HR (95% CI)	1.37 (0.94, 2.00)	
Time to deterioration EORTC QLQ-H&N35 Pain		HR (95% CI)	1.37 (0.93, 2.02)	
Time to deterioration EORTC QLQ-H&N35 Swallowing		HR (95% CI)	1.05 (0.69, 1.59)	

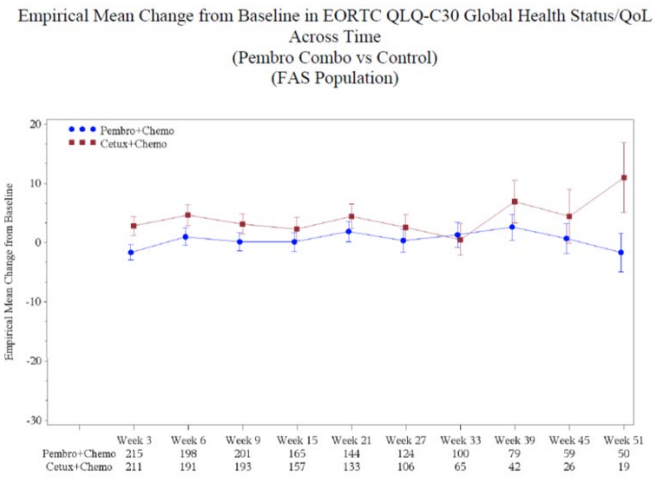
Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, LS = least-squares mean, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, QLQ = Quality of Life Questionnaire

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

Figure 25: Change from baseline in EORTC-QLQ global health status for PEMB-chemo versus CET-chemo in KEYNOTE-048, FAS population, IA2



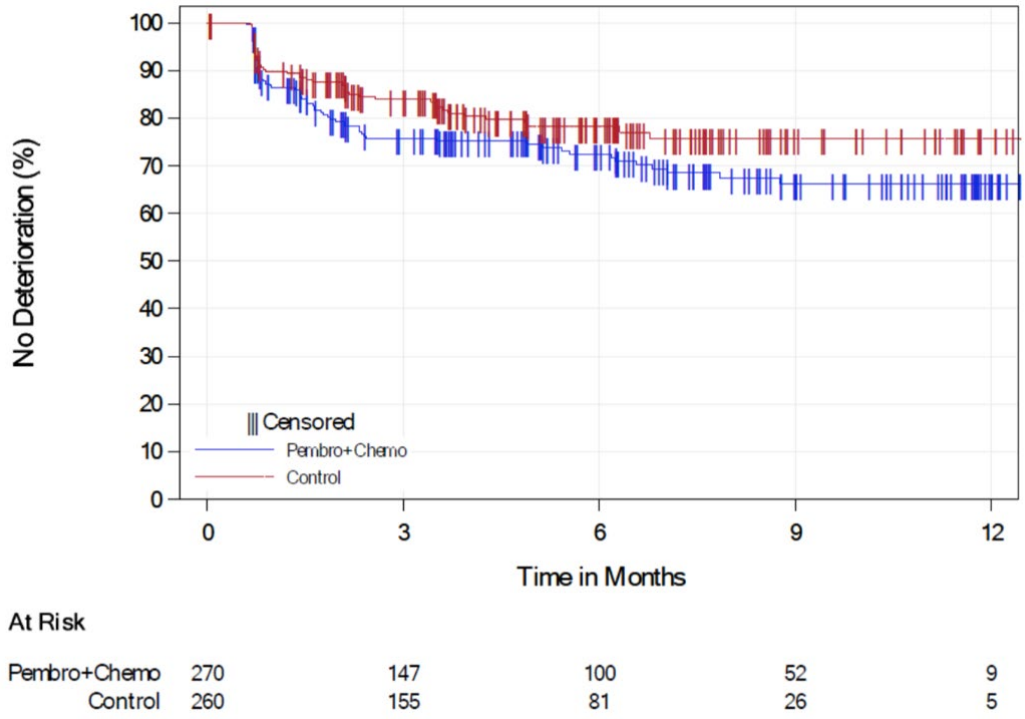


Abbreviations: Cetux+chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, LS = least squares, QLQ = Quality of Life Questionnaire, QoL = quality of life, Pembro+chemo or PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: June 13, 2018

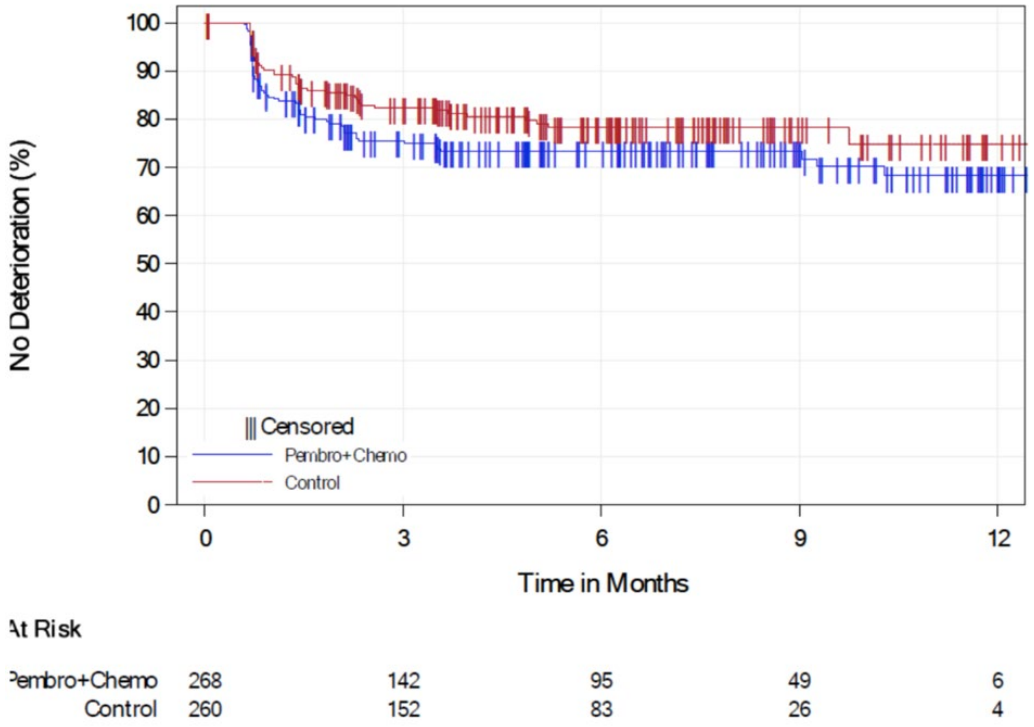
Figure source: EPAR 2019[26]

Figure 26: Time to deterioration in EORTC-QLQ global health status for PEMB-chemo versus CET-chemo in KEYNOTE-048, FAS population, IA2



Abbreviations: Control or CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, Pembro+chemo or PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, QLQ = Quality of Life Questionnaire
Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

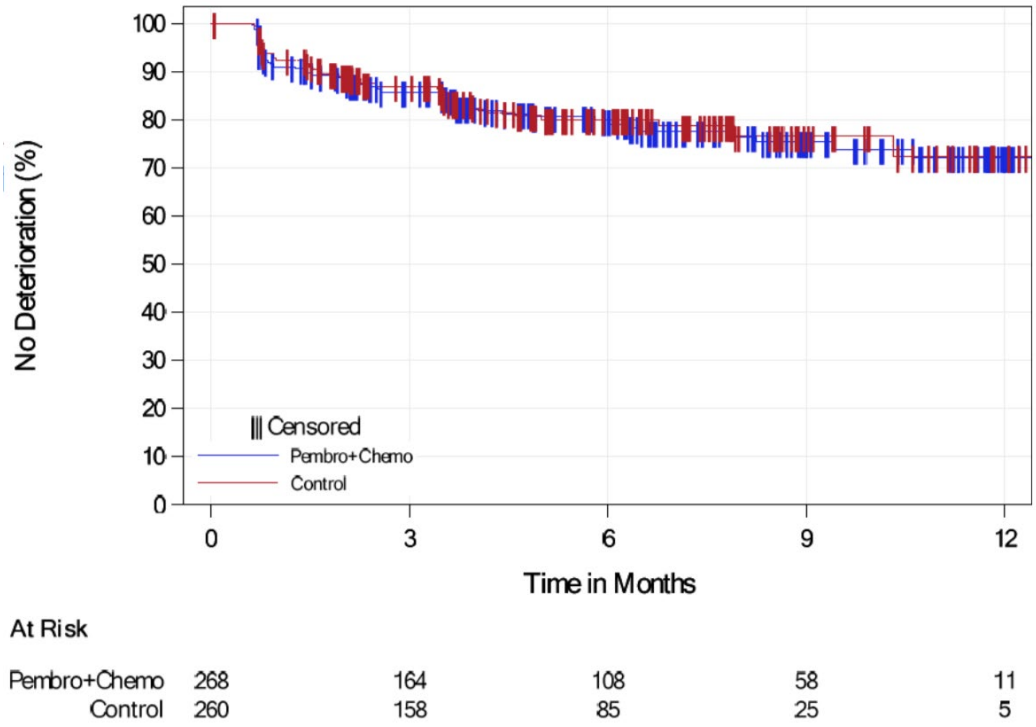
Figure 27: Change from baseline in EORTC-H&N35 pain for PEMB-chemo versus CET-chemo in KEYNOTE-048, FAS population, IA2



Abbreviations: Control or CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, H&N = head and neck, Pembro+chemo or PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

Figure 28: Change from baseline in EORTC- H&N35 swallowing for PEMB-chemo for PEMB-chemo versus CET-chemo in KEYNOTE-048, FAS population, IA2



Abbreviations: Control or CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, EORTC = European Organization for Research and Treatment of Cancer, H&N = head and neck, Pembro+chemo or PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: June 13, 2018
Data source: EPAR 2019[26]

Patients receiving a second course of pembrolizumab

The protocol allowed patients who discontinued pembrolizumab (whether as PEMB-mono or PEMB-chemo) following CR to receive a second course for up to a year. In an exploratory analysis of KEYNOTE-048 data with four-year follow-up reported in abstract form (data cut-off March 25, 2020),[4] a total of 11 patients (5 randomized to PEMB-chemo) received second course PEMB, with overall ORR 36.4%.

Treatment after discontinuation of study therapy

Table 30 summarizes the subsequent cancer therapies (second-line treatment as determined by investigators' choice) received by patients who discontinued study treatments PEMB-chemo and CET-chemo.

A greater proportion of patients randomized to CET-chemo received subsequent cancer therapy, 53.0%, compared to 40.9% randomized to PEMB-chemo. A similar proportion in the two groups received subsequent chemotherapy, while a higher proportion of those who received PEMB-chemo subsequently received EGFR inhibitor (13.2% versus 6.3%, for PEMB-chemo and CET-chemo respectively) and a higher proportion of those who received CET-chemo received immune checkpoint inhibitor (4.3% versus 16.7%, for PEMB-chemo and CET-chemo, respectively). Paclitaxel was the most frequently used second-line therapy (14% PEMB-chemo versus 11.9% CET-chemo) as well as the most frequently used third line therapy (4.6% PEMB-chemo versus 5.0% CET-chemo).

Table 30: Treatment after discontinuation for PEMB-chemo versus CET-chemo in KEYNOTE-048, ITT population, FA

	PEMB-chemo N = 281	CET chemo N = 300
Number (%) who received subsequent cancer therapy	115 (40.9)	159 (53.0)
Chemotherapy	88 (31.3)	102 (34.0)
EGFR inhibitor	37 (13.2)	19 (6.3)
Immune checkpoint inhibitor	12 (4.3)	50 (16.7)
Other immunotherapy	0	6 (2.0)
Kinase inhibitor	7 (2.5)	1 (0.3)
Other	1 (0.4)	2 (0.7)
Individual therapies received by >5 patients		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB mono = pembrolizumab monotherapy

Data cut-off: February 25, 2019

Data source: Harrington ASCO 2020,[25] Checkpoint responses[29]

c) Harms outcomes for PEMB mono monotherapy, PEMB-chemo, and CT-chemo

Exposure to study treatment

Table 31 shows a summary of drug exposure for KEYNOTE-048 for the Safety population (all patients who received at least one dose of study treatment, grouped according to the treatment they received) as of the second interim analysis (June 13, 2018). Duration of exposure was calculated from first to last dose dates, inclusive, and includes second course treatment for pembrolizumab.

Patients receiving PEMB-chemo had longer exposure and more administrations of study drug than either PEMB-mono or CET-chemo, with one month or more difference in mean duration of exposure and over two months difference in median duration between PEMB-mono and PEMB-chemo. PEMB-chemo and PEMB mono differed by one cycle of administration, and PEMB-chemo and CET-chemo by two cycles.

Table 31: Summary of drug exposure for KEYNOTE-048, Safety population, IA2

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Study time on therapy (months)			
Mean (SD)	6.4 (7.04)	7.4 (6.64)	6.1 (5.84)
Median (range)	3.50 (0.03 – 47.90)	5.78 (0.10 – 28.72)	4.86 (0.03 – 35.25)
Number of administrations			
Mean (SD)	9.7 (9.39)	10.7 (9.11)	8.7 (8.10)
Median (range)	6.00 (1.00 – 40.0)	8.00 (1.00 – 35.00)	7.00 (1.00 – 48.00)

Abbreviations: SD = standard deviation

Data cut-off: June 13, 2018

Data source: EPAR 2019[26]

Overall adverse events

Table 32 shows a summary of the adverse events for PEMB-mono, PEMB-chemo and CET-chemo in the safety population as of the final analysis (data cut-off February 25, 2019). Relationship for drug-related AEs was as assigned by the investigators.

Almost all patients in each of the three groups experienced one or more AEs. Patients receiving PEMB-mono generally had a lower proportion of drug-related or higher grade AEs than those receiving PEMB-chemo or CET-chemo: Drug-related AEs (58.3% versus 95.7% or 96.9%, for PEMB-chemo and CET-chemo, respectively), grade 3-5 AEs (54.7% versus 85.1% or 83.3%), drug-related grade 3-5 AEs (17.0% versus 71.7% or 69.3%), SAEs (41.0% versus 59.8% or 49.1%), and drug-related SAEs (9.3% versus 37.7% or 25.1%).

A smaller proportion of patients discontinued PEMB if they received it as monotherapy (12.0%) rather than in combination with chemotherapy (17.0%). Likewise, a smaller proportion of those receiving PEMB-mono required PEMB dose modification due to an adverse event, than those receiving PEMB-chemo (38.7% versus 57.6%), where dose modifications involved reduction, interruption, or discontinuation of a drug.

PEMB-chemo and CET-chemo had similar proportions of patients with drug related AEs (95.7% versus 96.9%), grade 3-5 AEs (85.1% versus 83.3%), drug-related grade 3-5 AEs (71.7% versus 69.3%), and dose modification of any component due to an adverse event (84.4% versus 83.6%). A higher proportion of patients receiving PEMB-chemo had SAEs (59.8% versus 49.1%), drug-related SAEs (37.7% versus 25.1%), or discontinuation of any drug due to an adverse event (32.6% versus 27.5%). There was some variability in proportions of patients with dose modification for individual components between the treatment arms. A lower proportion of patients who received PEMB-chemo had PEMB dose modification (57.6%) compared with the proportion of patients who received CET-chemo and had CET dose modification (66.2%). A higher proportion of patients who received PEMB-chemo had modification to

chemo dosing than those who received CET-chemo (79.7% versus 71.8%, for PEMB-chemo and CET-chemo, respectively) or to both PEMB/CET and chemo (44.6% versus 36.6%, for PEMB-chemo and CET-chemo, respectively). See Table 36 for more details.

Table 32: Summary of adverse events for KEYNOTE-048, PEMB mono, PEMB chemo, and CET-chemo (Safety population), FA

	PEMB mono N = 300	PEMB-chemo N = 276	CET plus chemo N = 287
Patients with one or more AEs, n (%)	290 (96.7)	271 (98.2)	286 (99.7)
Patients with one or more drug-related AEs, n (%)	175 (58.3)	264 (95.7)	278 (96.9)
Patients with one or more grade 3-5 AEs, n (%)	164 (54.7)	235 (85.1)	239 (83.3)
Patients with one or more drug related grade 3-5 AEs, n (%)	51 (17.0)	198 (71.7)	199 (69.3)
Patients with SAEs	123 (41.0)	165 (59.8)	141 (49.1)
Patients with drug-related SAEs	28 (9.3)	103 (37.7)	72 (25.1)
Patients who died, n (%)	25 (8.3)	32 (11.6)	28 (9.8)
Patients who died due to drug-related adverse event, n (%)	3 (1.0)	11 (4.0)	8 (2.8)
Patients with dose modification** due to an adverse event, n (%)	116 (38.7)	233 (84.4)	240 (83.6)
Patients with modification for PEMB or CET		159 (57.6)	190 (66.2)
Patients with modification for chemo		220 (79.7)	206 (71.8)
Patients with modification of all components		123 (44.6)	105 (36.6)
Patients who discontinued any drug due to an adverse event, n (%)	36 (12.0)	90 (32.6)	79 (27.5)
Patients who discontinued PEMB or CET		47 (17.0)	51 (17.8)
Patients who discontinued chemo		74 (26.8)	60 (20.9)
Patients who discontinued all components		23 (8.3)	26 (9.1)

* Relationship assessed by investigator

** Dose was reduced, drug was interrupted, or drug was withdrawn.

Abbreviations: AE = adverse events, CET = cetuximab, CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil,PEMB = pembrolizumab, PEMB mono = pembrolizumab monotherapy, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil

Data cut-off: February 25, 2019

Data source: EPAR 2019[26]

Individual adverse events

Table 33 shows results for selected individual adverse events that occurred in ≥10% of patients in the safety population, regardless of causal attribution, for any grade. Table 34 shows results for treatment-related AEs that occurred in ≥5% of patients. Results were similar at the IA2 (June 13, 2018) and FA (February 25, 2019) analyses with no new safety concerns identified at the final analysis; therefore, the results of the IA2 analysis are discussed below.

At all grades, a lower proportion of patients receiving PEMB-mono experienced blood and lymphatic disorders, gastrointestinal disorders, general disorders and site administration disorders (with the exception of pyrexia), investigations (primarily haematological abnormalities) and metabolism and nutrition disorders (with the exception of weight loss) compared with those receiving PEMB-chemo or CET-chemo. For patients receiving PEMB-mono, the most reported individual AEs were fatigue (27.7% of patients), anemia (21.0%), constipation (19.7%), and hypothyroidism (18.0%). For patients receiving PEMB-chemo, the most reported individual AEs were anemia (57.6% of patients), nausea (50.7%), constipation (37.0%) and fatigue (34.4%). For patients receiving CET-chemo, the most reported individual AEs were nausea (51.2% of patients), anemia (46.0%), hypomagnesemia (40.4%), and rash (38.7%). A lower proportion of patients who received pembrolizumab, whether as monotherapy or combination therapy, experienced skin and subcutaneous disorders (rash). A similar proportion of patients in each of the three groups experienced respiratory disorders (cough). Patients who received pembrolizumab experienced more hypothyroidism than those who received CET-chemo.

A lower proportion of patients receiving PEMB-mono experienced treatment-related adverse events than patients receiving PEMB-chemo and CET-chemo. This difference was seen for gastrointestinal symptoms, haematological abnormalities, and systemic symptoms. For patients receiving PEMB-mono, the most reported treatment-related AEs were fatigue (14.3% of patients), hypothyroid (13.0%), rash (8.3%), and pruritis (7.0%). For patients receiving PEMB-chemo, the most reported treatment-related AEs were anemia (48.2% of patients), nausea (44.9%), neutropenia (33.0%), and fatigue (30.4%). For patients receiving CET-chemo, the most reported treatment-related AEs were nausea (41.1% of patients), nausea (45.6%), rash (35.2%), and hypomagnesemia (33.1%). Fewer patients who received PEMB (as PEMB-mono or PEMB-chemo) experienced skin and nail conditions than those who received CET-chemo. More patients who received PEMB experienced treatment-related hypothyroidism than those who received CET-chemo.

Table 33: Adverse events of any cause and grade that occurred in ≥10% of patients, safety population, IA2

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Patients with at least one AE, n (%)	290 (96.7)	271 (98.2)	286 (99.7)
Individual AEs, n (%)			
Anemia	63 (21.0)	159 (57.6)	132 (46.0)
Nausea	50 (16.7)	140 (50.7)	147 (51.2)
Constipation	59 (19.7)	102 (37.0)	95 (33.1)
Fatigue	83 (27.7)	95 (34.4)	102 (35.5)
Neutropenia	6 (2.0)	93 (33.7)	95 (33.1)
Vomiting	33 (11.0)	89 (32.2)	80 (27.9)
Mucosal inflammation	13 (4.3)	85 (30.8)	81 (28.2)
Decreased appetite	44 (14.7)	80 (29.0)	85 (29.6)
Thrombocytopenia	6 (2.0)	79 (28.6)	72 (25.1)
Diarrhoea	46 (15.3)	77 (27.9)	99 (34.5)
Stomatitis	9 (3.0)	72 (26.1)	80 (27.9)
Platelet count decreased	3 (1.0)	56 (20.3)	49 (17.1)
Cough	40 (13.3)	51 (18.5)	37 (12.9)
Neutrophil count decreased	1 (0.3)	51 (18.5)	57 (19.9)
Asthenia	17 (5.7)	47 (17.0)	44 (15.3)
Pyrexia	38 (12.7)	45 (16.3)	35 (12.2)
Weight decreased	44 (14.7)	44 (15.9)	60 (20.9)
Hypomagenesaemia	12 (4.0)	43 (15.6)	116 (40.4)
Hypothyroidism	54 (18.0)	42 (15.2)	18 (6.3)
Blood creatinine increased	12 (4.0)	39 (14.1)	24 (8.4)
Hyponatraemia	25 (8.3)	39 (14.1)	36 (12.5)
Leukopenia	4 (1.3)	37 (13.4)	41 (14.3)
White blood cell count decreased	4 (1.3)	36 (13.0)	47 (16.4)
Dysphagia	24 (8.0)	32 (11.6)	28 (9.8)
Headache	36 (12.0)	31 (11.2)	24 (8.4)
Hypokalaemia	23 (7.7)	30 (10.9)	52 (18.1)

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Dizziness	14 (4.7)	28 (10.1)	37 (12.9)
Insomnia	21 (7.0)	28 (10.1)	24 (8.4)
Rash	30 (10.0)	27 (9.8)	111 (38.7)
Pruritus	33 (11.0)	23 (8.3)	30 (10.5)
Dyspnoea	39 (13.0)	21 (7.6)	20 (7.0)
Oedema peripheral	12 (4.0)	17 (6.2)	17 (5.9)
Arthralgia	16 (5.3)	15 (5.4)	7 (2.4)
Back pain	21 (7.0)	12 (4.3)	11 (3.8)
Abdominal pain	3 (1.0)	10 (3.6)	20 (7.0)
Dry skin	13 (4.3)	9 (3.3)	37 (12.9)
Skin fissures	0	2 (0.7)	38 (13.2)
Dermatitis acneiform	8 (2.7)	1 (0.4)	83 (28.9)
Paronychia	1 (0.3)	0	36 (12.5)

Every patient is counted once for each treatment and AE combination. Counts include non-serious AEs up to 30 days and SAEs up to 90 days. Counts exclude MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" that were not considered drug-related.

Data cut-off: Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

Table 34: Treatment-related adverse events that occurred in ≥5% of patients, safety population

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Patients with at least one related AE, n (%)	175 (58.4)	263 (95.3)	278 (96.9)
Individual AEs, n (%)			
Anaemia	12 (4.0)	133 (48.2)	118 (41.1)
Nausea	12 (4.0)	124 (44.9)	131 (45.6)
Neutropenia	3 (1.0)	91 (33.0)	90 (31.4)
Fatigue	43 (14.3)	84 (30.4)	83 (28.9)
Mucosal inflammation	8 (2.7)	77 (27.9)	76 (26.5)
Thrombocytopenia	4 (1.3)	75 (27.2)	63 (22.0)
Vomiting	7 (2.3)	75 (27.2)	64 (22.3)
Stomatitis	2 (0.7)	67 (24.3)	69 (24.0)
Decreased appetite	16 (5.3)	62 (22.5)	62 (21.6)
Platelet count decreased	1 (0.3)	51 (18.3)	46 (16.0)
Diarrhoea	16 (5.3)	49 (17.8)	75 (26.1)
Neutrophil count decreased	1 (0.3)	46 (16.7)	54 (18.8)
White blood cell count decreased	2 (0.7)	36 (13.0)	43 (15.0)
Hypothyroidism	39 (13.0)	35 (12.7)	1 (0.3)
Leukopenia	2 (0.7)	34 (12.3)	38 (13.2)
Asthenia	7 (2.3)	33 (12.0)	30 (10.5)
Blood creatinine increased	2 (0.7)	30 (10.9)	15 (5.2)
Hypomagnesemia	3 (1.0)	29 (10.5)	95 (33.1)

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Constipation	9 (3.0)	28 (10.1)	31 (10.8)
Hyponatremia	9 (3.0)	23 (8.3)	20 (7.0)
Rash	25 (8.3)	22 (8.0)	101 (35.2)
Febrile neutropenia	0	21 (7.6)	12 (4.2)
Weight decreased	9 (3.0)	21 (7.6)	30 (10.5)
Malaise	4 (1.4)	18 (6.5)	9 (3.1)
Dysgeusia	6 (2.0)	16 (5.8)	15 (5.2)
Pyrexia	10 (3.3)	16 (5.8)	12 (4.2)
Acute kidney injury	4 (1.3)	15 (5.4)	6 (2.1)
Hypokalaemia	4 (1.3)	15 (5.4)	36 (12.5)
Peripheral sensory neuropathy	1 (0.3)	15 (5.4)	6 (2.1)
Tinnitus	0	15 (5.4)	16 (5.6)
Pruritis	21 (7.0)	14 (5.1)	24 (8.4)
Alanine aminotransferase increased	7 (2.3)	10 (3.6)	15 (5.2)
Arthralgia	6 (2.0)	9 (3.3)	3 (1.0)
Hypophosphataemia	1 (0.3)	6 (2.2)	19 (6.6)
Dry skin	6 (2.0)	5 (1.8)	27 (9.4)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	4 (1.4)	20 (7.0)
Infusion related reactions	1 (0.3)	2 (0.7)	16 (5.6)
Skin fissures	0	2 (0.7)	36 (12.5)
Dermatitis aceneiform	6 (2.0)	1 (0.4)	82 (28.6)
Paronychia	0	0	33 (11.5)

Every patient is counted once for each treatment and AE combination. Counts include non-serious AEs up to 30 days and SAEs up to 90 days. Counts exclude MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" that were not considered drug-related.

Data cut-off: Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

Grade 3 to 5 adverse events

Table 35 shows grade 3 to 5 adverse events of any cause that occurred in ≥2% of patients in either of the PEMB groups. In the PEMB mono group 54% of patients had at least one grade 3 to 5 AE compared with 83.6% in the CET-chemo group. In the PEMB-chemo group 84.8% of patients had at least one grade 3 to 5 AE compared with 83.6% in the CET-chemo group. Results were similar at the IA2 (June 13, 2018) and FA (February 25, 2019) analyses with no new safety concerns identified at the final analysis; therefore, the results of the IA2 analysis are discussed below.

The proportions of patients experiencing individual grade 3 to 5 adverse events were low in all three treatment groups, with the exception of blood and lymphatic disorders (anaemia, neutropenia, and thrombocytopenia) and the corresponding investigations (primarily of hematologic disorders) in patients receiving chemotherapy. For patients receiving PEMB-mono, the most reported grade 3 to 5 AEs were anemia (4.7% of patients), hyponatremia (5.7%), pneumonia (5.3%), and fatigue (3.0%). For patients receiving PEMB-chemo, the most reported grade 3 to 5 AEs were anemia (24.6% of patients), neutropenia (18.1%), neutrophil counts decreased (11.2%), and mucosal inflammation (9.8%). For patients receiving CET-chemo, the most reported treatment-related AEs were neutropenia (21.6% of patients), anemia (16.4%), neutrophil count decreased (12.9%), and white blood cell decreased and thrombocytopenia (both 9.1%). A lower proportion of patients receiving PEMB-mono experienced grade 3 to 5 general disorders and site administration disorders, investigations (primarily haematological abnormalities) and metabolism and nutrition disorders compared with those receiving PEMB-chemo or CET-chemo. A lower proportion of patients who received pembrolizumab, whether as monotherapy or combination therapy, experienced skin and subcutaneous disorders. There were no grade 3 to 5 events of hypothyroidism.

Table 35: Adverse grade 3 to 5 events of any cause that occurred in ≥2% of patients, safety population

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Patients with at least one AE, n (%)	162 (54.0)	234 (84.8)	240 (83.6)
Individual AEs, n (%)			
Anaemia	14 (4.7)	68 (24.6)	47 (16.4)
Neutropenia	1 (0.3)	50 (18.1)	62 (21.6)
Neutrophil count decreased	0	31 (11.2)	37 (12.9)
Mucosal inflammation	4 (1.3)	27 (9.8)	15 (5.2)
Thrombocytopenia	1 (0.3)	25 (9.1)	26 (9.1)
Febrile neutropenia	0	23 (8.3)	15 (5.2)
Stomatitis	0	23 (8.3)	10 (3.5)
Hyponatraemia	17 (5.7)	22 (8.0)	18 (6.3)
Fatigue	9 (3.0)	20 (7.2)	14 (4.9)
Hypokalaemia	6 (2.0)	17 (6.2)	17 (5.9)
Nausea	0	16 (5.8)	17 (5.9)
Platelet count decreased	0	15 (5.4)	10 (3.5)
White blood cell count decreased	0	15 (5.4)	26 (9.1)
Pneumonia	16 (5.3)	14 (5.1)	19 (6.6)
Decreased appetite	3 (1.0)	13 (4.7)	10 (3.5)
Lymphocyte count decreased	2 (0.7)	11 (4.0)	9 (3.1)
Asthenia	3 (1.0)	10 (3.6)	9 (3.1)
Hypercalcaemia	6 (2.0)	10 (3.6)	2 (0.7)
Vomiting	1 (0.3)	10 (3.6)	8 (2.8)
Leukopenia	0	9 (3.3)	16 (5.6)
Pneumonia aspiration	5 (1.7)	9 (3.3)	3 (1.0)
Dysphagia	7 (2.3)	8 (2.9)	6 (2.1)
Lung infection	3 (1.0)	8 (2.9)	1 (0.3)
Weight decreased	6 (2.0)	8 (2.9)	4 (1.4)
Dehydration	2 (0.7)	7 (2.5)	8 (2.8)
Diarrhoea	2 (0.7)	7 (2.5)	8 (2.8)
Hypercalcaemia	4 (1.3)	7 (2.5)	3 (1.0)
Hypertension	4 (1.3)	7 (2.5)	4 (1.4)
Dyspnoea	6 (2.0)	6 (2.2)	3 (1.0)
Hypomagnesaemia	0	6 (2.2)	14 (4.9)
Hypotension	5 (1.7)	6 (2.2)	6 (2.1)
Pulmonary embolism	4 (1.3)	6 (2.2)	8 (2.8)
Septic shock	1 (0.3)	6 (2.2)	2 (0.7)
Syncope	2 (0.7)	6 (2.2)	10 (3.5)

Every patient is counted once. Includes non-serious AEs up to 30 days and SAEs up to 90 days. Excludes MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" that were not considered drug-related.

Data cut-off: Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

Serious adverse events and adverse events leading to death

Table 36 shows SAEs of any cause that occurred in ≥2% of patients in either of the pembrolizumab groups. Results were similar at the IA2 (June 13, 2018) and FA (February 25, 2019) analyses with no new safety concerns identified at the final analysis; therefore, the results of the IA2 analysis are discussed below.

Patients who received PEMB-chemo had a higher proportion of SAEs than either of the other groups, overall and for most individual SAEs. The more common SAEs affected the haematological system or were infectious or inflammatory. For patients receiving PEMB-mono, the most common SAEs were pneumonia (5.7% of patients) and tumour hemorrhage (3.0%). For patients receiving PEMB-chemo, the most common SAEs were febrile neutropenia (5.8% of patients), pneumonia (5.4%), and anemia (5.1%). For patients receiving CET-chemo, the most reported treatment-related AEs were pneumonia (6.3%), febrile neutropenia (4.9% of patients), and anemia (3.1%).

Table 36: Serious adverse events of any cause occurring in ≥2% of patients, safety population

	PEMB mono N = 300	PEMB-chemo N = 276	CET-chemo N = 287
Patients with at least one related AE, n (%)	121 (40.3)	162 (58.7)	141 (49.1)
Individual AEs, n (%)			
Febrile neutropenia	0	16 (5.8)	14 (4.9)
Pneumonia	17 (5.7)	15 (5.4)	18 (6.3)
Anemia	1 (0.3)	14 (5.1)	9 (3.1)
Lung infection	3 (1.0)	9 (3.3)	2 (0.7)
Pneumonia aspiration	5 (1.7)	8 (2.9)	3 (1.0)
Stomatitis	0	8 (2.9)	4 (1.4)
Hyponatraemia	1 (0.3)	7 (2.5)	3 (1.0)
Neutropenia	0	7 (2.5)	5 (1.7)
Pyrexia	2 (0.7)	7 (2.5)	1 (0.3)
Dehydration	1 (0.3)	6 (2.2)	4 (1.4)
Mucosal inflammation	1 (0.3)	6 (2.2)	1 (0.3)
Nausea	0	6 (2.2)	8 (2.8)
Septic shock	1 (0.3)	6 (2.2)	2 (0.7)
Thrombocytopenia	0	6 (2.2)	0
Tumour haemorrhage	9 (3.0)	6 (2.2)	5 (1.7)
Sepsis	6 (2.0)	5 (1.8)	3 (1.0)
Dyspnoea	6 (2.0)	3 (1.1)	2 (0.7)

Every patient is counted once. Includes SAEs up to 90 days. Excludes MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" that were not considered drug-related.

Data cut-off: Data cut-off: June 13, 2018.

Data source: EPAR 2019[26]

Deaths

Twenty-five patients (8.3%) who received PEMB mono, 32 patients (11.6%) who received PEMB-chemo, and 27 patients (9.4%) who received CET-chemo experienced one or more adverse events leading to death, by the final analysis cut-off date of February 25, 2019. Events involving tumour or diseases progression unrelated to the drug were not included in these totals. Infections were the most common cause of death, in 9 (3.0%), 12 (4.3%), and 13 (4.5%) patients, followed by respiratory, thoracic and mediastinal disorders, in 4 (1.3%), 6 (2.2%), and 6 (2.1%) patients, and cardiac disorders 3 (1.0%), 4 (1.4%), and 3 (1.0%) patients, in patients receiving PEMB-mono, PEMB-chemo, and CET-chemo, respectively. Three patients receiving PEMB-mono, 11 receiving PEMB-chemo, and 8 receiving CET-chemo were considered by the treating investigator to have drug related AEs leading to death. For

PEMB-mono, one patient each had pneumonitis, disseminated intravascular coagulation, and antinflammatory disease. For PEMB-chemo, there were five patients with septic shock and one each with sepsis, interstitial lung disease, tumour hemorrhage, hemorrhage, and cerebral ischemia. One additional patient died due to bronchitis, considered related to carboplatin, but not related to carboplatin. For CET-chemo, there were three patients with pneumonia, two with sepsis, and one each with hypoxia, osteomyelitis, and pulmonary artery thrombosis.

Adverse events of interest to pembrolizumab

Table 37 shows adverse events identified as being of interest for pembrolizumab, at any grade and grades 3 to 5, occurring in ≥1% of patients, as of FA, data cut-off February 25, 2019.

For patients receiving PEMB-mono, the most common AEs of interest were hypothyroidism (18% of patients), pneumonitis (6%), hyperthyroidism and severe skin reactions (3%). For patients receiving PEMB-chemo, the most common AEs of interest were hypothyroidism (16% of patients), pneumonitis (5%), and hyperthyroidism (4%). For patients receiving CET-chemo, the most reported treatment-related AEs were infusion reactions (9%), severe skin reactions (7%), and hypothyroidism (6%).

Table 37: Adverse events of interest for pembrolizumab in KEYNOTE-048, safety population, FA

Table S11: Adverse events of interest to pembrolizumab at the final analysis*

Event	Pembrolizumab (N=300)		Pembrolizumab-Chemotherapy (N=276)		Cetuximab-Chemotherapy (N=287)	
	Any Grade	Grade 3, 4, or 5†	Any Grade	Grade 3, 4, or 5‡	Any Grade	Grade 3, 4, or 5
Any event	93 (31%)	21 (7%)	73 (26%)	15 (5%)	68 (24%)	30 (10%)
Hypothyroidism	55 (18%)	0	44 (16%)	0	18 (6%)	0
Pneumonitis	19 (6%)	5 (2%)	15 (5%)	5 (2%)	3 (1%)	2 <1%)
Hyperthyroidism	8 (3%)	1 (<1%)	12 (4%)	0	3 (1%)	0
Severe skin reactions	8 (3%)	6 (2%)	2 (<1%)	2 (<1%)	20 (7%)	19 (7%)
Infusion reactions	4 (1%)	2 (<1%)	6 (2%)	2 (<1%)	27 (9%)	6 (2%)
Colitis	3 (1%)	2 (<1%)	7 (3%)	2 (<1%)	2 (<1%)	2 (<1%)
Hepatitis	3 (1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0
Nephritis	3 (1%)	2 (<1%)	2 (<1%)	0	1 (<1%)	0
Pancreatitis	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Adrenal insufficiency	2 (<1%)	1 (<1%)	0	0	0	0
Encephalitis	1 (<1%)	1 (<1%)	0	0	0	0
Hypophysitis	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Uveitis	1 (<1%)	0	0	0	0	0
Myocarditis	0	0	1 (<1%)	1 (<1%)	0	0
Myositis	0	0	0	0	1 (<1%)	1 (<1%)
Thyroiditis	0	0	1 (<1%)	0	0	0

* Listed are all adverse events of interest to pembrolizumab that occurred during randomly allocated study treatment or within the 30 days thereafter (within 90 days for serious events) regardless of their attribution to treatment or immune relatedness by the investigator. The as-treated population included all participants who underwent randomization and received ≥1 dose of study treatment. Events are listed in descending order of frequency in the pembrolizumab group.

† One (<1%) participant in the pembrolizumab group died from an adverse event of interest: pneumonitis.

‡ One (<1%) participant in the pembrolizumab-chemotherapy group died from an adverse event of interest: pneumonitis (recorded in the study database by the investigator as interstitial lung disease).

Abbreviations: CET-chemo = cetuximab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB-chemo = pembrolizumab plus cisplatin/carboplatin plus 5-fluoruracil, PEMB mono = pembrolizumab monotherapy

Data cut-off: February 25, 2019.

Data source: Reprinted from Burtness et al. Lancet. 2019;394(10212):1915-1928 with permission from Elsevier.[1]

6.4 Ongoing Trials

Ongoing trials of PEMB-mono or PEMB-chemo as first-line treatment recurrent or metastatic HNSCC are listed in Table 38. Both trials could contribute data on patients receiving PEMB-mono. The principal reason for exclusion of screened patients in KEYNOTE-048 was ECOG = 2, and NCT03193931 may provide evidence for the use of PEMB-mono in this group of patients, as well as those who are eligible on account of reduced renal function. The second included trial (NCT03358472) contains a comparison of PEMB-mono with the EXTREME protocol (CET-chemo), the same contrast as studied in KEYNOTE-048.

Table 38: Ongoing trials of pembrolizumab monotherapy and pembrolizumab plus chemotherapy in recurrent or metastatic HNSCC, first line therapy

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study comparing pembrolizumab with methotrexate in elderly, frail, or cisplatin-ineligible patients with head and neck cancers (ELDORANDO; NCT03193931) **Characteristics:** Phase 2, open-label, randomized (1:1) N= 100 (planned) Number of centres and number of countries: One listed, Germany **Dates:** Study start: February 2, 2018 Estimated primary completion: December 30, 2012 Study completion date: September 1, 2023. Funding: AIO-Studien-gGMbH	**Key Inclusion Criteria** • Recurrent or metastatic HNSCC • Progressive disease at study entry with at least 1 measurable lesion • No previous systematic treatment for metastatic disease • Not eligible for cisplatin-based chemotherapy (ECOG = 2 and/or CrCl<60 mL/min) • ECOG 0 to 2 **Key Exclusion Criteria:** • NP carcinoma • History of allogenic tissue/solid organ transplant • History of pneumonitis requiring steroids • Evidence of interstitial lung disease • Prior anti PD-L1 therapy • Autoimmune disease, immunodeficiency or chronic systemic steroid therapy	**Intervention:** Pembrolizumab 200 mg IV q3w, until disease progression or non-tolerable toxicity, to a maximum 2 years. **Comparator:** Methotrexate 40 mg/m^2 IV q1w, until disease progression or non-tolerable toxicity, to a maximum 2 years.	**Primary:** • OS **Secondary:** • QoL (EOTRC QLQ-C30, EORTC-H&N35) • TTFS • ORR • TEAE
Pembrolizumab plus epacadostat (indoleamine 2,3-dioxygenase-1 inhibitor), pembrolizumab monotherapy, and the EXTREME regimen in R/M HNSCC (KEYNOTE-669/ECHO-304; NCT03358472) **Characteristics:** Phase 3, open-label, randomized (1:1) N = 89 Number of centres and number of countries: 224 study locations, US, Canada, Australia, EU, Asia. **Dates:** Study start: December 1, 2017 Primary completion date: July 18, 2018 Study completion date: June 2020 Funding: Merck Sharp and Dohme Corp.	**Key inclusion criteria**: • Recurrent or metastatic HNSCC • No previous systematic treatment for metastatic disease • ECOG 0 or 1 • Results of HPV testing available • Tissue available for testing **Key exclusion criteria**: • Carcinoma of the nasopharynx, salivary gland, unknown primary, primary of non-squamous histology • Disease profession within 6 months of systemic treatment for locoregional disease • Known active CNS metastases and/or carcinomatous meningitis • Active autoimmune disease requiring systemic treatment in past 2 years • Known immunodeficiency, history or active hepatitis B or C	**Intervention:** Pembrolizumab* IV q3w Epacadostat* orally bid **Intervention:** Pembrolizumab* IV q3w **Comparator:** Cetuximab* IV q1w Cisplatin* IV q3w or Carboplatin* IV q3w for ≤6 cycles 5-FU* IV q3w for ≤6 cycles * Comparator doses were not reported but was described as the EXTREME regimen.	**Primary:** • ORR **Secondary**: • AEs • Discontinuations of study treatment

Abbreviations: 5-FU = 5-fluorouracil, AE = adverse events, CNS = central nervous system, ECOG = Eastern Cooperative Oncology Group, EORTC = European Organization for Research and Treatment of Cancer, H&N35= Head and Neck questionnaire 35 questions, HPV = human papilloma virus, IV = intravenous, ORR = overall response rate, OS = overall survival, QLQ-30 = Quality of Life Questionnaire 30 (questions), TTFS = time to failure of strategy

7 Supplemental Questions

The following supplemental question were identified during development of the review protocol as relevant to the CADTH review of pembrolizumab monotherapy or pembrolizumab plus platinum chemotherapy and 5-FU:

- Network Meta-analysis of Pembrolizumab for the First-line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (recurrent or metastatic HNSCC)

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Network Meta-analysis of Pembrolizumab for the First-line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (recurrent or metastatic HNSCC)

7.1.1 Objective

The comparator used in the single identified trial (KEYNOTE-048) is CET-chemo. As cetuximab is not funded for HNSCC in Canada, current standard of care is represented by platinum doublet chemotherapy, with a minority of patients receiving cetuximab through provincial case-by-case reviews or patient access programs where available. Single agent cisplatin, methotrexate, capecitabine or docetaxel are options considered for patients for whom doublet chemotherapy is not appropriate. The CGP, PAG, and EGP were interested in the results of indirect treatment comparisons of pembrolizumab or pembrolizumab with chemotherapy with Canadian SOC.

7.1.2 Findings

One manufacturer-provided SR[30] followed by an ITC[31] compared PEMB-mono and PEMB-chemo with other treatments.

Systematic literature review

The primary objective of the systematic literature review was to compare the efficacy and safety of pembrolizumab monotherapy or pembrolizumab in combination with platinum and 5-FU chemotherapy with the current Canadian standard of care for first-line systematic treatment for recurrent or metastatic HNSCC, platinum and 5FU.

Table 39 shows the selection criteria for the systematic review. The 1L patients correspond to those included in the KEYNOTE-048, while the platinum/chemotherapy progressed (PCP) patients would have been excluded on account of recurrence/progression within 6 months after prior systemic therapy for locally advanced disease. The interventions listed include those in current Canadian practice, while the comparators allow for any treatment directed towards the indication. Dose of interventions and comparators were not specified. The review was restricted to RCTs published in English, but was not restricted to fully published papers.

Bibliographic databases OVID, EMBASE, MEDLINE, CCRCT were searched, with a date of search November 13, 2019. Filters were used to limit the search to RCTs. Conference abstracts were searched for by a manual search the Northern Light Life Sciences database of conference abstracts. ClinicalTrials.gov was searched for nearly completed trials that might be expected to report data.

Two reviewers conducted independent reviews of abstracts, selected papers for full text review (if available), and screened the full-text papers for the final selection. Differences in selection were referred to a third reviewer. Data were extracted by two reviewers, working independently.

Two reviewers conducted independent appraisals of study quality, with a third investigator included if needed to reconcile discrepancies. The Cochrane Collaboration Risk of Bias tool was used, which assesses seven domains: sequence generation; allocation concealment; blinding of participants, personnel, outcome assessors; incomplete outcome data; selective outcome reporting; other sources of bias. Overall assessments for each study were assigned as: low risk of bias (all domains low), unclear risk of bias (unclear for one or more key domains), or high risk of bias (high risk in one or more key domains). Quality appraisal was not used to select studies, but was used in the interpretation of final results.

Table 39: Study selection criteria for systematic review

Criteria	Description
Population	Patients with R/M HNSCC ineligible for curative treatment and either: • 1L – No prior systemic therapy administered in either the LA or R/M setting, or who have received prior systemic therapy as part of multimodal treatment for LA disease ≥6 months before study entry • PCP – Progressed during or after treatment with systemic therapy for R/M disease, or those with recurrence/progression <6 months after initiation of prior systemic therapy as part of multimodal treatment for LA disease
Interventions	*Combination therapies*: • Cisplatin or carboplatin + cetuximab ± 5-FU or docetaxel or paclitaxel • Cisplatin or carboplatin + 5-FU or docetaxel or paclitaxel • Cetuximab + methotrexate • Nivolumab + ipilimumab • Durvalumab + tremelimumab • Pembrolizumab + platinum + 5-FU *Single agents* • Pembrolizumab • Nivolumab • Durvalumab • Cetuximab • Docetaxel • Paclitaxel • Methotrexate • Cisplatin • Carboplatin • 5-FU • Gemcitabine • Capecitabine • Vinorelbine • Afatinib* *Any of the following treatments alone or in combination with other treatments:* • Bleomycin • Ifosfamide • Mitomycin • Tegafur/uracil
Comparators	• Any comparator
Outcomes	At least one of the following outcomes: • Overall survival • Progression-free survival • Objective response (complete response + partial response) • Complete response • Partial response • Duration of response • Health-related quality of life • Treatment duration • Grade 3 or 4 AEs**
Study design	Studies with the following study designs: • Phase 2 or 3 RCTs.
Other	The following other restrictions were employed: • Only studies published in English will be included

* Afatinib was included in the SLR on the basis of NCCN recommendations in PCP R/M HNSCC; however, trials of afatinib were ultimately excluded from the scope of the NMA as it has not been approved by any major regulatory agency and therefore is not considered relevant for purposes of HTA submissions.

** Includes overall grade 3-4 treatment-related AEs, and individual grade 3-4 treatment-related adverse events that meet a threshold frequency of ≥5% in any of the treatment arms.

Abbreviations: 1L = first-line, 5-FU = 5-fluorouracil, AE = adverse event, HTA = health technology assessment, PCP = platinum/chemotherapy progressed, RCT = randomized controlled trial, R/M HNSCC = recurrent and/or metastatic head and neck squamous cell carcinoma.

Source: Systematic review report[30]

Results of systematic literature review and feasibility assessment

The search and selection retrieved 84 full-text reports, 34 abstracts, 2 citations found by hand search, and two CSRs (for KEYNOTE-040 and KEYNOTE-048), which described 85 clinical trials in total. All trials were conducted in the recurrent or metastatic HNSCC population, regardless of prior treatment experience. Thirty-one RCTs were conducted in the 1L population, 21 in the platinum/chemotherapy progressed (PCP) population, and 33 in a mixed 1L and PCP population. The 31 RCTs conducted in the 1L population are of interest to this review. As they were heterogeneous in inclusion/exclusion criteria and characteristics, they were grouped into a Tier system for consideration for analysis. The Tiers were defined and populated as followed.

- Tier 1: Patients had no prior systemic therapy in relapsed/metastatic setting. Past systemic therapy for locally advanced disease was allowed if received >6 months pre study entry. Twenty-three trials were included in this group, summarized in Table 40. Criteria match KEYNOTE-48 inclusion criteria.
- Tier 2: Patients had no prior systemic therapy in relapsed/metastatic setting. Systemic therapy for locally advanced disease was allowed if received >3 months pre study entry (and implicitly, ≤6 months before study entry). Five trials were included in this group, summarized in Table 41.
- Tier 3: All patients were treated in the relapsed/metastatic setting, with no limitations on time-frame or setting for previous systemic therapy. Three trials were included in this group, summarized in Table 42. In all three, fewer than <20% of patients had previously received chemotherapy.

Table 40: Summary of 1L trials retrieved in systematic review and included in Tier 1

Principal publication	Type of study Name	Comparison	Patients	Prior therapy
Clinical study report (KEYNOTE-048)	Phase 3, multicentre, RCT KEYNOTE-048	• Pembrolizumab as monotherapy • Pembrolizumab plus with platinum + 5-FU • Standard treatment (platinum + 5-FU + cetuximab)	HNSCC patients	• No prior systemic therapy in either LA or R/M setting • Prior systemic therapy only as part of multimodal treatment for LA disease ≥6 months before study entry.
Airoldi et al, 1987		• Methotrexate • Methotrexate plus 5-FU	Recurrent SCC of the oral cavity	• Chemo-naïve
Bossi et al, 2017a	Phase 2 B490 study (EudraCT# 2011-002564-24)	• Cisplatin + cetuximab • Cisplatin + cetuximab + paclitaxel	R/M HNSCC with	• No previous chemotherapy (CT) or biological therapy in the R/M setting • Prior CT only allowed if received in the LA setting >6 months before study entry.
Ferris et al, 2018	Phase 2 Active8 study (NCT01836029)	• Platinum + 5-FU + cetuximab + motolimod • Platinum + 5-FU + cetuximab	R/M HNSCC	• No prior CT in the R/M setting. • Prior CT was only allowed if received ≥6 months before study entry.
Davis and Kessler, 1979		• Cisplatin • Cisplatin + methotrexate + bleomycin	Recurrent HNSCC	• All patients chemo-naïve
Eisenberger et al, 1989		• Methotrexate • Methotrexate + carboplatin	R/M HNSCC	• All patients chemo-naïve
Forastiere et al, 1992		• Cisplatin + 5-FU • Carboplatin + 5-FU	R/M HNSCC	• All chemo-naïve in the R/M setting

Principal publication	Type of study Name	Comparison	Patients	Prior therapy
		• Methotrexate		• Prior CT only allowed if administered for LA disease ≥6 months before study entry.
Forastiere et al, 2001	Phase 3 E1393 (ECOG)	• Cisplatin + paclitaxel + G-CSF • Cisplatin + paclitaxel in patients	R/M HNSCC	• All chemo-naïve in the R/M setting • Prior CT only allowed if administered for LA disease ≥6 months before study entry.
Gibson et al, 2005	Phase 3 trial E1395 (NCT00002888)	• Cisplatin + 5-FU • Cisplatin + paclitaxel in patients	R/M HNSCC	• Patients were chemo-naïve in the R/M setting • Prior CT only allowed if administered in the LA setting. Treatment with paclitaxel or 5-FU had to be completed >12 months before study entry, and treatment with cisplatin had to be completed >6 months before study entry.
Guigay et al, 2019a	Phase 2 RCT	• Csplatin + docetaxel + cetuximab • Platinum + 5-FU + cetuximab	R/M HNSCC not suitable for locoregional treatment.	• Prior CT only allowed if administered for LA disease ≥6 months before study entry.
Guigay et al, 2019b	Phase 3 RCT ELAN-UNFIT	• Cetuximab • Methotrexate	R/M HNSCC not suitable for local treatment	• Prior systemic therapy allowed if administered for LA disease ≥6 months before study entry.
Harrington et al, 2018	Phase 2 RCT	• Platinum + cetuximab + patritumab • Platinum + cetuximab	R/M HNSCC originating from the oral cavity, oropharynx, hypopharynx, and larynx	• Patients with prior EGFR-targeted regimen or prior anti-HER3 therapy excluded. Patients excluded if they had prior chemotherapy for the R/M disease or platinum-containing drug therapy with radiotherapy less than 6 months before study drug treatment.
Hong et al, 1983		• Methotrexate • Cisplatin	Recurrent HNSCC	• Patients were chemo-naïve.
Issell et al, 1982		• Bleomycin • Bleomycin + dibromodulcitol	Recurrent HNSCC	• Patients were chemo-naïve.
Jacobs et al, 1992	3- arm RCT	• Cisplatin • 5-FU • Cisplaitin + 5FU	R/M HNSCC	• Patients were chemo-naïve.
Keilholz et al, 2018	Phase 2 RCT RESGEX trial (NCT02052960)	• Cisplatin + 5-FU + tomuzotuximab • Cisplatin + 5-FU + cetuximab.	Recurrent and/or metastatic EGFR-positive HNSCC not eligible for local treatment.	• Prior systemic chemotherapy not allowed except if given as part of a multimodal treatment for LA disease which was completed more than 6 months prior to screening.
Schornagel et al, 1995	Phase 3	• Edatrexate • Methotrexate	R/M HNSCC	• None of the subjects had received CT in the R/M setting; induction with cisplatin, 5-FU or bleomycin before treatment of the LA disease

Principal publication	Type of study Name	Comparison	Patients	Prior therapy
				was allowed only if completed >1 year before study entry.
Vermorken et al, 2008	Phase 3 multinational (Europe)	• Platinum + 5-FU + cetuximab • Platinum + 5-FU	R/M HNSCC	• All patients chemo-naïve in the R/M setting. • Prior CT was only allowed if administered as part of multimodal treatment in the LA setting >6 months before study entry.
Vermorken et al, 2013	Phase 3 RCT, international SPECTRUM trial (NCT00460265)	• Cisplatin + 5-FU + panitumumab • Cisplatin + 5-FU	R/M HNSCC	• All patients chemo-naïve in R/M setting • Prior CT was only allowed if administered in the LA setting >6 months before study entry.
Vermorken et al, 2014a	Phase 2 ADVANTAGE trial (NCT00705016)	• Cilengitide [once weekly] + cisplatin + 5-FU + cetuximab • Cilengitide [twice weekly] + cisplatin + 5-FU + cetuximab • Cisplatin + 5-FU + cetuximab	R/M HNSCC	• All patients chemo-naïve in the R/M setting • Prior CT was only allowed if administered in the LA setting >6 months before study entry.
Vogl et al, 1982		• Corynebacterium parvum • Methotrexate	R/M HNSCC	• Patients assumed to be chemo-naïve, as prior use of cisplatin unlikely at time of trial • Recurrence had to have happened after radiotherapy • Patients with previous methotrexate therapy not eligible
Williams et al, 1986	RCT	• Methotrexate • Cisplatin + vinblastine + bleomycin	R/M HNSCC	• All patients chemo-naïve
Wirth et al, 2016	Phase 2 RCT, international PARTNER trial (NCT00454779)	• Cisplatin + docetaxel + panitumumab • Cisplatin + docetaxel	R/M HNSCC After trial began, protocol amendment excluded patients >70 years. Already-recruited patients excluded from analysis set.	• All patients chemo-naïve in the R/M setting. • Prior CT as primary therapy was not allowed unless completed >24 weeks before study entry.

Abbreviations: 5-FU = 5-fluorouracil, CT = chemotherapy, EGFR = epidermal growth factor receptor, G-CSF = granulocyte colony stimulating factor, HER3 = human epidermal growth factor receptor 3, HNSCC = head and neck squamous cell carcinoma, LA = locally advanced, RCT = randomized controlled trial, R/M = relapsed or metastatic, SLR = systematic literature review

Source: Systematic review report[30]

Table 41: Summary of 1L trials retrieved in systematic review and included in Tier 2

Principal publication	Type of study Name	Comparison	Patients	Prior therapy
Argiris et al, 2017	Phase 3 multicentre RCT ECOG-ACRIN E1305 (NCT00588770)	• Platinum-based chemotherapy • Bevacizumab plus platinum-based chemotherapy Platinum-based chemotherapy: investigator's choice of cisplatin + 5-FU, carboplatin + 5 FU, cisplatin + docetaxel, or carboplatin + docetaxel	R/M HNSCC	• All patients chemo-naïve in the R/M setting • Minimum 4 months between last dose of CT and entry • At least 4 months progression-free after last CT
Burtness et al, 2005	Phase 3 multicentre RCT	• Cisplatin + cetuximab • Cisplatin	R/M HNSCC	• All patients chemo-naïve in the R/M setting • CT not allowed within 3 months of study entry
Friesland et al, 2018	Phase 2 RCT CETMET (NCT01830556)	• Platinum + 5-FU + cetuximab • Carboplatin + cetuximab + paclitaxel	R/M HNSCC	• Previous treatment with cetuximab, cisplatin/carboplatin, 5-FU, or taxanes for LA disease within 3 months of study entry not allowed
Ham et al, 2018	Phase 2 RCT COMMENCE (NCT02054442)	• Methotrexate + cetuximab • Methotrexate	R/M HNSCC, ineligible due comorbidities or intolerant to platinum-based chemotherapy	• At least 3 months between prior treatment and study entry
Schrijvers et al, 1998	Phase 3 RCT	• Cisplatin + 5-FU • Cisplatin + 5-FU + Interferon α-2b	R/M HNSCC	• No prior chemotherapy for R/M • At least 3 months free of CT and locoregional progression before study entry

Abbreviations: 5-FU = 5-fluorouracil, CT = chemotherapy, HNSCC = head and neck squamous cell carcinoma, PBT = platinum-based chemotherapy, RCT = randomized controlled trial, R/M = recurrent and/or metastatic.

Source: Systematic review report[30]

Table 42: Summary of 1L trials retrieved in systematic review and included in Tier 3

Principal publication	Type of study Name	Comparison	Patients	Prior therapy
Amrein and Fabian, 1922		• Cisplatin + 5-FU • Cisplatin + 5-FU + bleomycin + methotrexate	R/M HNSCC	• Patients with prior CT not excluded. 7/60 (11.7%) of evaluable population received CT (time-frame not specified)
Jacobs et al, 1983	Phase 3, multicentre RCT	• Cisplatin • Cisplatin + methotrexate	R/M HNSCC	• Patients with prior CT not excluded. 3/80 (3.8%) eceived prior CT.
Paredes et al, 1988		• Cisplatin + 5-FU • Cisplatin + 5-FU +sodium diethyldithiocarbamate	R/M HNSCC	• Patients with prior cisplatin-containing CT excluded; patients with non-cisplatin CT not excluded. 10/60 (16.7%) had prior CT (time-frame not specified)

Abbreviations: 5-FU = 5-fluorouracil, CT = chemotherapy, HNSCC = head and neck squamous cell carcinoma, RCT = randomized controlled trial, R/M = recurrent and/or metastatic.

The NMA for 1L treatment was conducted on the Tier 1 studies. Tier 2 studies were eligible for inclusion if they allowed an additional Tier 1 study to be connected to the network.

Of the 23 eligible Tier 1 studies, one trial, ELAN-UNFIT (reported in Guigay et al, 2019a), included patients ≥70 years who were classed as unfit by the ELAN score; these patients were considered clinically too dissimilar those in KEYNOTE-048 for inclusion, and so the trial was not considered for inclusion into the NMA. Of the remaining 22 studies, 20 reported OS data, 10 reported median PFS, 22 reported a measure of response (ORR, CR, and/or PR), 3 reported time-to-progression, 12 reported DOR, 2 reported HRQoL, 10 reported grade 3 to 4 AEs, 7 reported SAEs, and 14 reported deaths due to treatment-related AEs.

Seven trials formed a connective network: KEYNOTE-048, Jacobs 1992, Hong 1983, Forastiere 1992, E1395, EXTREME, and TPExtreme. Further detailed review led to the decision to exclude studies published before 1990, since it was believed that the oldest studies would not reflect current standards for trial conduct and standard of care, which led to the exclusion of Hong 1983. Table 43 shows the number of patients and interventions in Tier 1 studies that were not included in the NMA, with those that were identified as being of interest in bold. Therapies of interest that were not included in the network were carboplatin, paclitaxel, docetaxel, cetuximab monotherapy, platinum-docetaxel, and platinum plus cetuximab plus paclitaxel.

Table 43: Trials included in Tier 1 that were not included in the NMA network, with reasons for exclusion

Study	N	Intervention	Reason for exclusion
Airoldi et al, 1987	24	**Methotrexate**	Did not form connected network
	24	Methotrexate + 5-FU	
Bossi et al, 2017 (B490)	100	**Cisplatin + cetuximab**	Did not form connected network
	91	**Cisplatin + cetuximab + paclitaxel**	
Ferris et al, 2018 (Active8)	100	Platinum + 5-FU + Cetuximab + Motolimod	Did not form connected network
	95	**Platinum + 5-FU + Cetuximab**	
Davis and Kessler, 1979	30	**Cisplatin**	Did not form connected network
	27	Cisplatin + Methotrexate + Bleomycin	

Study	N	Intervention	Reason for exclusion
Eisenberger et al, 1989	20	**Methotrexate**	Did not form connected network
	20	Methotrexate + Carboplatin	
Forastiere et al, 2001 (E1393)	105	Cisplatin + Paclitaxel + G-CSF	Did not form connected network
	104	**Cisplatin + Paclitaxel**	
Guigay 2019 (ELAN-UNFIT)		**Cetuximab**	Patients too clinically dissimilar to KEYNOTE-048
		Methotrexate	
Harrington et al 2018	44	Platinum + Cetuximab + Patritumab	Did not form connected network
	43	**Platinum + Cetuximab**	
Hong et al, 1983	21	**Methotrexate**	Older trial, conduct not reflective of current practice
	23	**Cisplatin**	
Issell et al, 1982	18	**Bleomycin**	Did not form connected network
	44	Dibromodulcitol + Bleomycin	
Keilholz et al, 2018 (RESGEX)	117	Cisplatin + 5-FU + Tomuzotuximab	Did not form connected network
	123	**Cisplatin + 5-FU + Cetuximab**	
Schornagel et al, 1995	131	Edatrexate	Did not form connected network
	133	**Methotrexate**	
Vermorken et al, 2013 (SPECTRUM)	327	Cisplatin + 5-FU + Panitumumab	Did not form connected network
	330	**Cisplatin + 5-FU**	
Vermorken et al, 2014a (ADVANTAGE)	62	Cilengitide (once weekly) + Cisplatin + 5-FU + Cetuximab	Did not form connected network
	60	Cilengitide (twice weekly) + Cisplatin + 5-FU + Cetuximab	
	62	Cisplatin + 5-FU + Cetuximab	
Vogl et al, 1982	38	Methotrexate + C. Parvum	Did not form connected network
	35	**Methotrexate**	
Williams et al, 1986	98	**Methotrexate**	Did not form connected network
	92	Cisplatin + Vinblastine + Bleomycin	
Wirth et al, 2016 (PARTNER)	56	Cisplatin + Docetaxel + Panitumumab	Did not form connected network
	55	**Cisplatin + Docetaxel**	

Source: NMA report[31]

Table 44 summarizes key study characteristics for the six trials included in the network for the NMA, and Table 45 summarizes the treatments used in the trials. All were Phase 3 multi-centre trials. Three were described as open label and three did not report blinding. Four trials excluded patients with nasopharyngeal primary tumours, while the other two did not specify whether or not they were included. Jacobs 1992 restricted patients to those who had not previously received chemotherapy, while the other trials allowed patients with prior chemotherapy as part of multimodal therapy for locoregional disease, if it were completed more than 6 months earlier. Three trials restricted enrolment to patients with ECOG 0 to 1, while the other three allowed patients with ECOG>1 or the equivalent (KPS ≥70, in EXTREME, was considered equivalent to ECOG 0 to 2).

Table 44: Summary of the study characteristics of 1L trials connected within the network

Study	Phase	Masking	Eligible patients	PS	NPC	Prior chemotherapy
KEYNOTE-048	3	Open-label	R/M HNSCC patients ≥18 years old	ECOG 0-1	Excluded	Not allowed in the R/M setting. Allowed if received in the LA setting ≥6 months BSE.
E1395	3	--	HNSCC patients ≥18 years old who are not curable with Sx or RT.	ECOG 0-1	Excluded	Not allowed for recurrent disease. Allowed if delivered as part of initial curative therapy (treatment with paclitaxel or FU had to be completed ≥12 months BSE and treatment with cisplatin had to be completed ≥6 months BSE).
EXTREME	3	Open-label	HNSCC patients ≥18 years old who are not eligible for local therapy.	KPS ≥70	Excluded	Not allowed unless part of multimodal treatment for LA disease completed ≥6 months BSE.
Forastiere 1992	3	--	HNSCC patients who are either recurrent after attempted cure with Sx and RT or newly diagnosed disease with distant metastases.	ECOG 0-2	--	Not allowed for recurrent disease. Allowed if received in the LA setting ≥6 months BSE.
Jacobs 1992	3	--	HNSCC patients ≥18 years old with recurrence after primary therapy or metastatic at diagnosis.	ECOG 0-3	--	Not allowed in any setting.
TPExtreme	3	Open-label	HNSCC patients ≥18 years old who are not eligible for local therapy.	ECOG 0-1	Excluded	Not allowed unless part of multimodal treatment for LA disease completed ≥6 months BSE.

Abbreviations: 1L, first line; BSE, before study entry; ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil; HNSCC, head and neck squamous cell carcinoma; KPS, Karnofsky performance score; NPC, nasopharyngeal carcinoma; PS, performance score; R/M, recurrent and/or metastatic; RT, radiotherapy; Sx, surgery.

Source: NMA report[31]

One trial each contributed data on PEMB mono, PEMB-chemo, methotrexate monotherapy, 5-FU as monotherapy, cisplatin chemotherapy, and cisplatin combined with paclitaxel. Three trials contributed data on cetuximab combined with platinum chemotherapy and 5-FU, two of which used the EXTREME regimen, with the same dosing, intervals and duration for all three components, and one (TPExtreme) of which limited cetuximab to 12 weeks maximum and administered the 5-FU dose as a single unfractionated dose as opposed to across 4 days. Four trials contributed data on platinum plus 5-FU, two of which included a choice between cisplatin and carboplatin, one of which included randomization of cisplatin versus carboplatin, and one of which included only cisplatin. Cisplatin and 5-FU dosing and treatment intervals were consistent across trials, while duration was until disease progression in three and for a maximum of six cycles in KEYNOTE-048. Carboplatin dosing varied in dose (AUC 5, AUC 6, and 300 mg/m^2), interval (every three weeks and every four weeks), and duration (until disease progression or limited to six cycles). The observed variability is not likely to contribute substantial heterogeneity.

Table 45: Summary of treatment information for the 1L trials connected within the network

Study	Regimens	Treatment duration	Dosing and schedules
KEYNOTE-048	PEMB	--	PEMB, IV (200 mg, every 3 weeks, up to 24 months)
	PEMB + platinum + 5-FU	Median: 25.1 weeks Range: 0.4-105.1 weeks	PEMB, IV (200 mg, every 3 weeks, up to 24 months) Investigator's choice of: • Cisplatin, IV (100 mg/m², every 3 weeks, up to 6 cycle(s)) OR • Carboplatin, IV (AUC 5 mg.h/L, every 3 weeks, up to 6 cycle(s)) 5-FU, IV (1000 mg/m², 4 days, every 3 weeks, up to 6 cycle(s))
	Platinum + 5-FU + cetuximab	Median: 21.1 weeks Range: 0.1-153.3 weeks	Cetuximab, IV (250 mg/m², every week, UDP) Investigator's choice of: • Cisplatin, IV (100 mg/m², every 3 weeks, up to 6 cycle(s)) • Carboplatin, IV (AUC 5 mg.h/L, every 3 weeks, up to 6 cycle(s)) 5-FU, IV (1000 mg/m², 4 days, every 3 weeks, up to 6 cycle(s))
E1395	Platinum + 5-FU	--	Cisplatin, IV (100 mg/m², every 3 weeks, UDP) Carboplatin, IV (AUC 6 mg.h/L every 3 weeks, UDP)[a] 5-FU, IV (1000 mg/m², 4 days, every 3 weeks, UDP)
	Platinum + paclitaxel		Cisplatin, IV (75 mg/m²; D1; every 3 weeks, UDP) Carboplatin, IV (AUC 6 mg.h/L every 3 weeks, UDP)[a] Paclitaxel, IV (175 mg/m² every 3 weeks, UDP)
EXTREME	Platinum + 5-FU + cetuximab	Cisplatin Median: 15 weeks; IQR: 6-19 weeks Cetuximab Median: 18 weeks; IQR: 8-29 weeks	Cetuximab, IV (250 mg/m², weekly, UDP) Cisplatin, IV (100 mg/m², every 3 weeks, up to 6 cycle(s)) OR Carboplatin, IV (AUC 5 mg.h/L, every 3 weeks, up to 6 cycle(s))[a] 5-FU, IV (1000 mg/m², 4 days, every 3 weeks, up to 6 cycle(s))
	Platinum + 5-FU	Median: 12 weeks; IQR: 6-19 weeks	Cisplatin, IV (100 mg/m², every 3 weeks, up to 6 cycle(s)) Carboplatin, IV (AUC 5 mg.h/L, every 3 weeks, up to 6 cycle(s))[a] 5-FU, IV (1000 mg/m², 4 days, every 3 weeks, up to 6 cycle(s))
Forastiere 1992	Cisplatin + 5-FU	Median: 4 courses; Range: 0-17 courses	Cisplatin, IV (100 mg/m², every 21 days, UDP) 5-FU, IV (1000 mg/m², 4 days, every 21 days, UDP)
	Carboplatin + 5-FU	Median: 2 courses; Range: 1-14 courses	Carboplatin, IV (300 mg/m², every 28 days, UDP) 5-FU, IV (1000 mg/m², 4 days, every 28 days, UDP)
	Methotrexate	Median: 8 weeks; Range: 0-49 weeks	Methotrexate, IV (40 mg/m², weekly, UDP)
Jacobs 1992	Cisplatin	--	Cisplatin, IV (100 mg/m², every 3 weeks, UDP)
	5-FU		5-FU, IV (1000 mg/m², 4 days, every 3 weeks, UDP)
	Cisplatin + 5-FU		Cisplatin, IV (100 mg/m², every 3 weeks, UDP) 5-FU, IV (1000 mg/m², 4 days, every 3 weeks, UDP)
TPExtreme	Cisplatin + docetaxel + cetuximab	--	Cisplatin, IV (75 mg/m², every 21 days, max. 4 cycle(s)) Docetaxel, IV (75 mg/m², every 21 days, max 4 cycle(s)) Cetuximab, IV (250 mg/m², weekly, max 18 week(s))

Study	Regimens	Treatment duration	Dosing and schedules
	Platinum + 5-FU + cetuximab		Cetuximab, IV (250 mg/m^2, every 7 days, max 12 week(s)) Platinum, IV (100 mg/m^2, every 21 days, max 6 cycle(s)) 5-FU, IV (4000 mg/m^2, every 21 days, max 6 cycle(s))

Abbreviations: 5-FU = 5-fluorouracil, IV = intravenous, UDP = until disease progression

Source: NMA report[31]

Table 46 summarizes the baseline patient characteristics for the trials included in the NMA. Median age was relatively consistent across arms, ranging from 56 to 62 years. Patients were predominately male and White, with the percentage male ranging from 78% to 94%, with most arms in the low to mid 80%s, and the proportion White around three-quarters in those studies that reported race. ECOG status reflected inclusion criteria. Studies that recruited patients with ECOG 0 or 1 had a higher percentage of patients with ECOG 1 (around 60% in KEYNOTE-048 and around 70% in Gibson and TPExtreme 70%). In studies that recruited patients with ECOG>1, the percentage of those higher than 1, 2 and above ranged from 1% to 42.2% (in Jacobs 1992). Most studies did not report HPV status. The distribution of recurrent varied: In KN-048 approximately 30% had recurrent disease across the arms and 70%, metastatic disease, while in Forastiere and Jacobs, 90% had recurrent disease and 10% metastatic. Sex and disease status are predictive of outcome and a potential source of heterogeneity

Table 46: Baseline patient characteristics of trials and subgroups included in the NMA

Study	Treatment	N	Age, median (range)	Male, n (%)	White, n (%)	ECOG Score, n (%)				HPV, n (%)			Recurrent, n(%)	Metastatic, n(%)
						0	1	2	3	+	-	Miss.		
KEYNOTE-048	PEMB-chemo (PD-L1 CPS ≥1)	242	61 (20-85)	188 (77.7)	178 (73.6)	92 (38)	150 (62)	0 (0)	0 (0)	53 (21.9)	189 (78.1)	0 (0)	65 (26.9)	173 (71.5)
	CET-chemo (PD-L1 CPS ≥1) *	235	61 (24-84)	203 (86.4)	173 (73.6)	94 (40)	141 (60)	0 (0)	0 (0)	50 (21.3)	185 (78.7)	0 (0)	78 (33.2)	154 (65.5)
	PEMB-chemo (ITT)	281	61 (20-85)	224 (79.7)	203 (72.2)	110 (39.1)	171 (60.9)	0 (0)	0 (0)	60 (21.4)	221 (78.6)	0 (0)	76 (27)	201 (71.5)
	CET-chemo (ITT) *	278	61 (24-84)	242 (87.1)	207 (74.5)	108 (38.8)	170 (61.2)	0 (0)	0 (0)	61 (21.9)	217 (78.1)	0 (0)	88 (31.7)	187 (67.3)
	PEMB mono (PD-L1 CPS ≥1)	257	62 (22-94)	209 (81.3)	188 (73.2)	104 (40.5)	153 (59.5)	0 (0)	0 (0)	54 (21)	203 (79)	0 (0)	75 (29.2)	179 (69.6)
	CET-chemo (PD-L1 CPS ≥1) *	255	61 (24-84)	220 (86.3)	189 (74.1)	101 (39.6)	154 (60.4)	0 (0)	0 (0)	55 (21.6)	200 (78.4)	0 (0)	84 (32.9)	168 (65.9)
	CET-chemo (ITT)*	300	61 (24-84)	261 (87)	224 (74.7)	117 (39)	183 (61)	0 (0)	0 (0)	67 (22.3)	233 (77.7)	0 (0)	94 (31.3)	203 (67.7)
Forastiere et al, 1992	Cisplatin + 5-FU	87	61 (39-82)	76 (87)	67 (77)	63 (72)		24 (28)	0 (0)	--			81 (93)	6 (7)
	Carboplatin + 5-FU	86	61 (43-77)	71 (83)	71 (83)	61 (71)		25 (29)	0 (0)				82 (95)	4 (5)
	Methotrexate	88	60 (28-80)	73 (83)	68 (77)	63 (72)		25 (28)	0 (0)				80 (91)	8 (9)
Gibson et al, 2005 (E1395)	Platinum + 5-FU	104	61 (35-84)	87 (83.6)	83 (79.8)	29 (27.9)	74 (71.1)	1 (1)	--	--			90 (86.5)	63 (60.6)
	Cisplatin + paclitaxel	100	61 (37-81)	78 (78)	77 (77)	25 (25)	75 (75)	0 (0)	--				89 (89)	52 (52)
Guigay et al, 2019 (TPExtreme)	Cisplatin + docetaxel + cetuximab	269	60 (38-70)	240 (89)	--	86 (32)	183 (68)	0 (0)	0 (0)	56 (21)	--	--		
	Platinum + 5-FU + cetuximab	270	60 (23-71)	231 (86)		86 (32)	184 (68)			31 (11)				
Jacobs et al, 1992	Cisplatin	83	59[c]	78 (94)	--	53 (63.9)		30 (36.1)		--			73 (88)	10 (12)
	5-FU	83	58[c]	73 (88)		48 (57.8)		35 (42.2)					76 (91.6)	7 (8.4)
	Cisplatin + 5-FU	79	57[c]	75 (95)		50 (63.3)		29 (36.7)					70 (88.6)	9 (11.4)

Study	Treatment	N	Age, median (range)	Male, n (%)	White, n (%)	ECOG Score, n (%)				HPV, n (%)			Recurrent, n(%)	Metastatic, n(%)
						0	1	2	3	+	-	Miss.		
Vermorken et al, 2008 (EXTREME)	Platinum + 5-FU + cetuximab	222	56	197 (89)	--	KPS median: 80 KPS IQR: 80-90				--			--	104 (47)
	Platinum + 5-FU	220	57	202 (92)		KPS median: 80 KPS IQR: 80-90							--	102 (46)

* As a result of the pause in recruitment reported for the PEMB-chemo arm, the CET-chemo comparison group differs for PEMB mono versus CET-chemo and PEMB-chemo versus CET-chemo for both the ITT population and the CPS≥1 population.

Source: NMA report[31]

Table 47 summarizes the Cochrane Risk of Bias assessment for the trials included in the NMA. None of the domains were rated as high risk of bias. A number of domains were rated as unclear risk of bias. The majority of trials were open label, and methods of randomization were infrequently described clearly. Where a protocol was available for comparison, there was no evidence of selective reporting, and the majority of studies addressed missing or incomplete data. The authors rated the risk of bias as low overall.

Table 47: Cochrane risk of bias assessment of 1L trials connected within the network

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Funding bias	Comments
	Sequence generation	Allocation concealment						
KEYNOTE-048	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Sponsored by Merck and Co, Inc..
E1395	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	--
EXTREME	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Sponsored by Merck KGaA
Forastiere 1992	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	--
Jacobs 1992	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	--
TPExtreme	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	--

Abbreviations: 1L, first line.

Source: NMA report[31]

Table 48 summarizes the reported OS, PFS, response (ORR, CR, and/or PR) and DOR for the individual treatment arms of the trials included in the network meta-analysis, grouped by treatment.

Table 48: Reported efficacy outcomes from the trials connected within the network

Treatment	Study	N	Follow-up (months)	OS* median (95% CI)	PFS*, median (95% CI)	Response proportion n, (%, 95% CI)			DOR*, median (95% CI)
						OR	CR	PR	
Pembrolizumab + platinum + 5-FU	KEYNOTE-048 – ITT	281	13.0	13 (10.9-14.7)	4.9 (4.7-6.1)	100 (35.6, 30.0-41.5)	17 (6)	83 (29.5)	6.7 (1.6-39.0)[b]
	KEYNOTE-048 – PD-L1 CPS ≥1	242		13.6 (10.7-15.5)	5.1 (4.7-6.2)	88 (36.4, 30.3-42.8)	16 (6.6)	72 (29.8)	6.7 (1.6- 39.0)[b]
Pembrolizumab	KEYNOTE-048 – PD-L1 CPS ≥1	257		12.3 (10.8-14.3)	3.2 (2.2-3.4)	49 (19.1, 14.5-24.4)	14 (5.4)	35 (13.6)	23.4 (1.5-43.0)[b]
Cisplatin + 5-FU + cetuximab	KEYNOTE-048** – Combo - ITT	278	10.7	10.7 (9.3-11.7)	5.2 (4.9-6.1)	101 (36.3, 30.7-42.3)	8 (2.9)	93 (33.5)	4.3 (1.2-31.5)[b]
	KEYNOTE-048** – Combo - PD-L1 CPS ≥1	235		10.4 (9.1-11.7)	5.0 (4.8-6.0)	84 (35.7, 29.6-42.2)	7 (3.0)	77 (32.8)	4.3 (1.2-31.5)[b]
	KEYNOTE-048** – Mono - PD-L1 CPS ≥1	255		10.3 (9.0-11.5)	5.0 (4.8-6.0)	89 (34.9, 29.1-41.1)	7 (2.7)	82 (32.2)	4.5 (1.2-38.7)[b]
	Vermorken et al, 2008 (EXTREME)	222	19.1	10.1 (8.6-11.2)	5.6 (5-6)	80 (36, 29-42)	--	--	5.6 (4.7-6)
	Vermorken et al, 2014b (EXTREME)	221	5 years	10.1 (8.6-11.2)					
	Guigay et al, 2019 (TPExtreme)	270	31.6	13.4	6.1	109 (40.0)			
Cisplatin + 5-FU	Forastiere et al, 1992	87		6.6	--	28 (32)	5 (6)	23 (26)	4.2
	Gibson et al, 2005 (E1395)	104	8.3	8.7 (6.7-12.2)	--	31 (29.8)	7 (6.7)	24 (23.1)	--
	Jacobs et al, 1992	79	--	5.5 (4-8.8)		25 (32, 21-42)	5 (6.3)	20 (25.3)	--
	Vermorken et al, 2008 (EXTREME)	220	19.2	7.4 (6.4-8.3)	3.3 (2.9-4.3)	44 (20, 15-25)	--	--	4.7 (3.6-5.9)
	Vermorken et al, 2014b (EXTREME)	220	5 years	7.4 (6.4-8.3)					

Treatment	Study	N	Follow-up (months)	OS* median (95% CI)	PFS*, median (95% CI)	Response proportion n, (%, 95% CI)			DOR*, median (95% CI)
						OR	CR	PR	
Cisplatin + docetaxel + cetuximab	Guigay et al, 2019 (TPExtreme)	269	32.6	14.5	6.0	123 (46.0)			
Carboplatin + 5-FU	Forastiere et al, 1992	86	--	5	--	18 (21)	2 (2)	16 (19)	5.1
Cisplatin + paclitaxel	Gibson et al, 2005 (E1395)	100	8.3	8.1 (6.1-10)	--	26 (26)	7 (7)	19 (19)	--
Cisplatin	Jacobs et al, 1992	83	--	5 (4.1-7.2)	--	14 (17, 9-25)	3 (3.6)	11 (13.3)	--
5-FU	Jacobs et al, 1992	83	--	6.1 (4.6-7.2)	--	11 (13, 6-21)	2 (2.4)	9 (10.8)	--
Methotrexate	Forastiere et al, 1992	88	--	5.6	--	9 (10)	2 (2)	7 (8)	4.1

* Durations reported in other than months were converted to months, assuming 1 month = 365/12 days. ** For safety reasons, there was a pause in enrollment to the PEMB-chemo arm during KEYNOTE-048. Twenty-two patients randomized to CET-chemo during that pause are excluded from the PEMB-chemo versus CET-chemo comparison, and included in the PEMB mono versus CET-chemo comparison.

Abbreviations: CPS = Combined Proportion Score, CR = complete response, PD-L1 = programmed death ligand 1, PR = partial response, TPS = Tumour Proportion Score

Source: NMA report[31]

Methods for ITC

From the SR to the ITC, the inclusion criteria for studies were narrowed so as to only include patients receiving 1L therapy, i.e., patients with recurrent or metastatic HNSCC ineligible for curative treatment with no prior systemic therapy administered in either the LA or recurrent or metastatic setting, or who had received prior systemic therapy as part of multimodal treatment for locally advanced disease ≥6 months before study entry. A subgroup of interest was added, PD-L1 CPS≥1. PEMB-chemo was added to the intervention, and the comparators included placebo, best supportive care, and any intervention of interest, i.e., any treatment that facilitated the indirect comparison. Afatinib was ultimately excluded as a therapy as it was not an approved treatment.

The ITC used Bayesian fixed effects models. The authors acknowledged that random effects models would be preferable because of the expected heterogeneity, but ultimately used fixed effects models because the small number of trials would make it difficult to estimate variables, particularly the between-study heterogeneity.

Time to event outcomes were analyzed using reported constant HRs, under the proportional hazards assumption. A regression model was used with a contrast-based normal likelihood for log HR and SE, and non-informative priors with a normal distribution, mean 0, variance 10,000. These results were not reported, as subsequent emphasis was placed on models that did not assume proportional hazards.

As the proportional hazards assumption had been observed to be violated in trials comparing immunotherapy with chemotherapy, time-to-event outcomes were also modeled using fractional polynomials. Multivariate models were fitted, selecting amongst candidate polynomials, Weibull, Gompertz, and second order fractional polynomials described by p_1=0 or 1 and p_2= -1, 0.5, 0, 0.5, or 1. To simplify the model, it was assumed treatment only affected two of three parameters (one scale, one shape), or three out of three (one scale, two shape). The time to event data for each study were reconstructed from the reported KM curves: the curves were divided into sections, numbers at risk and events estimated within each segment, assuming a binomial likelihood distribution of incident events for every interval. The models were estimated using non-informative prior distributions and covariance matrices.

Selection amongst models used the Bayesian Difference Information Criterion (DIC), which is a standard measure of model fit that penalizes complexity. Lower DIC suggests better fit, and a difference of about 5 points was considered meaningful. Models were examined for plausibility, particularly where survival was extrapolated to longer intervals.

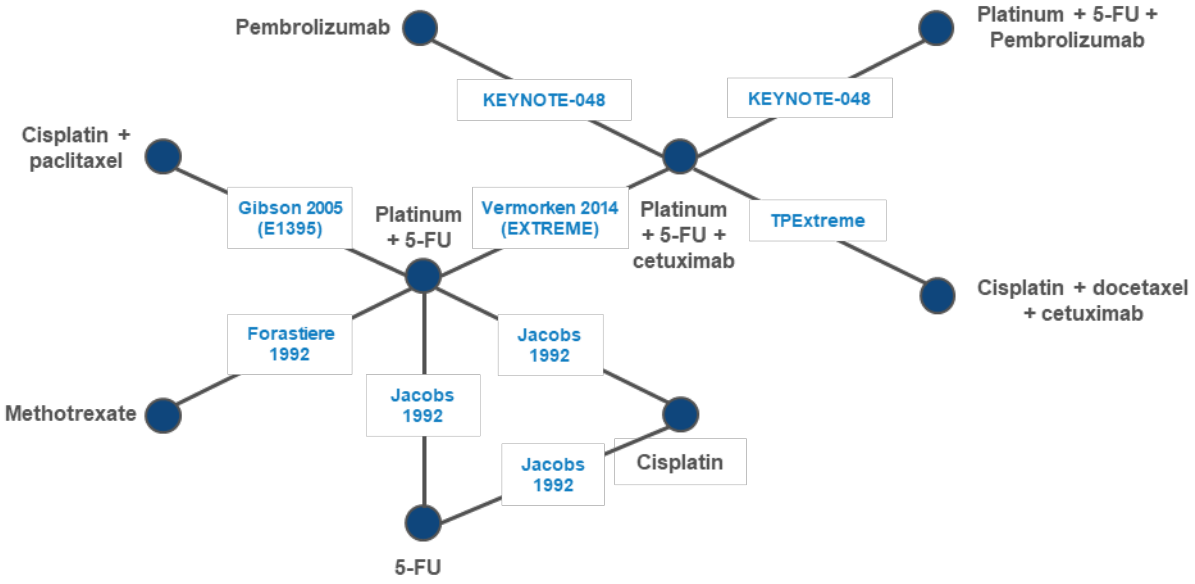
Estimates of treatment effects of each intervention were reported relative to reference treatments. The posterior distributions from the models summarized by median estimate and 95% CrIs. Results from the fractional polynomials were reported up to 36 months.

Construction of networks

Figure 29 shows the overall network of comparisons for the analysis of OS for all patients. Figure 30 shows the corresponding network for PFS for all patients. The network for OS contained six trials of nine treatments arranged in a star-shaped configuration with two centres, with no closed loops and each arm informed by data from one trial. For analysis involving the ITT population, the trials included 2573 patients. The network for PFS contained three trials of four treatments, arranged in a star-shaped configuration, again with no closed loops and each arm informed by data from one trial. For the analysis involving the ITT population, the trials included 1863 patients.

Only KEYNOTE-048 reported the PD-L1 CPS≥1 subgroup. The analysis of this subgroup used the data for the PD-L1 CPS≥1 subgroup and all patients from the other five trials. The networks were the same as those for the analysis of all patients.

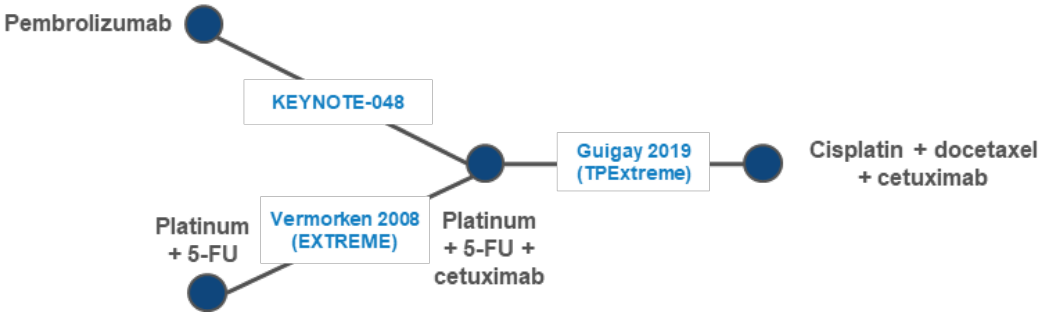
Figure 29: Overall network of comparisons, OS, all comparators



Abbreviations: 5-FU = 5-fluorouracil

Source: NMA report[31]

Figure 30: Overall network of comparisons, PFS, all comparators



Abbreviations: 5-FU = 5-fluorouracil

Source: NMA report[31]

Critical appraisal of NMA

Table 49 shows a summary of the critical appraisal for the NMA according to the ISPOR criteria. The SR was well conducted and documented and the NMA used appropriate methods to model survival in the presence of proportional hazards. Only a minority of the identified trials could be incorporated into a connected network (six trials), meaning that trials of comparators of interest were not included, including other tyrosine kinase inhibitors. The dataset was sparse, meaning that only fixed effects analyses could be conducted and no adjustment done for baseline clinical heterogeneity (ECOG status and recurrent/metastatic disease). Wide credible intervals, particularly for later time-points, indicated uncertainty in the estimates.

Data were not available for outcomes of interest ORR, DOR, quality of life, and safety. Data representing the PD-L1 CPS≥1 population were only available for the KEYNOTE-048 trial, so the network meta-analysis involving that subgroup involved the assumption that the presence of PD-L1 expression would not influence response to comparators. In addition, the stratification factor

for PD-L1 expression in KEYNOTE-048 was PD-L1 TPS, which was related to but not the same as the stratification factor for selecting the subgroup, indicating that randomization was not preserved and introducing the potential for bias.

Survival data were not mature for all trials, resulting in the need to extrapolate survival, with results for later time-points in the time varying analysis that are uncertain and sensitive to model selection. In particular, median follow-up in the KEYNOTE-048 trial was 10.7 to 13.0 months (maximum 45.7 months) depending on the group.

Table 49: Summary of critical appraisal of NMA of pembrolizumab for the first-line treatment of recurrent or metastatic HNSCC according to the ISPOR criteria.

ISPOR questions	Details and comments
1. Is the population relevant	Yes. The NMA included patients with recurrent or metastatic HNSCC ineligible for curative treatment with no prior systemic therapy administered in either the locally advanced or recurrent or metastatic setting, or who had received prior systemic therapy as part of multimodal treatment for L1 locally advanced disease ≥6 months before study entry. The systematic review criteria did not impose a limitation on prior therapy but following search and selection the studies were grouped according to whether patients were 1L, treated following progression on platinum therapy, or a mixed population. 1L studies were subsequently tiered according to the time interval between prior systemic therapy, with Tier 1 meeting the criterion of ≥6 months interval.
2. Are any critical interventions missing.	Yes. The SR search was comprehensive and included all interventions of interest. 31 RCTs of 1L therapy were retrieved and 23 were considered Tier 1. Only seven of these formed a connected network, and one of the seven was excluded because of its age (published 1983). Not all trials reported the endpoints of interest. Six trials were included in the OS analysis and three in the PFS analysis. Therapies of interest not included in the network were carboplatin, paclitaxel, docetaxel, cetuximab monotherapies, and platinum-docetaxel, platinum plus cetuximab plus paclitaxel as combination therapies.
3. Are any relevant outcomes missing?	Yes. Networks and NMA results were only available for OS and PFS. The systematic review also included objective response (ORR, CR, and PR), HRQoL, and AEs, but the data were not available to construct networks for these outcomes.
4. In the context (e.g., settings and circumstances) applicable to your population?	Yes. The Tier 1 selection criteria align with the population of interest, and studies were conducted within the applicable environment (cancer centres and oncology departments).
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The search included the major bibliographic databases (MEDLINE, EMBASE, and Cochrane Controlled Trials), as well as conference abstracts. Search was comprehensive and included validated search filters to restrict findings to RCTs. It is unlikely that relevant RCTs were missed.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Not all. Seven of the 1L trials form a connected network (with one excluded from the NMA on account of age) for OS, and three for PFS.
7. Is it apparent that poor quality studies were included thereby leading to bias?	No studies in any domains were identified as having high risk of bias. The predominate concern was with unclear risk of bias in allocation and blinding, arising from missing or unclear reporting.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Probably at low risk of bias. Four of the six included studies were reported as having low risk of bias in this domain, having protocols available. The others did not have the information available. This limitation is offset by use of the objective endpoint OS.

ISPOR questions	Details and comments
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Potentially. Reported baseline characteristics included age, sex/gender, race, HPV status, ECOG performance status, and disease status (relapsed/metastatic). The allowed ECOG performance score varies, and frailty potentially affects tolerability of therapy. In individual arms, number of patients with ECOG ≥ 2 ranged from 0 (ineligible) to 42.2%. PD-L1 expression was identified as a potential treatment effect modifier, and a subgroup analysis was planned and conducted around that subgroup, but only KEYNOTE-048 reported that subgroup. In addition, randomization in the KEYNOTE-048 trial was stratified on PD-L1 TPS score rather than the PD-L1 CPS score.
10. If yes (i.e., there are such systematic differences in treatment effect), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	No. The sparsity of the dataset did not allow for statistical adjustment, e.g., meta-regression.
11. Were statistical methods used that preserve within-study randomization?	In the ITT analysis, yes. Models used were fixed-effects regression models assuming constant HRs and time-varying HRs (fractional polynomials). The latter were used to account for identified deviations from the non-proportional hazards assumption for OS and PFS (a known feature in trials comparing immunotherapy with chemotherapy). In the PD-L1 CPS≥1 subgroup analysis, the within-trial randomization for KEYNOTE-048 was not preserved, as the variable used to select the subgroup (PD-L1 CPS) was related but not the same as that used to stratify the original trial randomization (PD-L1 TPS).
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops) was agreement in treatment effects (i.e., consistency) evaluated or discussed?	There were no closed loops in the network. Consistency could not be assessed.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	There were no closed loops in the network. Consistency could not be assessed.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The sparsity of the network did not allow for statistical adjustment or examination of subgroups, with the exception of PD-L1 CPS≥1, which was only available as population for one trial.
15. Was a valid rationale provided for the use of random effects or fixed effects models?	Yes. Authors acknowledged that random effects models would be preferable, but small number of studies meant that parameters in random effects models would be difficult to estimate.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Random effects model was not used due to sparse data.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analyses with pre-specified covariates performed?	The systematic review retrieved 31 1L studies which were prospectively grouped to reduce heterogeneity in study design and patient selection. 23 Tier 1 studies were considered for the NMA. The final analysis used 6 studies which could be connected in the NMA. Data were too sparse to allow meta-regression.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. Network diagrams were provided.
19. Are the individual study results reported?	Yes. A summary of individual study results was provided.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analyses?	Not applicable. A summary table of results of individual studies was provided.

ISPOR questions	Details and comments
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All time-varying pairwise contrasts were reported. Constant HR contrasts were not reported.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No. In this case, ranking would not be appropriate, as the sparse data means that the estimates would be highly uncertain.
23. Is the impact of important patient characteristics on treatment effects reported?	A subgroup with PD-L1 expression, PD-L1 CPS≥1, was prospectively identified as being of interest for comparisons involving pembrolizumab Only KEYNOTE-048 reported separately on this subgroup, so a separate analysis was done with the PD-L1 CPS≥1 subgroup compared with all patients from the other trials. The impact of other important patients characteristics was not explored.
24. Are the conclusions fair and balanced?	The conclusions seem fair and the limitations are acknowledged. The authors concluded that there was a statistically meaningful improvement on OS for pembrolizumab monotherapy and pembrolizumab combined with chemotherapy in comparison with platinum plus 5-FU in the total population. The limitations of the analysis in terms of the small number of studies in the network and in each arm and therefore the inability to adjust for baseline variability and heterogeneity were acknowledged.
25. Were there any potential conflicts of interest?	Report was manufacturer-supported.
26. If yes, were steps taken to address these?	No.

Results of NMA

7.1.3 Summary of results

Pembrolizumab monotherapy

Overall survival

Table 50 shows the results for the time-varying analysis of OS for PEMB mono versus comparators, for all patients including the ITT population from KEYNOTE-048. Table 51 shows the corresponding results incorporating the KEYNOTE-048 PD-L1 CPS≥1 population. The available comparators to PEMB-mono were CET-chemo (the comparator in KEYNOTE-048), platinum plus 5-FU, 5-FU, cisplatin, cisplatin plus paclitaxel, and cisplatin plus docetaxel plus cetuximab and methotrexate. The best-fitting fixed-effects model for both analyses was the second-order fractional polynomial (p1 = 0 and p2 = 1). The modeled survival function of platinum plus 5-FU, which was the comparator with the highest number of treatment arms, was used as the reference to generate the OS proportions over time from the estimated time-varying HRs.

For all patients, estimates of OS HR favoured PEMB mono over comparators platinum plus 5-FU, 5-FU monotherapy, methotrexate, cisplatin, and CET-chemo (the KEYNOTE-048 comparator) for most time-points from six months on. The effect on HR appears more marked at later time-points, however these later time-points involve extrapolation. Differences were not observed for cisplatin plus paclitaxel and cisplatin plus docetaxel plus cetuximab.

For the analysis incorporating the KEYNOTE PD-L1 CPS≥1 population, estimates of OS HR favoured PEMB mono over all comparators for most time-points from six months on, although the difference was lost for cisplatin plus paclitaxel at later time-points. The effect on HR appears more marked at later time-points, however, these later time-points involve extrapolation.

Table 50: Estimated overall survival hazard ratios for PEMB mono versus comparators from fixed effects NMA fractional polynomial model (P1 = 0, P2 = 1), all-comers ITT population

Time point (months)	Overall Survival Hazard Ratio (95% Credible Interval)						
	Platinum+ 5-FU	5-FU	Methotrexate	Cisplatin	Cisplatin+ Paclitaxel	Platinum+ 5-FU+ Cetuximab	Cisplatin+ Docetaxel+ Cetuximab
1	1.23 (0.64, 2.37)	1.29 (0.47, 3.54)	1.63 (0.68, 4.36)	1.30 (0.50, 3.60)	0.92 (0.32, 2.67)	*1.83 (1.15, 2.91)*	1.77 (0.88, 3.63)
3	0.91 (0.62, 1.34)	0.81 (0.46, 1.42)	0.92 (0.55, 1.57)	0.84 (0.48, 1.50)	0.78 (0.42, 1.44)	1.21 (0.92, 1.59)	1.28 (0.84, 1.95)
6	**0.75 (0.57, 0.99)**	**0.61 (0.39, 0.93)**	**0.63 (0.43, 0.93)**	**0.63 (0.42, 0.97)**	0.71 (0.47, 1.08)	0.93 (0.77, 1.13)	1.04 (0.78, 1.38)
9	**0.67 (0.51, 0.88)**	**0.51 (0.33, 0.80)**	**0.51 (0.34, 0.76)**	**0.54 (0.35, 0.83)**	0.67 (0.45, 1.00)	**0.80 (0.67, 0.96)**	0.92 (0.71, 1.20)
12	**0.62 (0.47, 0.83)**	**0.45 (0.27, 0.76)**	**0.43 (0.28, 0.68)**	**0.48 (0.30, 0.79)**	**0.64 (0.42, 0.99)**	**0.72 (0.59, 0.87)**	0.84 (0.64, 1.12)
15	**0.59 (0.42, 0.81)**	**0.41 (0.23, 0.75)**	**0.38 (0.23, 0.64)**	**0.44 (0.25, 0.76)**	0.62 (0.38, 1.01)	**0.66 (0.53, 0.82)**	0.79 (0.58, 1.09)
18	**0.56 (0.39, 0.80)**	**0.38 (0.20, 0.74)**	**0.35 (0.20, 0.62)**	**0.41 (0.22, 0.75)**	0.61 (0.35, 1.04)	**0.62 (0.49, 0.78)**	0.75 (0.53, 1.07)
21	**0.54 (0.36, 0.79)**	**0.35 (0.18, 0.74)**	**0.32 (0.17, 0.60)**	**0.38 (0.20, 0.75)**	0.59 (0.33, 1.08)	**0.58 (0.45, 0.75)**	0.71 (0.49, 1.05)
24	**0.52 (0.34, 0.78)**	**0.33 (0.16, 0.74)**	**0.30 (0.15, 0.58)**	**0.36 (0.18, 0.74)**	0.58 (0.30, 1.11)	**0.55 (0.42, 0.73)**	0.68 (0.46, 1.04)
27	**0.50 (0.32, 0.78)**	**0.32 (0.14, 0.74)**	**0.28 (0.14, 0.57)**	**0.35 (0.16, 0.74)**	0.57 (0.28, 1.14)	**0.53 (0.39, 0.71)**	0.66 (0.43, 1.03)
30	**0.49 (0.30, 0.77)**	**0.30 (0.13, 0.74)**	**0.26 (0.13, 0.56)**	**0.33 (0.15, 0.74)**	0.57 (0.27, 1.18)	**0.51 (0.37, 0.70)**	0.64 (0.40, 1.03)
33	**0.47 (0.29, 0.77)**	**0.29 (0.12, 0.74)**	**0.25 (0.11, 0.55)**	**0.32 (0.14, 0.74)**	0.56 (0.25, 1.20)	**0.49 (0.35, 0.68)**	0.62 (0.38, 1.02)
36	**0.46 (0.28, 0.77)**	**0.28 (0.11, 0.74)**	**0.24 (0.11, 0.54)**	**0.31 (0.13, 0.75)**	0.55 (0.24, 1.23)	**0.47 (0.33, 0.67)**	0.61 (0.36, 1.02)

Values in parentheses are credible intervals. Cells in bold pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in italics indicate that the comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Source: NMA report[31]

Table 51: Estimated overall survival hazard ratios for PEMB mono versus competing interventions from fixed-effects network meta-analysis (P1=0, P2=1); PD-L1 CPS ≥1 subgroup

Time point (months)	Overall Survival Hazard Ratio (95% Credible Interval)						
	Platinum +5-FU +Cetuximab	Platinum +5-FU	Cisplatin +Paclitaxel	Cisplatin +Docetaxel +Cetuximab	Cisplatin	5-FU	Methotrexate
1	*1.70 (1.02, 2.89)*	1.17 (0.56, 2.31)	0.86 (0.28, 2.60)	1.63 (0.78, 3.50)	1.25 (0.43, 3.53)	1.22 (0.40, 3.62)	1.53 (0.58, 3.98)
3	1.11 (0.82, 1.51)	0.84 (0.54, 1.26)	0.72 (0.38, 1.36)	1.16 (0.75, 1.82)	0.78 (0.42, 1.42)	0.75 (0.40, 1.36)	0.84 (0.48, 1.44)
6	0.84 (0.68, 1.04)	**0.68 (0.50, 0.91)**	**0.65 (0.41, 0.98)**	0.94 (0.69, 1.27)	**0.58 (0.37, 0.88)**	**0.55 (0.35, 0.85)**	**0.57 (0.38, 0.84)**
9	**0.72 (0.59, 0.87)**	**0.61 (0.46, 0.80)**	**0.60 (0.40, 0.90)**	0.83 (0.63, 1.09)	**0.49 (0.31, 0.75)**	**0.46 (0.29, 0.72)**	**0.46 (0.30, 0.69)**
12	**0.64 (0.52, 0.79)**	**0.55 (0.41, 0.75)**	**0.57 (0.37, 0.89)**	0.76 (0.56, 1.02)	**0.43 (0.26, 0.70)**	**0.40 (0.24, 0.68)**	**0.39 (0.25, 0.62)**
15	**0.59 (0.47, 0.74)**	**0.52 (0.37, 0.72)**	**0.55 (0.34, 0.91)**	**0.71 (0.51, 0.98)**	**0.39 (0.22, 0.68)**	**0.36 (0.20, 0.67)**	**0.34 (0.20, 0.58)**
18	**0.55 (0.42, 0.71)**	**0.49 (0.34, 0.71)**	**0.54 (0.31, 0.93)**	**0.67 (0.46, 0.96)**	**0.36 (0.19, 0.67)**	**0.33 (0.18, 0.66)**	**0.31 (0.18, 0.55)**
21	**0.52 (0.39, 0.68)**	**0.47 (0.31, 0.71)**	**0.52 (0.29, 0.96)**	**0.64 (0.43, 0.94)**	**0.34 (0.17, 0.67)**	**0.31 (0.16, 0.66)**	**0.29 (0.15, 0.53)**
24	**0.49 (0.36, 0.66)**	**0.45 (0.29, 0.70)**	**0.51 (0.27, 0.99)**	**0.61 (0.40, 0.93)**	**0.32 (0.15, 0.67)**	**0.29 (0.14, 0.66)**	**0.27 (0.14, 0.52)**
27	**0.47 (0.34, 0.64)**	**0.44 (0.28, 0.70)**	0.50 (0.25, 1.01)	**0.59 (0.37, 0.92)**	**0.30 (0.14, 0.67)**	**0.28 (0.13, 0.66)**	**0.25 (0.12, 0.51)**
30	**0.45 (0.32, 0.63)**	**0.42 (0.26, 0.69)**	0.49 (0.24, 1.04)	**0.57 (0.35, 0.92)**	**0.29 (0.13, 0.67)**	**0.27 (0.11, 0.66)**	**0.24 (0.11, 0.50)**
33	**0.43 (0.30, 0.61)**	**0.41 (0.25, 0.69)**	0.48 (0.22, 1.06)	**0.55 (0.33, 0.91)**	**0.28 (0.12, 0.67)**	**0.25 (0.11, 0.66)**	**0.22 (0.10, 0.49)**
36	**0.42 (0.29, 0.60)**	**0.40 (0.24, 0.69)**	0.48 (0.21, 1.08)	**0.54 (0.32, 0.91)**	**0.27 (0.11, 0.67)**	**0.24 (0.10, 0.66)**	**0.21 (0.09, 0.48)**

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Source: NMA report[31]

Progression free survival

Table 52 shows the results for the time-varying analysis of PFS for PEMB mono versus comparators, for all patients including the ITT population for KEYNOTE-048, and Table 53 shows the corresponding results incorporating the KEYNOTE-048 PD-L1 CPS≥1 population. The available comparators to pembrolizumab monotherapy were platinum plus 5-FU, CET-chemo, and cisplatin plus docetaxel plus cetuximab. The best-fitting fixed-effects model for both analyses was the second-order fractional polynomial (p1 = 1 and p2 = 0). The modeled survival function of platinum plus 5-FU, which was the comparator with the highest number of treatment arms, was used as the reference to generate the PFS proportions over time from the estimated time-varying HRs.

For all patients, estimates of PFS HR favoured PEMB mono over the other three comparators from 15 months on, and over two of three (platinum plus 5-FU and CET-chemo) from nine months on. The comparators were mostly favoured in the early intervals, at

one and three months. The favourable effect on HR appears more marked at later time-points, however, these later time-points involve extrapolation. Differences were not observed for cisplatin plus paclitaxel and cisplatin plus docetaxel plus cetuximab.

For the analysis incorporating the KEYNOTE PD-L1 CPS≥1 population, estimates of PFS HR favoured PEMB mono over all comparators for most time-points from six months on. Two of the three comparators were favoured at one and three months (CET-chemo and cisplatin plus docetaxel plus cetuximab). The effect on HR appears more marked at later time-points, however, these later time-points involve extrapolation.

Table 52: Estimated progression-free survival hazard ratios for PEMB mono versus competing interventions from fixed-effects network meta-analysis (P1=0, P2=0); all comers (ITT) population

Time point (months)	Progression-free Survival Hazard Ratio (95% Credible Interval)		
	Platinum+ 5-FU	Platinum+ 5-FU+ Cetuximab	Cisplatin+ Docetaxel+ Cetuximab
1	*2.17 (1.15, 4.09)*	*4.32 (2.86, 6.62)*	*4.13 (2.28, 7.49)*
3	0.99 (0.72, 1.37)	*1.76 (1.43, 2.17)*	*1.92 (1.42, 2.58)*
6	**0.61 (0.43, 0.84)**	1.00 (0.83, 1.20)	1.18 (0.91, 1.51)
9	**0.46 (0.29, 0.70)**	**0.71 (0.56, 0.90)**	0.89 (0.65, 1.21)
12	**0.37 (0.22, 0.63)**	**0.56 (0.42, 0.75)**	0.72 (0.50, 1.06)
15	**0.32 (0.17, 0.58)**	**0.47 (0.33, 0.66)**	**0.62 (0.40, 0.96)**
18	**0.28 (0.14, 0.54)**	**0.40 (0.28, 0.59)**	**0.55 (0.34, 0.89)**
21	**0.25 (0.12, 0.52)**	**0.36 (0.24, 0.54)**	**0.49 (0.29, 0.83)**
24	**0.23 (0.10, 0.49)**	**0.32 (0.20, 0.49)**	**0.45 (0.25, 0.79)**
27	**0.21 (0.09, 0.47)**	**0.29 (0.18, 0.46)**	**0.41 (0.22, 0.75)**
30	**0.20 (0.08, 0.46)**	**0.27 (0.16, 0.43)**	**0.38 (0.20, 0.72)**
33	**0.18 (0.07, 0.45)**	**0.25 (0.15, 0.41)**	**0.36 (0.18, 0.69)**
36	**0.17 (0.07, 0.43)**	**0.23 (0.13, 0.39)**	**0.33 (0.17, 0.67)**

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil.

Source: NMA report[31]

Table 53: Estimated progression-free survival hazard ratios for PEMB mono versus competing interventions from fixed-effects network meta-analysis (P1=0, P2=0); PD-L1 CPS ≥1 subgroup

Time point (months)	Progression-free Survival Hazard Ratio (95% Credible Interval)		
	Platinum+5-FU +Cetuximab	Platinum+5-FU	Cisplatin+Docetaxel +Cetuximab
1	*3.46 (2.26, 5.43)*	1.75 (0.89, 3.52)	*3.33 (1.85, 6.14)*
3	*1.49 (1.21, 1.86)*	0.84 (0.61, 1.16)	*1.64 (1.19, 2.25)*
6	0.88 (0.72, 1.07)	**0.53 (0.38, 0.74)**	1.04 (0.79, 1.36)
9	**0.64 (0.50, 0.83)**	**0.41 (0.26, 0.63)**	0.80 (0.58, 1.11)
12	**0.52 (0.38, 0.70)**	**0.34 (0.19, 0.57)**	**0.66 (0.45, 0.98)**
15	**0.44 (0.30, 0.62)**	**0.29 (0.15, 0.54)**	**0.57 (0.37, 0.90)**
18	**0.38 (0.25, 0.56)**	**0.26 (0.13, 0.51)**	**0.51 (0.31, 0.84)**
21	**0.34 (0.22, 0.52)**	**0.23 (0.11, 0.49)**	**0.46 (0.27, 0.79)**
24	**0.30 (0.19, 0.48)**	**0.21 (0.09, 0.47)**	**0.42 (0.24, 0.75)**
27	**0.28 (0.17, 0.45)**	**0.20 (0.08, 0.46)**	**0.39 (0.21, 0.72)**
30	**0.26 (0.15, 0.43)**	**0.18 (0.07, 0.44)**	**0.37 (0.19, 0.70)**
33	**0.24 (0.14, 0.41)**	**0.17 (0.07, 0.43)**	**0.34 (0.17, 0.67)**
36	**0.22 (0.12, 0.39)**	**0.16 (0.06, 0.42)**	**0.33 (0.16, 0.65)**

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Source: NMA report[31]

Pembrolizumab with chemotherapy

Overall survival

Table 54 shows the results for the time-varying analysis of OS for PEMB-chemo versus comparators, for all patients including the ITT population from KEYNOTE-048, and Table 55 shows the corresponding results incorporating the KEYNOTE-048 PD-L1 CPS≥1 population. The available comparators to PEMB-chemo were CET-chemo (the comparator in KEYNOTE-048), platinum plus 5-FU, 5-FU, cisplatin, cisplatin plus paclitaxel, and cisplatin plus docetaxel plus cetuximab and methotrexate. The best-fitting fixed-effects model for both analyses was the second-order fractional polynomial (p1 = 1 and p2 = 0). The modeled survival function of platinum plus 5-FU, which was the comparator with the highest number of treatment arms, was used as the reference to generate the OS proportions over time from the estimated time-varying HRs.

For all patients, estimates of OS HR favoured PEMB-chemo over five comparators, CET-chemo, platinum plus 5-FU, 5-FU, cisplatin, and methotrexate for most time-points from six months on. The effect on HR appears more marked at later time-points, however,

these later time-points involve extrapolation. PEMB-chemo was favoured over cisplatin plus paclitaxel at the early time-points (before 18 months) but not the later, while cisplatin plus docetaxel plus cetuximab was favoured at the later time-points (after 18 months).

For the analysis incorporating the KEYNOTE PD-L1 CPS≥1 population, estimates of OS HR favoured PEMB-chemo over six of the seven comparators from six months on. The effect on HR appears more marked at later time-points, however, these later time-points involve extrapolation. PEMB-chemo was favoured over cisplatin plus paclitaxel at the early time-points (before 24 months) but not the later.

Table 54: Estimated overall survival hazard ratios for pembrolizumab combination therapy versus competing interventions from fixed-effects network meta-analysis (P1=1, P2=0); all comers (ITT) population

Time point (months)	Overall Survival Hazard Ratio (95% Credible Interval)						
	Platinum +5-FU +Cetuximab	Platinum +5-FU	Cisplatin +Paclitaxel	Cisplatin +Docetaxel +Cetuximab	Cisplatin	5-FU	Methotrexate
1	1.05 (0.77, 1.43)	0.78 (0.51, 1.18)	0.59 (0.32, 1.08)	1.10 (0.71, 1.71)	0.67 (0.36, 1.25)	0.70 (0.37, 1.29)	0.78 (0.44, 1.34)
3	0.98 (0.75, 1.29)	0.74 (0.51, 1.08)	0.59 (0.34, 1.01)	1.04 (0.71, 1.54)	0.63 (0.37, 1.09)	0.64 (0.37, 1.09)	0.70 (0.43, 1.14)
6	0.88 (0.70, 1.10)	**0.69 (0.50, 0.94)**	**0.59 (0.37, 0.94)**	0.96 (0.69, 1.33)	**0.58 (0.37, 0.92)**	**0.57 (0.36, 0.89)**	**0.61 (0.40, 0.92)**
9	**0.79 (0.65, 0.95)**	**0.64 (0.48, 0.84)**	**0.60 (0.40, 0.90)**	0.88 (0.66, 1.17)	**0.53 (0.35, 0.81)**	**0.50 (0.33, 0.77)**	**0.52 (0.36, 0.77)**
12	**0.71 (0.59, 0.85)**	**0.59 (0.45, 0.77)**	**0.60 (0.40, 0.90)**	0.81 (0.62, 1.07)	**0.49 (0.31, 0.76)**	**0.45 (0.28, 0.71)**	**0.45 (0.31, 0.67)**
15	**0.63 (0.52, 0.77)**	**0.55 (0.41, 0.73)**	**0.60 (0.39, 0.94)**	0.75 (0.56, 1.00)	**0.45 (0.27, 0.74)**	**0.40 (0.23, 0.70)**	**0.39 (0.25, 0.63)**
18	**0.57 (0.45, 0.72)**	**0.51 (0.36, 0.70)**	0.60 (0.36, 1.03)	**0.69 (0.49, 0.96)**	**0.41 (0.22, 0.76)**	**0.35 (0.18, 0.71)**	**0.34 (0.19, 0.60)**
21	**0.51 (0.38, 0.68)**	**0.47 (0.32, 0.69)**	0.61 (0.33, 1.14)	**0.63 (0.42, 0.94)**	**0.38 (0.18, 0.78)**	**0.31 (0.14, 0.73)**	**0.29 (0.15, 0.59)**
24	**0.46 (0.32, 0.64)**	**0.44 (0.27, 0.69)**	0.61 (0.29, 1.27)	**0.58 (0.36, 0.93)**	**0.35 (0.14, 0.82)**	**0.28 (0.10, 0.76)**	**0.25 (0.11, 0.58)**
27	**0.41 (0.27, 0.61)**	**0.41 (0.24, 0.69)**	0.61 (0.26, 1.45)	**0.54 (0.31, 0.93)**	**0.32 (0.11, 0.86)**	**0.25 (0.08, 0.81)**	**0.22 (0.09, 0.57)**
30	**0.37 (0.23, 0.58)**	**0.38 (0.20, 0.69)**	0.62 (0.23, 1.65)	**0.49 (0.26, 0.93)**	**0.29 (0.09, 0.91)**	**0.22 (0.06, 0.85)**	**0.19 (0.07, 0.57)**
33	**0.33 (0.19, 0.56)**	**0.35 (0.17, 0.69)**	0.62 (0.20, 1.89)	**0.45 (0.22, 0.93)**	**0.27 (0.07, 0.98)**	**0.19 (0.04, 0.90)**	**0.16 (0.05, 0.57)**
36	**0.30 (0.16, 0.53)**	**0.32 (0.15, 0.70)**	0.62 (0.18, 2.17)	**0.42 (0.18, 0.93)**	0.24 (0.05, 1.04)	**0.17 (0.03, 0.96)**	**0.14 (0.04, 0.56)**

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that compartor is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil ITT, intention to treat.

Source: NMA report[31]

Table 55: Estimated overall survival hazard ratios for pembrolizumab combination therapy versus competing interventions from fixed-effects network meta-analysis (P1=1, P2=0); PD-L1 CPS ≥1 subgroup

Time point (months)	Overall Survival Hazard Ratio (95% Credible Interval)						
	Platinum +5-FU +Cetuximab	Platinum +5-FU	Cisplatin +Paclitaxel	Cisplatin +Docetaxel +Cetuximab	Cisplatin	5-FU	Methotrexate
1	1.09 (0.80, 1.52)	0.81 (0.52, 1.26)	0.62 (0.33, 1.16)	1.15 (0.74, 1.80)	0.70 (0.37, 1.35)	0.73 (0.37, 1.42)	0.79 (0.45, 1.41)
3	0.99 (0.75, 1.33)	0.75 (0.51, 1.12)	0.60 (0.35, 1.06)	1.06 (0.71, 1.58)	0.64 (0.37, 1.15)	0.65 (0.36, 1.17)	0.70 (0.43, 1.17)
6	0.85 (0.68, 1.09)	**0.67 (0.48, 0.93)**	**0.58 (0.37, 0.93)**	0.94 (0.67, 1.31)	**0.57 (0.36, 0.92)**	**0.56 (0.34, 0.90)**	**0.58 (0.38, 0.91)**
9	**0.74 (0.60, 0.91)**	**0.60 (0.45, 0.80)**	**0.56 (0.38, 0.86)**	0.83 (0.62, 1.11)	**0.50 (0.33, 0.77)**	**0.47 (0.31, 0.72)**	**0.49 (0.33, 0.73)**
12	**0.64 (0.52, 0.78)**	**0.53 (0.40, 0.70)**	**0.55 (0.36, 0.83)**	**0.73 (0.55, 0.97)**	**0.44 (0.28, 0.70)**	**0.40 (0.25, 0.64)**	**0.41 (0.27, 0.61)**
15	**0.55 (0.44, 0.68)**	**0.48 (0.35, 0.64)**	**0.53 (0.33, 0.84)**	**0.65 (0.48, 0.88)**	**0.39 (0.23, 0.66)**	**0.34 (0.20, 0.60)**	**0.34 (0.21, 0.55)**
18	**0.47 (0.37, 0.61)**	**0.43 (0.30, 0.60)**	**0.51 (0.30, 0.88)**	**0.58 (0.40, 0.81)**	**0.34 (0.18, 0.64)**	**0.29 (0.15, 0.59)**	**0.28 (0.16, 0.50)**
21	**0.41 (0.30, 0.56)**	**0.38 (0.25, 0.58)**	**0.49 (0.26, 0.94)**	**0.51 (0.34, 0.77)**	**0.30 (0.14, 0.64)**	**0.25 (0.11, 0.59)**	**0.24 (0.12, 0.47)**
24	**0.35 (0.24, 0.51)**	**0.34 (0.21, 0.56)**	0.48 (0.22, 1.02)	**0.45 (0.28, 0.73)**	**0.27 (0.11, 0.65)**	**0.21 (0.08, 0.59)**	**0.20 (0.09, 0.44)**
27	**0.30 (0.20, 0.47)**	**0.30 (0.17, 0.55)**	0.46 (0.19, 1.11)	**0.40 (0.22, 0.70)**	**0.23 (0.08, 0.67)**	**0.18 (0.06, 0.61)**	**0.16 (0.07, 0.42)**
30	**0.26 (0.16, 0.43)**	**0.27 (0.14, 0.53)**	0.45 (0.16, 1.23)	**0.35 (0.18, 0.68)**	**0.21 (0.06, 0.68)**	**0.15 (0.04, 0.62)**	**0.14 (0.05, 0.40)**
33	**0.23 (0.13, 0.40)**	**0.24 (0.11, 0.52)**	0.43 (0.14, 1.35)	**0.31 (0.15, 0.66)**	**0.18 (0.05, 0.70)**	**0.13 (0.03, 0.63)**	**0.11 (0.03, 0.39)**
36	**0.20 (0.10, 0.37)**	**0.22 (0.09, 0.51)**	0.42 (0.12, 1.50)	**0.28 (0.12, 0.64)**	**0.16 (0.04, 0.72)**	**0.11 (0.02, 0.65)**	**0.10 (0.03, 0.37)**

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Source: NMA report[31]

Progression free survival

Table 56 shows the results for the time-varying analysis of PFS for PEMB-chemo versus comparators, for all patients including the ITT population for KEYNOTE-048, and Table 57 shows the corresponding results incorporating the KEYNOTE-048 PD-L1 CPS≥1 population. The available comparators to PEMB-chemo were platinum plus 5-FU, CET-chemo, and cisplatin plus docetaxel plus cetuximab. The best-fitting fixed-effects model for both analyses was the second-order fractional polynomial (p1 = 1 and p2 = 0). The modeled survival function of platinum plus 5-FU, which was the comparator with the highest number of treatment arms, was used as the reference to generate the PFS proportions over time from the estimated time-varying HRs.

For all patients, estimates of PFS HR favoured PEMB-chemo over two of the other three comparators from nine months (CET-chemo and platinum plus 5-FU), and over platinum plus 5-FU from three months on. The effect on HR appears more marked at later time-points, however, these later time-points involve extrapolation. No difference was observed for cisplatin plus docetaxel plus cetuximab.

Results of the analysis incorporating the KEYNOTE PD-L1 CPS≥1 population were very similar. Estimates of PFS HR favoured PEMB-chemo over two of the other three comparators from six months (CET-chemo and platinum plus 5-FU), and over platinum plus 5-FU from three months on. The effect on HR appears more marked at later time-points, however these later time-points involve extrapolation. No difference was observed for cisplatin plus docetaxel plus cetuximab.

Table 56: Estimated progression-free survival hazard ratios for pembrolizumab combination therapy versus competing interventions from fixed-effects network meta-analysis (P1=0, P2=0.5); all comers (ITT) population

Time point (months)	Progression-free Survival Hazard Ratio (95% Credible Interval)		
	Platinum+5-FU +Cetuximab	Platinum+5-FU	Cisplatin+Docetaxel +Cetuximab
1	*1.60 (1.05, 2.47)*	0.82 (0.41, 1.62)	1.55 (0.85, 2.85)
3	1.08 (0.87, 1.35)	**0.61 (0.44, 0.86)**	1.19 (0.86, 1.63)
6	0.85 (0.71, 1.01)	**0.52 (0.37, 0.71)**	1.00 (0.78, 1.30)
9	**0.73 (0.59, 0.91)**	**0.47 (0.30, 0.71)**	0.91 (0.67, 1.22)
12	**0.66 (0.51, 0.86)**	**0.43 (0.26, 0.72)**	0.85 (0.60, 1.21)
15	**0.61 (0.45, 0.82)**	**0.41 (0.22, 0.74)**	0.80 (0.53, 1.21)
18	**0.57 (0.41, 0.80)**	**0.39 (0.20, 0.76)**	0.77 (0.49, 1.21)
21	**0.54 (0.37, 0.78)**	**0.38 (0.18, 0.77)**	0.74 (0.45, 1.22)
24	**0.52 (0.34, 0.77)**	**0.36 (0.17, 0.79)**	0.72 (0.42, 1.23)
27	**0.49 (0.32, 0.75)**	**0.35 (0.15, 0.80)**	0.70 (0.39, 1.23)
30	**0.48 (0.30, 0.74)**	**0.34 (0.14, 0.81)**	0.68 (0.37, 1.24)
33	**0.46 (0.29, 0.73)**	**0.33 (0.13, 0.83)**	0.67 (0.35, 1.24)
36	**0.45 (0.27, 0.72)**	**0.33 (0.13, 0.84)**	0.65 (0.33, 1.25)

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil; ITT, intention to treat.

Source: NMA report[31]

Table 57: Estimated progression-free survival hazard ratios for pembrolizumab combination therapy versus competing interventions from fixed-effects network meta-analysis (P1=0, P2=0.5); PD-L1 CPS ≥1 subgroup

Time point (months)	Progression-free Survival Hazard Ratio (95% Credible Interval)		
	Platinum+5-FU +Cetuximab	Platinum+5-FU	Cisplatin+Docetaxel +Cetuximab
1	1.52 (0.97, 2.38)	0.76 (0.37, 1.50)	1.47 (0.80, 2.68)
3	1.01 (0.80, 1.27)	**0.57 (0.40, 0.79)**	1.10 (0.80, 1.51)
6	**0.78 (0.64, 0.94)**	**0.47 (0.33, 0.65)**	0.92 (0.71, 1.20)
9	**0.67 (0.53, 0.84)**	**0.42 (0.26, 0.65)**	0.83 (0.61, 1.13)
12	**0.60 (0.45, 0.79)**	**0.39 (0.22, 0.67)**	0.77 (0.53, 1.12)
15	**0.55 (0.39, 0.76)**	**0.37 (0.19, 0.69)**	0.73 (0.47, 1.11)
18	**0.51 (0.35, 0.74)**	**0.35 (0.17, 0.71)**	0.69 (0.43, 1.11)
21	**0.48 (0.32, 0.72)**	**0.33 (0.15, 0.72)**	0.67 (0.39, 1.12)
24	**0.46 (0.30, 0.71)**	**0.32 (0.14, 0.74)**	0.64 (0.37, 1.12)
27	**0.44 (0.28, 0.69)**	**0.31 (0.13, 0.75)**	0.62 (0.34, 1.13)
30	**0.42 (0.26, 0.68)**	**0.30 (0.12, 0.77)**	0.61 (0.32, 1.13)
33	**0.41 (0.25, 0.67)**	**0.29 (0.11, 0.78)**	0.59 (0.31, 1.14)
36	**0.39 (0.23, 0.66)**	**0.29 (0.11, 0.79)**	0.58 (0.29, 1.14)

Values in parentheses are credible intervals. Cells in **bold** pembrolizumab monotherapy is favoured at the given time point, indicated by a hazard ratio less than 1 and 95% credible interval excluding 1. Cells in *italics* indicate that comparator is favoured at the given time point, indicated by a hazard ratio more than 1 and 95% credible interval excluding 1.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Source: NMA report[31]

7.1.3 Summary and conclusion

Thirty-one trials met the systematic review inclusion criteria as studies conducted in the first-line population of patients with recurrent or metastatic HNSCC, and 23 included patients with at least 6 months between systemic therapy given for locoregional disease. Of these 23, 7 formed a connected network for OS and 3 for PFS, for comparisons with both PEMB mono and PEMB chemo. One further study was excluded for OS on account of its age. Available comparators for OS were platinum plus 5-FU, 5-FU, methotrexate, cisplatin, cisplatin plus paclitaxel, CET-chemo, and cetuximab plus platinum plus docetaxel. Available comparators for PFS were platinum plus 5-FU, CET-chemo, and cetuximab plus platinum plus docetaxel. Two sets of analyses were conducted, using the ITT populations for all trials and using the PD-L1 CPS≥1 population of the KEYNOTE-048 trial with the ITT populations of all other trials, since a PD-L1 selected population was not available.

In the analysis using the ITT population, PEMB-mono had lower hazard of death compared with 5-FU, 5-FU, methotrexate, cisplatin, and CET-chemo after six or nine months. No difference was seen for cisplatin plus paclitaxel (with the exception of one time-point) or cetuximab plus platinum plus docetaxel. In the analysis using the KEYNOTE-048 PD-L1 CPS≥1 population, PEMB-mono had lower hazard of death compared with six comparators from the sixth month on, and for cisplatin plus docetaxel plus cetuximab from the eighteenth month on. In the PFS analyses for both populations, PEMB-mono had lower hazard of progression from six to fifteen months on for all comparisons, but no difference or higher hazard in the early months.

In the analysis using the ITT population, PEMB-chemo had lower hazard of death compared with 5-FU, 5-FU, methotrexate, cisplatin, and CET-chemo after six or nine months, and for early time-points for cisplatin plus paclitaxel and later time-points for cetuximab plus cisplatin plus docetaxel. Results for analyses using the KEYNOTE-048 PD-L1 CPS≥1 population were similar. In the PFS analyses for both populations, PEMB-mono had lower hazard of progression from three to six months on for CET-chemo and platinum plus 5-FU, but not for cetuximab plus cisplatin plus docetaxel.

The SR was well conducted and documented and the NMA used appropriate methods to model survival in the presence of proportional hazards. The NMA had the following limitations: Only a minority of trials could be incorporated into a connected network, and the included comparators did not represent other PD-L1 targeting therapies. The dataset was relatively sparse, meaning that only fixed effects analyses could be conducted and no adjustment done for baseline clinical heterogeneity (ECOG status and recurrent/metastatic) or potential effect modifiers. Data representing the PD-L1 CPS≥1 population were only available for the KEYNOTE-048 trial, so the comparison of that subgroup assumed that the presence of PD-L1 expression would not influence response to comparators. In addition, the stratification factor for PD-L1 expression in KEYNOTE-048 was PD-L1 TPS, which was related to but not the same as the stratification factor for selecting the subgroup, indicating that randomization was not preserved and introducing the potential for bias. Survival data were not mature for all trials, resulting in the need to extrapolate survival, with results for the time-varying analyses that are uncertain and sensitive to model selection. Due to the above limitations, the comparative efficacy estimates obtained may be biased, and it is not possible to quantify or identify the direction of the bias. Results of this NMA must be interpreted with caution.

8 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Head and Neck Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on pembrolizumab for NNSCC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations. This information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

Literature Search Methods

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials April 2020, Embase 1974 to 2020 May 22, Ovid MEDLINE(R) ALL 1946 to May 22, 2020
Search Strategy:

#	Searches	Results
1	(Keytruda* or pembrolizumab* or lambrolizumab* or MK 3475 or MK3475 or Merck 3475 or HSDB 8257 or HSDB8257 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,rn,nm.	20614
2	"Squamous Cell Carcinoma of Head and Neck"/	18301
3	"Carcinoma, squamous cell of head and neck"/	5210
4	exp Carcinoma, Squamous Cell/ and exp "Head and neck neoplasms"/	133771
5	((head adj3 neck) or SCCHN or HNSCC or HN-SCC).ti,ab,kf,kw.	229036
6	((hypopharyn* or laryn* or mouth or oropharyn* or sinonasal or oral or auditory canal* or temporal or tongue or lip or lips or gingiva* or mandib* or glotti* or head or neck or sinus cavit* or nasal cavit* or sinus* or salivary gland* or ear or nose or throat or cervicofacial or otorhinolaryng*) adj7 (squamous cell* or cancer* or carcinoma* or neoplas* or adenocarcinoma*)).ti,ab,kf,kw.	316414
7	or/2-6	457607
8	1 and 7	1410
9	8 use medall	223
10	limit 9 to english language	212
11	8 use cctr	133
12	*pembrolizumab/	4384
13	(Keytruda* or pembrolizumab* or lambrolizumab* or MK 3475 or MK3475 or Merck 3475 or HSDB 8257 or HSDB8257 or Sch 900475 or Sch900475).ti,ab,kw,dq.	13615
14	12 or 13	14192
15	exp "Head and neck squamous cell carcinoma"/	29233
16	exp "Head and neck carcinoma"/ and exp Squamous cell carcinoma/	37653
17	((head adj3 neck) or SCCHN or HNSCC or HN-SCC).ti,ab,kw,dq.	227567
18	((hypopharyn* or laryn* or mouth or oropharyn* or sinonasal or oral or auditory canal* or temporal or tongue or lip or lips or gingiva* or mandib* or glotti* or head or neck or sinus cavit* or nasal cavit* or sinus* or salivary gland+ or ear or nose or throat or cervicofacial or otorhinolaryng*) adj7 (squamous cell* or cancer* or carcinoma* or neoplas* or adenocarcinoma*)).ti,ab,kf,kw.	314040
19	or/15-18	420621
20	14 and 19	968
21	20 use oemezd	648
22	limit 21 to english language	643
23	22 not conference abstract.pt.	263
24	10 or 11 or 23	608
25	remove duplicates from 24	429
26	22 and conference abstract.pt.	380
27	limit 26 to yr="2015 -Current"	378

#	Searches	Results
28	remove duplicates from 27	346
29	25 or 28	775

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Results
#8	Search: #1 AND #6 AND publisher[sb] Filters: English	17
#7	Search: #1 AND #6 Filters: English	280
#6	Search: #2 OR #3 OR #4 OR #5 Filters: English	232,423
#5	Search: (hypopharyn*[tiab] OR laryn*[tiab] OR mouth[tiab] OR oropharyn*[tiab] OR sinonasal[tiab] OR oral[tiab] OR auditory canal*[tiab] OR temporal[tiab] OR tongue[tiab] OR lip[tiab] OR lips[tiab] OR gingiva*[tiab] OR mandib*[tiab] OR glotti*[tiab] OR head[tiab] OR neck[tiab] OR sinus cavit*[tiab] OR nasal cavit*[tiab] OR sinus*[tiab] OR salivary gland*[tiab] OR ear[tiab] OR nose[tiab] OR throat[tiab] OR cervicofacial[tiab] OR otorhinolaryng*) AND (squamous cell*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab] OR adenocarcinoma*[tiab]) Filters: English	186,974
#4	Search: “head and neck”[tiab] OR SCCHN[tiab] OR HNSCC[tiab] OR HN-SCC[tiab] Filters: English	73,916
#3	Search: Carcinoma, Squamous Cell[mh] AND "Head and neck neoplasms"[mh] Filters: English	60,667
#2	Search: Squamous Cell Carcinoma of Head and Neck[mh] Filters: English	4,975
#1	Search: pembrolizumab [Supplementary Concept] OR Keytruda*[tiab] OR pembrolizumab*[tiab] OR lambrolizumab*[tiab] OR MK 3475[tiab] OR MK3475[tiab] OR Merck 3475[tiab] OR HSDB 8257[tiab] OR HSDB8257[tiab] OR Sch 900475[tiab] OR Sch900475[tiab] OR DPT0O3T46P[rn] Filters: English	3,679

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Keytruda/pembrolizumab, HNSCC

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Keytruda/pembrolizumab, HNSCC

Conference abstracts:
American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Keytruda/pembrolizumab, HNSCC — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[32]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Keytruda/pembrolizumab and head and neck squamous cell carcinoma.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of October 22, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[33] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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