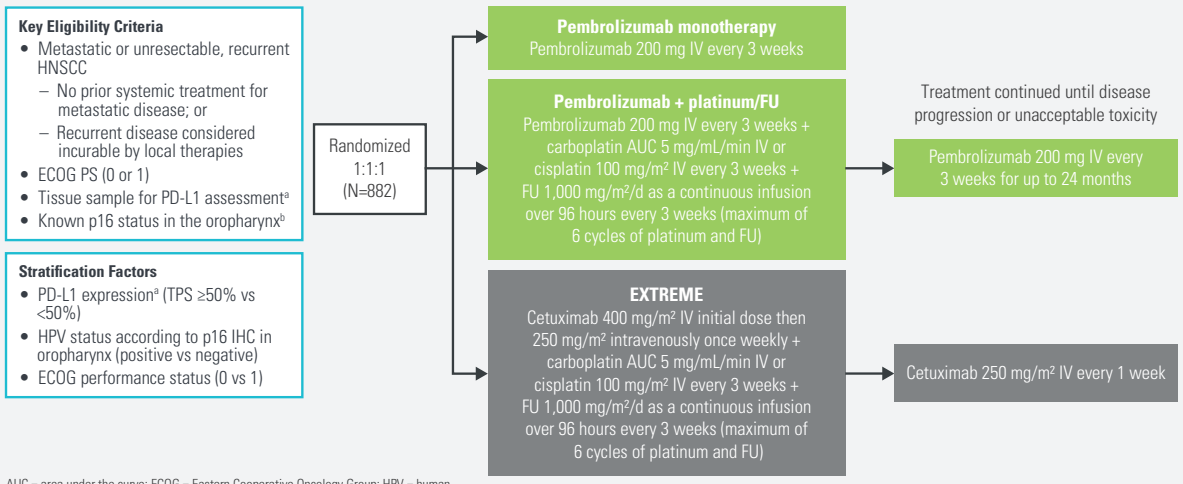
Head and Neck Cancer Clinical Study Summary

Welcome to the head and neck cancer clinical study summary. This clinical study summary is specific to head and neck cancer as it pertains to the treatment of metastatic or unresectable, recurrent squamous cell carcinoma of the head and neck (HNSCC). This summary will provide you with the clinical data that supports the approval of a first-line treatment option for metastatic or unresectable, recurrent HNSCC. Each backgrounder represents a key clinical study and includes an overview of the trial's background and objective, study design, and results. This information is provided for your background and not for use in discussions with customers.

KEYNOTE-048 Trial With Final Analysis

KEYNOTE-048 was a multicenter, open-label, randomized (1:1:1), active-controlled trial that evaluated the efficacy and safety of pembrolizumab as a single agent and in combination with platinum (cisplatin or carboplatin) and fluorouracil (FU) chemotherapy compared to cetuximab in combination with platinum and FU in patients with metastatic or unresectable, recurrent HNSCC who had not previously received systemic therapy for metastatic or unresectable, recurrent disease who were considered incurable by local therapies.

Study Design



AUC = area under the curve; ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; IHC = immunohistochemistry; IV = intravenously; PD-L1 = programmed death-ligand 1; PS = performance status; TPS = tumor proportion score
[a]PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit.
[b]Assessed using the CINtec Histology assay (Ventana); cutpoint for positivity = 70%.

KEYNOTE-048 included 2 interim analyses and a planned final analysis. The first interim analysis was performed after at least 9 months of follow-up from the last patient enrolled in addition to having met the criteria of a certain number of pre-specified events having occurred. The second interim analysis (IA2) was performed 17 months after the last patient was enrolled. The final analysis was planned to occur about 44 months after the first participant was enrolled.

The data included in this summary are from IA2 analysis (noted as the pre-specified interim analysis) and the final analysis (noted as the pre-specified final analysis). The following icons are provided throughout this summary to denote whether data was from the IA2 or final analysis:

IA2 — Interim analysis 2

FA — Final analysis

Table 1 Baseline Characteristics

Characteristic	N=882
Median age, years (range)	61 (20–94)
Age ≥65 years, %	36
Male, %	83
Race, %	
White	73
Asian	20
Black	2.4
ECOG performance status of 1, %	61
Former/current smoker, %	79
HPV-positive, %	22
Stage IV disease, %	95
Stage IVA, %	19
Stage IVB, %	6
Stage IVC, %	70
Tumor PD-L1 expression	
CPS ≥1, %	85
CPS ≥20, %	43
TPS ≥50%, %	23

CPS = combined positive score

Endpoints

Main efficacy outcome measures:

- Overall survival (OS)
- Progression-free survival (PFS)*

*As assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)

Efficacy outcomes were sequentially tested in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1, and the overall population. Safety was also evaluated.

Results

PD-L1 CPS ≥1 Population

IA2

At the pre-specified interim analysis, for patients randomized to pembrolizumab as a single agent, there was a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 compared to those randomized to cetuximab in combination with platinum and FU. (See Table 2.) At the time of the interim and final analyses, there was no significant difference in OS between the pembrolizumab single-agent arm and the control arm for the overall population (data not shown).

IA2

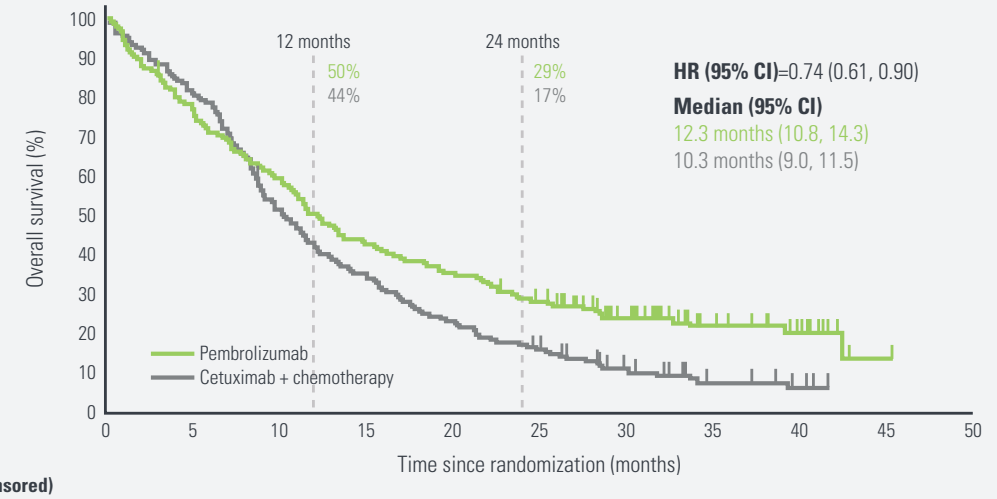
Table 2 Efficacy Results at a Pre-Specified Interim Analysis for Pembrolizumab as a Single Agent in Patients with CPS ≥1 and CPS ≥20

Endpoint	CPS ≥1		CPS ≥20	
	Pembrolizumab 200 mg every 3 weeks n=257	Cetuximab plus platinum and FU n=255	Pembrolizumab 200 mg every 3 weeks n=133	Cetuximab plus platinum and FU n=122
OS				
Number of events (%)	177 (69)	206 (81)	82 (62)	95 (78)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio* (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
P value†	0.0171		0.0015	
PFS				
Number of events (%)	225 (88)	231 (91)	113 (85)	111 (91)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
Hazard ratio* (95% CI)	1.15 (0.95, 1.38)		0.97 (0.74, 1.27)	
Objective Response Rate				
ORR‡ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)	23% (16.4, 31.4)	36% (27.6, 45.3)
Complete response rate	5%	3%	8%	3%
Partial response rate	14%	32%	16%	33%
Duration of Response				
Median in months (range)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)	20.9 (2.7, 34.8+)	4.2 (1.2+, 22.3+)

CI = confidence interval; + = ongoing response
*Based on the stratified Cox proportional hazard model.
†Based on a stratified log-rank test.
‡Response: Best objective response as confirmed complete response or partial response.

FA At the pre-specified final OS analysis comparing pembrolizumab as a single agent to cetuximab in combination with chemotherapy, the hazard ratio for the subgroup of patients with CPS ≥1 was 0.74 (95% CI: 0.61, 0.90) (See Figure 1), and the hazard ratio for the subgroup of patients with CPS ≥20 was 0.58 (95% CI: 0.44, 0.78).

FA **Figure 1 Estimated Kaplan–Meier Curves for Overall Survival for Pembrolizumab as a Single Agent in Patients with CPS ≥1 at the Final Analysis**



Number at risk (censored)

Pembrolizumab	257 (0)	197 (1)	152 (1)	110 (1)	91 (1)	70 (3)	43 (21)	21 (41)	13 (48)	1 (59)	0 (60)
Cetuximab + chemotherapy	255 (0)	207 (1)	131 (2)	89 (2)	59 (2)	40 (3)	21 (11)	9 (18)	5 (21)	0 (26)	0 (26)

FA In an exploratory subgroup analysis for patients with CPS 1–19 HNSCC at the time of the pre-specified final OS analysis, the median OS was 10.8 months (95% CI: 9.0, 12.6) for pembrolizumab as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.86 (95% CI: 0.66, 1.12).

Overall Population

IA2 At the pre-specified interim analysis, there was a statistically significant improvement in OS for patients randomized to pembrolizumab in combination with platinum and FU compared to those randomized to cetuximab in combination with platinum and FU in the overall population. (See Table 3.)

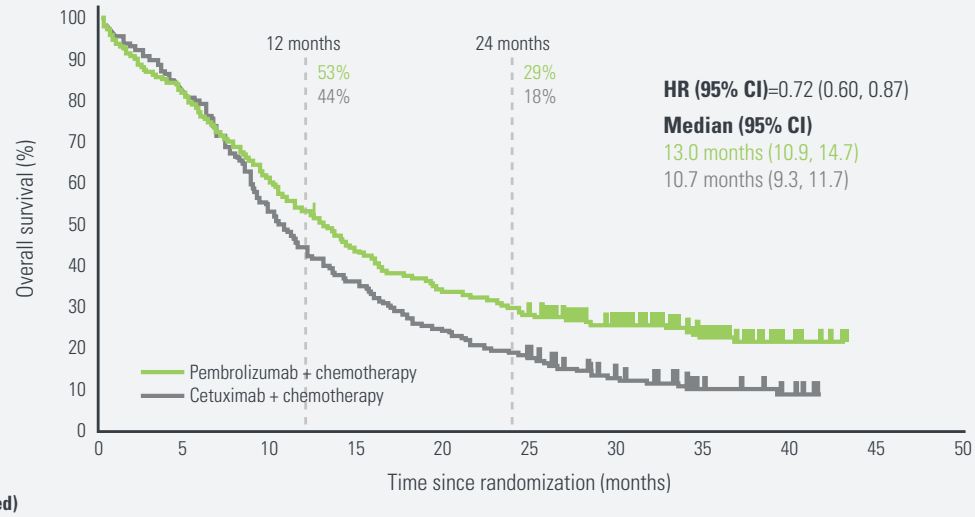
IA2 **Table 3 Efficacy Results at a Pre-specified Interim Analysis in Patients in the Overall Population**

Endpoint	Pembrolizumab plus platinum and FU n=281	Cetuximab plus platinum and FU n=278
OS		
Number of events (%)	197 (70)	223 (80)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio* (95% CI)	0.77 (0.63, 0.93)	
P value†	0.0067	
PFS		
Number of events (%)	244 (87)	253 (91)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
Hazard ratio* (95% CI)	0.92 (0.77, 1.10)	
P value†	0.3394	
Objective Response Rate		
ORR‡ (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response rate	6%	3%
Partial response rate	30%	33%
Duration of Response		
Median in months (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)

*Based on the stratified Cox proportional hazard model.
†Based on stratified log-rank test.
‡Response: Best objective response as confirmed complete response or partial response.

FA At a pre-specified final OS analysis for the intention-to-treat (ITT) population, the hazard ratio was 0.72 (95% CI: 0.60, 0.87). (See Figure 2.) In addition, KEYNOTE-048 demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 (HR=0.65, 95% CI: 0.53, 0.80) and CPS ≥20 (HR=0.60, 95% CI: 0.45, 0.82).

FA **Figure 2 Estimated Kaplan–Meier Curves for Overall Survival in the Overall Population at the Final Analysis**



Number at risk (censored)

Pembrolizumab + chemotherapy	281 (0)	227 (0)	169 (0)	122 (1)	94 (1)	77 (2)	55 (18)	29 (40)	5 (63)	0 (68)	0 (68)
Cetuximab + chemotherapy	278 (0)	227 (1)	147 (2)	100 (2)	66 (2)	45 (3)	23 (14)	6 (26)	1 (30)	0 (36)	0 (36)

The median duration of exposure to pembrolizumab was 3.5 months (range: 1 day to 24.2 months) in the pembrolizumab single agent arm and was 5.8 months (range: 3 days to 24.2 months) in the combination arm. Seventeen percent of patients in the pembrolizumab single agent arm and 18% of patients in the combination arm were exposed to pembrolizumab for ≥12 months. Fifty-seven percent of patients receiving pembrolizumab in combination with chemotherapy started treatment with carboplatin.

Pembrolizumab was discontinued for adverse reactions in 12% of patients receiving pembrolizumab as a single agent and in 16% of patients receiving pembrolizumab in combination with platinum and FU. Adverse reactions occurring in ≥10% of patients receiving pembrolizumab are provided in Table 4.

The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC (16%) receiving pembrolizumab as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism.

Table 4 Adverse Reactions Occurring in ≥10% of Patients Receiving Pembrolizumab

Adverse Reaction	Pembrolizumab 200 mg every 3 weeks n=300		Pembrolizumab 200 mg every 3 weeks plus platinum and FU n=276		Cetuximab plus platinum and FU n=287	
	All Grades* (%)	Grades 3–4 (%)	All Grades* (%)	Grades 3–4 (%)	All Grades* (%)	Grades 3–4 (%)
General						
Fatigue[†]	33	4	49	11	48	8
Pyrexia	13	0.7	16	0.7	12	0
Mucosal inflammation	4.3	1.3	31	10	28	5
Gastrointestinal						
Constipation	20	0.3	37	0	33	1.4
Nausea	17	0	51	6	51	6
Diarrhea[‡]	16	0.7	29	3.3	35	3.1
Vomiting	11	0.3	32	3.6	28	2.8
Dysphagia	8	2.3	12	2.9	10	2.1
Stomatitis	3	0	26	8	28	3.5
Skin						
Rash[§]	20	2.3	17	0.7	70	8
Pruritus	11	0	8	0	10	0.3
Respiratory, Thoracic, and Mediastinal						
Cough[¶]	18	0.3	22	0	15	0
Dyspnea[#]	14	2.0	10	1.8	8	1.0
Endocrine						
Hypothyroidism	18	0	15	0	6	0
Metabolism and Nutrition						
Decreased appetite	15	1.0	29	4.7	30	3.5
Weight loss	15	2	16	2.9	21	1.4
Infections						
Pneumonia[Þ]	12	7	19	11	13	6
Nervous system						
Headache	12	0.3	11	0.7	8	0.3
Dizziness	5	0.3	10	0.4	13	0.3
Peripheral sensory neuropathy[ß]	1	0	14	1.1	7	1
Musculoskeletal						
Myalgia[à]	12	1.0	13	0.4	11	0.3
Neck pain	6	0.7	10	1.1	7	0.7
Psychiatric						
Insomnia	7	0.7	10	0	8	0

*Graded per NCI CTCAE v4.0.
[†]Includes fatigue, asthenia.
[‡]Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis.
[§]Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, seborrheic dermatitis.
[¶]Includes cough, productive cough.
[#]Includes dyspnea, exertional dyspnea.
[Þ]Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal.
[ß]Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia.
[à]Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia.

Conclusion and Impact

At a pre-specified interim analysis, KEYNOTE-048 demonstrated a statistically significant improvement in OS for patients randomized to pembrolizumab in combination with platinum and FU compared to those randomized to cetuximab in combination with platinum and FU in the overall population (HR 0.77, 95% CI: 0.63, 0.93; *P*=0.0067) and for patients randomized to pembrolizumab as a single agent with PD-L1 CPS ≥1 compared to the control arm (HR 0.78, 95% CI: 0.64, 0.96; *P*=0.0171).

At the final analysis, continued improvements in OS were observed for patients randomized to pembrolizumab in combination with platinum and FU compared to those randomized to cetuximab in combination with platinum and FU in the overall population (HR 0.72, 95% CI: 0.60, 0.87) and for patients randomized to pembrolizumab as a single agent with PD-L1 CPS ≥1 compared to the control arm (HR 0.74, 95% CI: 0.61, 0.90).

These results continue to support the FDA approval of pembrolizumab

- In combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC
- As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test

References

Burtness B, Harrington K, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomized, open-label, phase 3 study. Lancet. 2019;394(10212):1915-1928.

KEYTRUDA [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2020.