ARTIGO ORIGINAL
ORIGINAL ARTICLE

Network meta-analysis of pembrolizumab as monotherapy and in combination with chemotherapy for first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma

Metanálise em rede comparativa de pembrolizumabe como monoterapia e em combinação com quimioterapia para tratamento de primeira linha de carcinoma de células escamosas da cabeça e pescoço recorrente ou metastático

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DOI: 10.21115/JBES.v16.n1.p25-64

Keywords:
head and neck squamous cell carcinoma, first-line, pembrolizumab, KEYNOTE-048, immuno-oncology, network meta-analysis

ABSTRACT

Pembrolizumab monotherapy or in combination with chemotherapy is approved as first-line treatment in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) based on improved overall survival (OS) versus EXTREME regimen in the KEYNOTE-048 trial. The clinical outcomes of pembrolizumab were compared with other recommended first-line treatments in R/M HNSCC in this study through a Bayesian network meta-analysis. A systematic literature review was conducted in July 2022, from which six trials that matched the KEYNOTE-048 patient eligibility criteria were included in the network. The OS and progression-free survival (PFS) outcomes were compared in the approved pembrolizumab indication (i.e., total population for pembrolizumab in combination with chemotherapy and combined positive score [CPS] ≥ 1 population for pembrolizumab monotherapy). A significant OS improvement was observed for pembrolizumab in combination with chemotherapy and pembrolizumab monotherapy versus EXTREME regimen (hazard ratio, 95% credible interval: 0.72, 0.60-0.86; 0.73, 0.60-0.88), platinum+5-FU (0.58, 0.43-0.76; 0.58, 0.44-0.78), and platinum+paclitaxel (0.53, 0.35-0.79; 0.53, 0.35-0.81), respectively. A non-significant numeric trend in OS improvement was observed versus the TPEx regimen. PFS was comparable with most first-line treatments and was improved versus platinum+5-FU (0.48, 0.36-0.64; 0.59, 0.45-0.79). Additional analyses in higher CPS subgroups also showed consistent results. Overall, our study results showed an improvement in OS outcomes versus alternative first-line treatments, consistent with the findings of the KEYNOTE-048 trial. These data support using pembrolizumab as a suitable first-line treatment option in R/M HNSCC.

Palavras-chave:
inibidores de PARP, câncer de ovário, custos, saúde suplementar

RESUMO

Pembrolizumabe em monoterapia ou em combinação com quimioterapia é aprovado como tratamento de primeira linha em carcinoma de células escamosas recorrente/metastático de cabeça e pescoço (CECCP R/M) com base na melhora da sobrevida global (OS), em comparação com o

Received on: 26/02/2024. **Approved for publication on:** 17/04/2024.
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Information about aid received in the form of financing, equipment, or medicines: AM, DA, and SK are employees of PRECISIONheor, which received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, to produce this work. DC, KR, and RB are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. Rahway, NJ, USA. DC, KR, and RB additionally own stock options from Merck & Co., Inc. Rahway, NJ, USA.
Congresses where the study was presented: American Society of Clinical Oncology (ASCO 2021): Ramakrishnan, K., Mojebi, A., Ayers, D., Chirovsky, D. R., Borse, R., & Keeping, S. (2021). Network meta-analysis (NMA) of pembrolizumab for first-line (1L) treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). DOI: 10.1200/JCO.2021.39.15_suppl.e18012.
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esquema EXTREME no estudo KEYNOTE-048. Esse estudo comparou os resultados clínicos de pembrolizumabe com outros tratamentos recomendados de primeira linha em CECCP R/M por meio de uma metanálise de rede bayesiana. Uma revisão sistemática da literatura foi conduzida em julho de 2022, a partir da qual seis ensaios clínicos que atendiam aos critérios de elegibilidade de pacientes do KEYNOTE-048 foram incluídos na rede. Os desfechos de OS e sobrevida livre de progressão (PFS) foram comparados na indicação de pembrolizumabe (população total para pembrolizumabe em combinação com quimioterapia e população com escore positivo combinado [CPS] ≥ 1 em monoterapia com pembrolizumabe). Foi observada melhora significativa na OS para pembrolizumabe em combinação com quimioterapia e monoterapia com pembrolizumabe *versus* o esquema EXTREME (razão de risco, intervalo de confiança de 95%: 0,72, 0,60-0,86; 0,73, 0,60-0,88), platina+5-FU (0,58, 0,43-0,76; 0,58, 0,44-0,78) e platina+paclitaxel (0,53, 0,35-0,79; 0,53, 0,35-0,81), respectivamente. Uma tendência numérica não significativa de melhoria na OS foi observada em relação ao esquema TPEx. A PFS foi comparável com a maioria dos tratamentos de primeira linha e melhor em relação à platina+5-FU (0,48, 0,36-0,64; 0,59, 0,45-0,79). Análises adicionais em subgrupos com CPS mais elevado também mostraram resultados consistentes. No geral, os resultados de nosso estudo mostraram melhora nos desfechos de OS em comparação aos tratamentos de primeira linha alternativos, consistentes com os achados do estudo KEYNOTE-048. Esses dados apoiam o uso de pembrolizumabe como opção de tratamento em primeira linha em pacientes com CECCP R/M.

Introduction

Head and neck squamous cell carcinoma (HNSCC) was ranked the eighth most common cancer worldwide and accounted for more than 700,000 new cases and 380,000 deaths in 2018 (Bray *et al.*, 2018). While the curative rate is high among patients with early-stage disease, 30% to 45% of those initially diagnosed with locoregionally advanced HNSCC develop disease recurrence within the first year following definitive treatment (Bernier *et al.*, 2004; Denaro *et al.*, 2016; Wang *et al.*, 2013). Prognosis is particularly poor for those who recur after primary treatment for local or locoregionally advanced (LA) disease, as well as those who have already developed metastases by the time they are diagnosed (Winquist *et al.*, 2017).

First-line (1L) treatments for recurrent and/or metastatic (R/M) HNSCC traditionally consisted of chemotherapy with single agents (*e.g.*, platinum, fluorouracil [5-FU], methotrexate) or their combination (*e.g.*, platinum+5-FU) and have been recommended for the 1L treatment of patients with R/M HNSCC (Cohen *et al.*, 2019a; D'Cruz *et al.*, 2013; Gilbert *et al.*, 2015; Machiels *et al.*, 2020; National Comprehensive Cancer Network). Cetuximab with platinum and 5-FU (the EXTREME regimen) was approved by the US Food and Drug Administration (FDA) and recommended by the National Comprehensive Cancer Network (NCCN) for the treatment of patients in this setting (Food and Drug Administration, 2011; National Comprehensive Cancer Network). Median survival with these 1L regimens ranged between 5 and 14.5 months (Forastiere *et al.*, 1992; Gibson *et al.*, 2005; Guigay *et al.*, 2021; Jacobs *et al.*, 1992; Vermorken *et al.*, 2014).

There has been increasing evidence supporting the role of immune checkpoint inhibitors (ICIs), demonstrating durable improvements in survival in the R/M HNSCC population (Forster & Devlin, 2018). Pembrolizumab (Keytruda®), a programmed cell death protein 1 (PD-1) inhibitor, was previously approved by the FDA for the treatment of patients with R/M HNSCC with disease progression on or after platinum-based chemotherapy and by the European Medicines Agency (EMA) for a subgroup of the above patients whose tumors express PD-L1 with a ≥ 50% Tumor Proportion Score (European Medicines Agency, 2019; Food and Drug Administration, 2020). In June 2019, the FDA also approved pembrolizumab (as monotherapy or combined with platinum+5-FU chemotherapy) in the 1L treatment of R/M HNSCC. Pembrolizumab monotherapy is approved in R/M HNSCC whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1), while pembrolizumab with chemotherapy is approved in the overall R/M HNSCC population (Food and Drug Administration, 2020). Pembrolizumab was subsequently approved in other regions, including Europe, Canada, and Japan, for the 1L treatment of R/M HNSCC (Merck, 2019a; 2019b; 2020).

The efficacy of pembrolizumab in the 1L setting, in combination with chemotherapy or as monotherapy, relative to the EXTREME regimen was evaluated in the KEYNOTE-048 trial (unique identifier: NCT02358031) (Burtness *et al.*, 2019). Results of the Final Analysis (data cutoff date: February 25, 2019), showed that pembrolizumab in combination with chemotherapy improved overall survival (OS) relative to the EXTREME regimen in the total population (hazard ratio [HR] 0.77 [95% confidence interval (CI) 0.63-0.93]) as well as the CPS ≥ 1 (HR 0.65 [0.53-0.80]) and CPS ≥ 20 (HR 0.60 [95% CI 0.45-0.82) subgroups. Pembrolizumab monotherapy improved OS relative to the EXTREME regimen in the CPS ≥ 1 subgroup (HR 0.78 [95% CI 0.64-0.96]) and the CPS ≥ 20 subgroups (HR 0.61 [95% CI 0.45-0.83]). Pembrolizumab, either in combination with chemotherapy or as monotherapy, did not improve progression-free survival (PFS) compared to the EXTREME regimen.

Apart from the KEYNOTE-048 trial, head-to-head RCT evidence is lacking for comparisons of pembrolizumab relative to other 1L combination and single-agent treatments for R/M HNSCC. The objective of the current study was to estimate

the comparative efficacy of pembrolizumab relative to 1L treatments through a network meta-analysis (NMA). Trials were identified through a comprehensive systematic literature review (SLR) based on established guidelines to minimize the risk of bias (Moher *et al.*, 2009).

Materials and methods

Systematic literature review

An SLR was conducted to identify relevant RCTs for the 1L treatment of R/M HNSCC (study eligibility PICOS criteria presented in Table 1). The criteria to define the target study population were designed to be consistent with the patient eligibility criteria of the KEYNOTE-048 study (Burtness *et al.*, 2019). Defined as Tier 1 trials, the target population included patients with R/M HNSCC ineligible for curative treatment with no prior systemic treatment administered in either the LA or R/M setting or who have received previous systemic therapy as part of multimodal treatment for LA disease ≥ 6 months before study entry. The study inclusion criteria were also relaxed to include additional RCTs where patients could have received a systemic treatment ≥ 3 months before trial entry (*i.e.*, Tier 2 trials).

Table 1. Study selection criteria to identify trials for the systematic literature review and network meta-analysis

Criteria	Description
Population	*Base case:* • Patients with R/M HNSCC ineligible for curative treatment with no prior systemic therapy administered in either the LA or R/M setting or who have received previous systemic therapy as part of multimodal treatment for LA disease ≥ 6 months before study entry *Sensitivity analysis:* • Patients with R/M HNSCC ineligible for curative treatment with no prior systemic therapy administered in either the LA or R/M setting or who have received previous systemic therapy as part of multimodal treatment for LA disease ≥ 3 months before study entry *Subgroups of interest:* • Combined positive score ≥ 1 (CPS ≥ 1) • Combined positive score ≥ 20 (CPS ≥ 20)
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
	Single agents • Pembrolizumab • Nivolumab • Durvalumab • Cetuximab • Docetaxel • Paclitaxel • Methotrexate • Cisplatin • Carboplatin • 5-FU • Gemcitabine • Capecitabine • Vinorelbine • Afatinib*
	Any of the following interventions alone or in combination with other interventions: • Bleomycin • Ifosfamide • Mitomycin • Tegafur/uracil
Comparators	• Placebo or best supportive care • Any intervention of interest • Any treatment that facilitates an indirect comparison
Outcomes	• Overall survival • Progression-free survival
Study design	• Randomized controlled trials only
Language	• Only studies published in English were included
Time	• Only studies published in or after 1990 were included (in the NMA only)

* Afatinib was included in the scope of the SLR based on NCCN recommendations in platinum-progressed R/M HNSCC.
5-FU, 5-fluorouracil; CPS, Combined Positive Score; HNSCC, head and neck squamous cell carcinoma; LA, locally advanced; NMA, network meta-analysis; R/M, recurrent and/or metastatic.

Treatments of interest for the SLR included those recommended by existing international clinical guidelines (pembrolizumab, various platinum/5-FU/cetuximab/taxane combinations, and single-agent chemotherapies) (D'Cruz *et al.*, 2013; Gilbert *et al.*, 2015; Gregoire *et al.*, 2010; Iglesias Docampo *et al.*, 2018; National Comprehensive Cancer Network; Peyrade *et al.*, 2013) in-class immuno-oncology treatments in phase II or III RCTs (*i.e.*, ipilimumab, durvalumab, tremelimumab), and other systemic treatments (*e.g.*, bleomycin, ifosfamide, mitomycin, tegafur/uracil) that have been used to treat this population, conventionally or in an experimental setting.

Relevant studies were identified by searching Embase, MEDLINE, and Cochrane Central Register of Controlled Trials on July 21, 2022, with predefined search strategies (Supplementary Tables A1-A3). Proceedings of relevant conferences from 2014 through 2022 were also searched (Supplementary Table A4). Two reviewers, working independently, conducted the screening and data extraction stages. The Cochrane Collaboration's Risk of Bias tool (Version 2) was used to assess the quality of studies (Sterne *et al.*, 2019). Following reconciliation between the two investigators at each stage, a third reviewer reached a consensus for any remaining discrepancies. Data were stored and managed in a Microsoft® Excel workbook. The study identification and selection process were summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Page *et al.*, 2021). PRISMA guidelines were followed when reporting the SLR and the NMA results (Hutton *et al.*, 2015). PROSPERO registration was not performed for this review.

Network meta-analysis

Tier 1 and 2 trials identified in the SLR were considered for the NMA. Trials published before 1990 were excluded from the NMAs because investigation procedures, data collection methods, and the general accuracy of the reported data were likely to have been different in those older studies than the ones from the more recent trials. Since race is a potential treatment effect modifier, trials exclusively conducted in the Asian population were also excluded because < 20% of patients in KEYNOTE-048 were Asian.

Efficacy outcomes of interest were OS and PFS endpoints. Reported OS and PFS Kaplan-Meier curves were digitized using the DigitizeIt® software to estimate the proportion of patients with an event and the number of patients at risk over time. The primary NMA focused on the FDA-approved populations for pembrolizumab with chemotherapy (*i.e.*, total population) and pembrolizumab monotherapy (*i.e.*, the PD-L1 CPS ≥ 1 subgroup). Given the improved efficacy of pembrolizumab observed in higher CPS subgroups (CPS ≥ 1 and CPS ≥ 20) within the KEYNOTE-048 trial, the NMA was expanded to include OS and PFS comparisons in the CPS ≥ 1 subgroup for pembrolizumab with chemotherapy and CPS ≥ 20 subgroup for pembrolizumab with chemotherapy and pembrolizumab monotherapy. Individual patient-level data from the KEYNOTE-048 trial were incorporated into the NMA (Burtness *et al.*, 2019). OS, PFS HRs, and Kaplan-Meier data from the total population were incorporated into the NMA for the comparator trials. Given that chemotherapy and cetuximab treatments do not interact with the PD-1/PD-L1 pathway, assuming treatment efficacy from the total population in the CPS ≥ 1 and CPS ≥ 20 subgroup analyses was biologically plausible.

Initial analyses were conducted assuming proportional hazards (constant HRs) between treatments. NMAs of reported HRs in terms of PFS and OS were performed using a regression model with a contrast-based normal likelihood incorporating the log HR (and corresponding standard error) of OS and PFS from each trial (or comparison) in the network, according to Dias *et al.* (Dias *et al.*, 2013). If the closed loops in the network provided indirect evidence, inconsistency was assessed following the approach outlined by Dias *et al.* (Dias *et al.*, 2013). Normal non-informative prior distributions for the parameters were also estimated with a mean of 0 and a variance of 10,000. Additional analyses were conducted to account for any potential violations of the proportional hazards assumption, assuming time-varying HRs, which modeled the log hazards over time as fractional polynomials (Jansen, 2011), allowing for the consideration of the following competing survival distributions: Weibull, Gompertz, and second-order fractional polynomials including p1 = 0 or 1 and p2 = -1, 0.5, 0, 0.5, or 1. These second-order fractional polynomial models are extensions of the Weibull and Gompertz models and allow for arc- and bathtub-shaped hazard functions, which emulate parametric distributions such as log-normal and log-logistic. Fixed and random effects models were considered for estimating constant and time-varying HRs. The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models (Dempster, 1997). A difference in DIC of about 5 points was considered meaningful. Log cumulative hazard plots for both OS and PFS were developed to test the assumption of proportional hazards for the treatment effects.

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the JAGS software package (Plummer, 2003). A first series of iterations from the JAGS sampler were discarded as 'burn-in', the inferences were based on additional iterations using two chains. All analyses were performed using R version 4.2.1 (http://www.r-project.org/) and JAGS version 4.3.1.

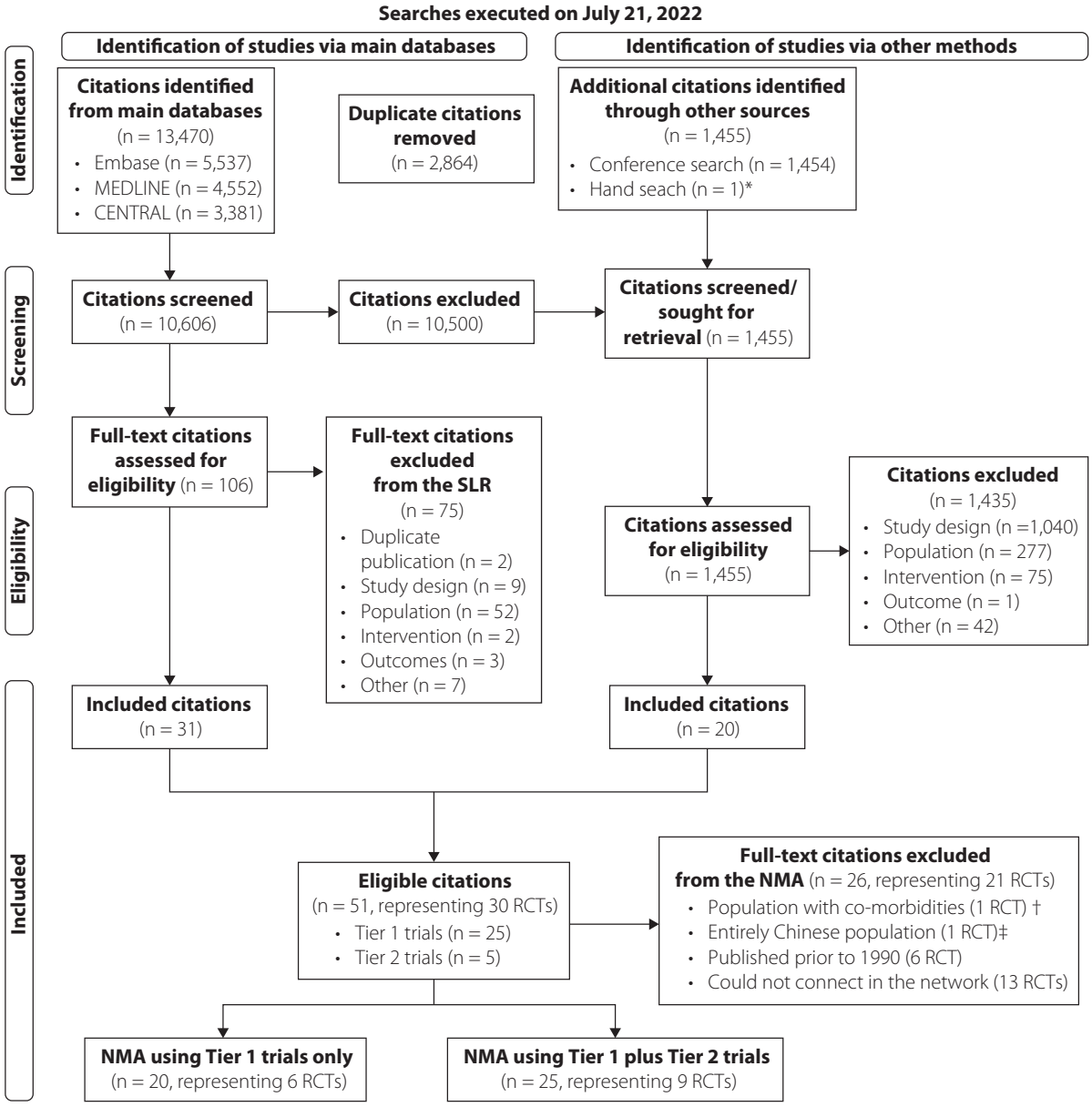
The results of the NMA are presented with estimates for treatment effects of pembrolizumab with chemotherapy and pembrolizumab monotherapy relative to each comparator treatment. The posterior distributions of relative

treatment effects are summarized by the median and 95% credible intervals (CrIs), constructed from the 2.5th and 97.5th percentiles of the posterior distributions. For time-varying HR models, the results of the NMA are presented in terms of HRs in 3-month intervals up until 36 months.

Results

Systematic literature review and network meta-analysis feasibility assessment

The study selection process for the searches to identify RCTs of interest in the SLR and the NMA is outlined in Figure 1. Reviewers had a high degree of agreement when making inclusion/exclusion decisions during full-text screening (80.19% agreement; Cohen's kappa: 0.54). Overall, 51 citations, corresponding to 30 RCTs, were included in the evidence base. Among these studies, 25 RCTs matched the description of Tier 1 trials, while five additional RCTs matched the description of Tier 2 trials. Further evaluation of the Tier 1 and Tier 2 trials was performed for inclusion in the NMA based on trial design, study population characteristics, and whether they evaluated interventions of interest and could be connected to the network. For these reasons, 21 RCTs (18 Tier 1 studies; three Tier 2 studies) were excluded (see Supplementary Table B1 for additional details).

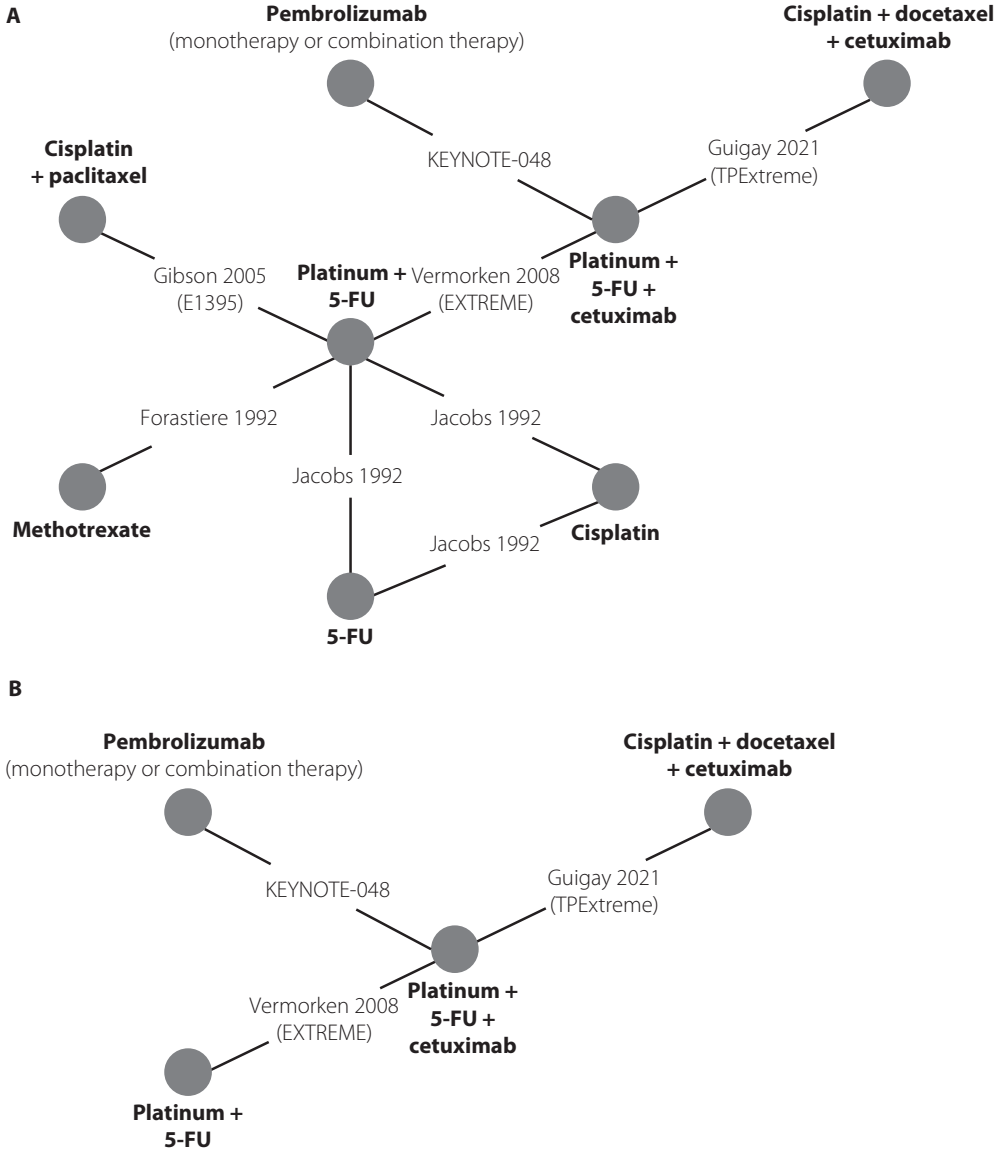


* The citation identified via hand search was Vermorken *et al.*, 2014 (Vermorken *et al.*, 2014).
† Such patients were excluded from KEYNOTE-048.
‡ Less than 20% of patients were Asian in KEYNOTE-048.
NMA, network meta-analysis; RCT, randomized controlled trial; SLR, systematic literature review.

Figure 1. PRISMA flow diagram for the selection of trials included in the network meta-analysis

The NMA was conducted separately using Tier 1 trials only and Tier 1 plus Tier 2 trials. Six RCTs formed a connected network in the OS NMA using Tier 1 trials only (Figure 2-A) (Burtness *et al.*, 2019; Forastiere *et al.*, 1992; Gibson *et al.*, 2005; Guigay *et al.*, 2021; Jacobs *et al.*, 1992; Vermorken *et al.*, 2008). Few comparator trials reported PFS outcomes, limiting data availability to inform the PFS NMA (Figure 2-B). In the OS and PFS NMAs using Tier 1 plus Tier 2 trials, one additional Tier 1 and two Tier 2 RCTs (Bossi *et al.*, 2017; Burtness *et al.*, 2005; Tsakonas *et al.*, 2020) (Supplementary Figures B1-A and B1-B, respectively) were included. Note that the additional Tier 1 trial, Bossi *et al.*, 2017 (Bossi *et al.*, 2017), could only be connected to the network via the additional Tier 2 trials.

The nine included trials were generally considered to have a low risk of bias (Supplementary Figure B2). The trials were largely multicenter RCTs, with the majority being phase III trials, except Guigay *et al.*, 2021 (TPExtreme), Bossi *et al.*, 2017, and Tsakonas *et al.*, 2020 (CETMET), which were phase II studies. All trials had smaller sample sizes compared to KEYNOTE-048 (N = 800); studies generally recruited fewer than 300 patients except for Vermorken *et al.*, 2008 (EXTREME) and Guigay *et al.*, 2021 (TPExtreme), with 442 and 539 patients, respectively. Tsakonas *et al.*, 2020 (CETMET) and Burtness *et al.*, 2005 had the smallest sample sizes, with 85 and 117 patients, respectively. Furthermore, most trials were similar to KEYNOTE-048 concerning the amount of time elapsed since patients' last



Networks of trials were the same for the analyses of pembrolizumab with chemotherapy (within the total population and the Combined Positive Score ≥ 1 and ≥ 20 subgroups) and pembrolizumab monotherapy (within the Combined Positive Score ≥ 1 and ≥ 20 subgroups).
5-FU, fluorouracil.

Figure 2. Network of Tier 1 trials only for the analysis of the (A) overall survival and (B) progression-free survival outcomes

dose of systemic chemotherapy administered in the LA setting, i.e., eligible patients were allowed to have received their last dose ≥ 6 months before trial entry; the only exceptions were Tsakonas *et al.*, 2020 (CETMET) and Burtness *et al.*, 2005, which additionally qualified patients who had received their last dose 3-6 months before study entry.

Around half of the patients had metastatic disease in the overall trial populations, including that of KEYNOTE-048 (70.3%), except for Forastiere *et al.*, 1992 (6.9%) and Jacobs *et al.*, 1992 (10.6%) (percentages calculated relative to the entire sample size of each trial). The rate of HPV-positive patients varied across the trials reporting this characteristic: KEYNOTE-048 (21.5%), Guigay *et al.*, 2021 (TPExtreme) (18.9%), Bossi *et al.*, 2017 (6.8%), and Tsakonas *et al.*, 2020 (CETMET) (30.6%). All populations, including KEYNOTE-048 (100%), predominantly had performance scores of ECOG 0 or 1 (or equivalent Karnofsky scores) (ECOG-ACRIN cancer research group) except Forastiere *et al.*, 1992 and Jacobs *et al.*, 1992, where 28.4% and 38.4% of patients had an ECOG score of 2, respectively. Where reported, baseline demographics (age, sex, and race) were similar, with reported median ages of around 60 years and predominantly male and Caucasian populations (Supplementary Tables B2-B3).

The observed OS and PFS outcomes for trials included in the NMA are summarized in Table 2. Median OS and median PFS ranged from 5 months and 2.7 months, respectively, with single-agent chemotherapies to 14.5 months and 7 months with platinum-based combination regimens.

Given that only one trial was available per comparison (Figures 2-A and 2-B, Supplementary Figures B1-A and B1-B), there was insufficient data to perform the analyses under a random effects model; therefore, all NMAs were performed using fixed effects models. Furthermore, for the analysis using fixed effects models, the log cumulative hazard plots for both OS and PFS suggested violations of the proportional-hazards assumption in KEYNOTE-048 (OS and PFS), Tsakonas *et al.*, 2020 (CETMET) (OS), and Burtness *et al.*, 2005 (PFS) (plots not shown). It was addressed by summarizing time-varying HR estimates. Lastly, inconsistency was not assessed in the NMA using Tier 1 trials only as it contained no closed loops (noting that there cannot be inconsistency within a three-arm trial; therefore, Jacobs 1992 is not considered a closed loop). For the NMA using Tier 1 plus Tier 2 trials, where a closed loop was present, inconsistency was assessed and did not appear to be an issue.

Table 2. Summary of previously reported overall survival and progression-free survival outcomes of trials included in the NMA in the base case analyses (Tier 1 trials) and additional trials included in the sensitivity analyses (Tier 1 + 2 trials)

Study	Phase		Intervention	N	Median OS (months)	OS HR (95% CI)	Maximum follow-up for OS (months)*	Median PFS (months)	PFS HR (95% CI)	Maximum follow-up for PFS (months)*
Base case analyses (Tier 1 trials)										
KEYNOTE-048 (Burtness *et al.*, 2019) (Final Analysis data; data cutoff date: February 25, 2019)	III	Total	P + C	281	13.0	0.72 (0.60-0.86)‡	43	4.9	0.89 (0.75-1.06)‡	40
			EXTREME regimen†	278	10.7		40	5.2		39
		PD-L1 CPS ≥ 1	P + C	242	13.6	0.66 (0.54-0.80)‡	43	5.1	0.82 (0.68-1.00)‡	40
			EXTREME regimen†	235	10.4		40	5.0		39
		PD-L1 CPS ≥ 20	P + C	126	14.7	0.61 (0.46-0.82)‡	42	5.8	0.75 (0.57-0.99)‡	40
			EXTREME regimen†	110	11.0		40	5.3		37
		PD-L1 CPS ≥ 1	P	257	12.3	0.73 (0.60-0.88)‡	45	3.2	1.10 (0.92-1.33)‡	45
			EXTREME regimen†	255	10.3		41	5.0		40
		PD-L1 CPS ≥ 20	P	133	14.8	0.63 (0.48-0.84)‡	45	3.4	0.99 (0.76-1.29)‡	45
			EXTREME regimen†	122	10.7		41	5.3		37
KEYNOTE-048 (Tahara *et al.*, 2022) (5-year data; data cutoff date: February 21, 2022)	III	Total	P + C	281	13.0	0.72 (0.60-0.86)‡	79	4.9	0.91 (0.77-1.08)‡	75
			EXTREME regimen†	278	10.7		75	5.3		69
		PD-L1 CPS ≥ 1	P + C	242	13.6	0.66 (0.55-0.80)‡	79	5.1	0.85 (0.71-1.03)‡	75
			EXTREME regimen†	235	10.6		75	5.0		69
		PD-L1 CPS ≥ 20	P + C	126	14.7	0.64 (0.48-0.84)‡	78	5.8	0.77 (0.59-1.02)‡	75
			EXTREME regimen†	110	11.1		75	5.3		47
		PD-L1 CPS ≥ 1	P	257	12.3	0.73 (0.61-0.88)‡	81	3.2	1.12 (0.94-1.34)‡	77
			EXTREME regimen†	255	10.4		77	5.0		75
		PD-L1 CPS ≥ 20	P	133	14.9	0.66 (0.80-0.86)‡	81	3.4	0.97 (0.75-1.25)‡	77
			EXTREME regimen†	122	10.8		77	5.3		68

Study	Phase	Intervention	N	Median OS (months)	OS HR (95% CI)	Maximum follow-up for OS (months)*	Median PFS (months)	PFS HR (95% CI)	Maximum follow-up for PFS (months)*
EXTREME Vermorken *et al.*, 2014 (Vermorken *et al.*, 2014) (OS data) Vermorken *et al.*, 2008 (Vermorken *et al.*, 2008) (PFS data)	III	The EXTREME regimen	222	10.1	0.80 (0.64-0.99)	60	5.6	0.54 (0.43-0.67)	15
		Platinum + 5-FU	220	7.4		60	3.3		15
Gibson *et al.*, 2005 (E1395) (Gibson *et al.*, 2005)	III	Cisplatin + paclitaxel	100	8.1	1.09 (0.82-1.46)[§]	55	--	--	--
		Platinum + 5-FU	104	8.7		52	--		
Guigay *et al.*, 2021 (TPExtreme) (Guigay *et al.*, 2021)	III	TPEx regimen	269	14.5	0.89 (0.74-1.08)	48	6.0	0.88 (0.74-1.04)	48
		EXTREME regimen	270	13.4		48	6.2		48
Jacobs *et al.*, 1992 (Jacobs *et al.*, 1992)	III	Cisplatin + 5-FU	79	5.5	0.8 (0.59-1.1)[§]	45	--	--	--
		5-FU	83	6.1	1.01 (0.74-1.37)[§]	30	--		
		Cisplatin	83	5.0	versus cisplatin	34	--		
Forastiere *et al.*, 1992 (Forastiere *et al.*, 1992)	III	Cisplatin + 5-FU	87	6.6	0.88 (0.65-1.2)	54	--	--	--
		Carboplatin + 5-FU	86	5.0	0.97 (0.72-1.31)	46	--		
		Methotrexate	88	5.6	versus methotrexate	39	--		
Sensitivity analyses (additional Tier 1 + 2 trials)									
Bossi *et al.*, 2017 (Bossi *et al.*, 2017)[‖]	II	Cisplatin + cetuximab	100	13.0	0.77 (0.53-1.11)	24	6.0	0.99 (0.72-1.36)	24
		Cisplatin + cetuximab + paclitaxel	91	11.0		21	7.0		24
Tsakonas *et al.*, 2020 (CETMET) (Tsakonas *et al.*, 2020)	II	Carboplatin + cetuximab + paclitaxel	43	10.2	0.71 (0.43-1.16)	60	6.5	0.65 (0.41-1.03)	60
		EXTREME regimen	42	8.4		45	4.4		45
Burtness *et al.*, 2005 (Burtness *et al.*, 2005)	III	Cisplatin + cetuximab	57	9.2	0.87 (0.6-1.27)[§]	44	4.2	0.75 (0.52-1.08)[§]	30
		Cisplatin	60	8.0		47	2.7		30

Double dashes indicate that data were not available. The EXTREME regimen consists of platinum + 5-FU + cetuximab. The TPEx regimen consists of cisplatin + docetaxel + cetuximab.

* Approximate value based on the latest time point Kaplan-Meier data were presented at.

† In KEYNOTE-048, enrollment in the pembrolizumab with chemotherapy arm was paused for a safety assessment. The protocol was then amended to exclude the 22 participants randomized to cetuximab + platinum + 5-FU (the "standard treatment") during the pause for the comparison between the pembrolizumab with chemotherapy group and the standard treatment group, and according to the intention-to-treat principle. Therefore, the number of participants in the standard treatment group was 278 compared to pembrolizumab with chemotherapy and 300 compared to pembrolizumab monotherapy.

‡ Unstratified hazard ratios were calculated from individual patient-level data.

§ Hazard ratio was calculated based on the presented Kaplan-Meier curves since it was not directly reported in the publication.

‖ Bossi *et al.*, 2017, was a Tier 1 trial that could only be connected to the network via the Tier 2 trials (see Supplementary Figures B1-A and B1-B). Therefore, it could only be included in the sensitivity (Tier 1+2 trials) analysis.

5-FU, fluorouracil; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; IQR, interquartile range; KPS, Karnofsky performance score; P, pembrolizumab monotherapy; P + C, pembrolizumab with chemotherapy.

Network meta-analysis: pembrolizumab with chemotherapy versus alternative treatments

Network meta-analysis using Tier 1 trials only in the total population

In the total population, OS improvement was observed for pembrolizumab with chemotherapy versus the EXTREME regimen (HR, 95% CrI: 0.72, 0.60-0.86), platinum+5-FU (0.58, 0.43-0.76) and cisplatin+paclitaxel (0.53, 0.35-0.79). Further, a numerical improvement in OS versus the TPEx regimen was observed (0.83, 0.63-1.08), which was not statistically significant (Table 3). The time-varying HR NMA generally showed improved OS HRs over time across all comparisons. Compared with the EXTREME regimen and platinum+5-FU, increased OS benefit was observed starting at approximately 6-9 months, whereas the OS benefit versus the TPEx regimen improved primarily after months 12. OS improvement was also observed while comparing pembrolizumab with chemotherapy versus single-agent chemotherapies (cisplatin, 5-FU, and methotrexate).

Table 3. Estimated overall survival hazard ratios in the base case analysis (Tier 1 trials) for pembrolizumab with chemotherapy in the total population relative to alternative interventions from fixed-effects network meta-analysis using constant proportional hazards and time-varying hazard ratios

	EXTREME regimen*	Platinum + 5-FU†	Cisplatin + paclitaxel‡	TPEx regimen§	Cisplatin‖	5-FU¶	Methotrexate**
	Constant Hazard Ratio (95% Credible Interval)						
	0.72 (0.60-0.86)	**0.58 (0.43-0.76)**	**0.53 (0.35-0.79)**	0.83 (0.63-1.08)	**0.46 (0.30-0.71)**	**0.57 (0.38-0.87)**	**0.50 (0.34-0.74)**
Time point (months)	Time-Varying Hazard Ratio (95% Credible Interval)						
1	1.25 (0.85-1.86)	0.88 (0.51-1.51)	0.77 (0.34-1.76)	1.22 (0.69-2.14)	0.75 (0.33-1.62)	0.78 (0.34-1.70)	0.95 (0.48-1.95)
3	1.04 (0.78-1.40)	0.77 (0.51-1.16)	0.68 (0.36-1.25)	1.06 (0.68-1.63)	0.66 (0.36-1.15)	0.66 (0.37-1.17)	0.75 (0.45-1.28)
6	0.87 (0.70-1.08)	**0.68 (0.50-0.92)**	**0.60 (0.38-0.94)**	0.92 (0.67-1.27)	**0.58 (0.37-0.90)**	**0.57 (0.36-0.87)**	**0.60 (0.40-0.89)**
9	**0.76 (0.63-0.91)**	**0.61 (0.47-0.80)**	**0.54 (0.36-0.80)**	0.83 (0.63-1.09)	**0.52 (0.34-0.80)**	**0.50 (0.32-0.77)**	**0.50 (0.34-0.73)**
12	**0.67 (0.56-0.81)**	**0.57 (0.43-0.74)**	**0.50 (0.33-0.76)**	**0.76 (0.58-0.99)**	**0.48 (0.30-0.78)**	**0.45 (0.27-0.74)**	**0.43 (0.28-0.67)**
15	**0.60 (0.49-0.75)**	**0.53 (0.39-0.71)**	**0.46 (0.29-0.76)**	**0.70 (0.52-0.93)**	**0.45 (0.25-0.79)**	**0.41 (0.23-0.75)**	**0.37 (0.23-0.63)**
18	**0.55 (0.43-0.70)**	**0.49 (0.35-0.70)**	**0.43 (0.25-0.77)**	**0.65 (0.46-0.91)**	**0.42 (0.22-0.82)**	**0.38 (0.19-0.77)**	**0.33 (0.19-0.61)**
21	**0.50 (0.38-0.67)**	**0.46 (0.31-0.69)**	**0.41 (0.21-0.79)**	**0.61 (0.41-0.90)**	**0.39 (0.18-0.85)**	**0.35 (0.16-0.80)**	**0.30 (0.15-0.60)**
24	**0.47 (0.34-0.64)**	**0.44 (0.28-0.69)**	**0.38 (0.19-0.81)**	**0.57 (0.37-0.89)**	**0.37 (0.16-0.89)**	**0.33 (0.13-0.82)**	**0.27 (0.13-0.60)**
27	**0.43 (0.30-0.62)**	**0.41 (0.25-0.69)**	**0.36 (0.16-0.84)**	**0.54 (0.33-0.88)**	**0.35 (0.14-0.94)**	**0.31 (0.11-0.85)**	**0.24 (0.11-0.59)**
30	**0.40 (0.27-0.60)**	**0.39 (0.22-0.69)**	**0.35 (0.14-0.87)**	**0.51 (0.29-0.88)**	**0.33 (0.12-0.98)**	**0.29 (0.10-0.89)**	**0.22 (0.09-0.59)**
33	**0.38 (0.24-0.58)**	**0.37 (0.20-0.69)**	**0.33 (0.12-0.90)**	**0.49 (0.27-0.88)**	0.32 (0.10-1.02)	**0.27 (0.08-0.92)**	**0.20 (0.08-0.58)**
36	**0.35 (0.22-0.57)**	**0.36 (0.18-0.69)**	**0.32 (0.11-0.94)**	**0.46 (0.24-0.88)**	0.30 (0.09-1.07)	**0.26 (0.07-0.95)**	**0.19 (0.07-0.58)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
* The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
† Survival data were available for platinum + 5-FU through month 36 (inclusive).
‡ Survival data were available for cisplatin + paclitaxel through month 36 (inclusive).
§ The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 36 (inclusive).
‖ Survival data were available for cisplatin through month 33 (inclusive).
¶ Survival data were available for 5-FU through month 27 (inclusive).
** Survival data were available for methotrexate through month 36 (inclusive).
5-FU, fluorouracil.

PFS was improved for pembrolizumab with chemotherapy in the total population compared to platinum+5-FU (HR, 95% CrI: 0.48, 0.36-0.64) and comparable to other treatments (Table 4). The time-varying HR NMA generally showed PFS improvement over time for pembrolizumab with chemotherapy versus alternative treatments. However, PFS improvement was less pronounced compared with the TPEx regimen.

Network meta-analysis using Tier 1 trials only in the CPS ≥ 1 and CPS ≥ 20 population

In the CPS ≥ 1 and CPS ≥ 20 subgroups, the OS benefit of pembrolizumab with chemotherapy relative to the alternative treatments was enhanced, with OS benefit generally observed at earlier time points compared to the total population (Supplementary Tables C1-C2). A more pronounced PFS benefit for pembrolizumab with chemotherapy was observed in comparison with alternative treatments in the CPS ≥ 1 and CPS ≥ 20 subgroups relative to the total population (Supplementary Tables C3-C4).

Network meta-analysis using Tier 1 plus Tier 2 trials in the total, CPS ≥ 1, and CPS ≥ 20 populations

Results were consistent with the Tier 1 NMA results (Supplementary Table D1). For the additional comparisons, the point estimates

Table 4. Estimated progression-free survival hazard ratios in the base case analysis (Tier 1 trials) for pembrolizumab with chemotherapy in the total population relative to alternative interventions from fixed-effects network meta-analysis using constant proportional hazards and time-varying hazard ratios

	EXTREME regimen*	Platinum + 5-FU†	TPEx regimen‡
	Constant Hazard Ratio (95% Credible Interval)		
	0.89 (0.75-1.06)	**0.48 (0.36-0.64)**	1.01 (0.79-1.30)
Time point (months)	Time-Varying Hazard Ratio (95% Credible Interval)		
1	**1.59 (1.04-2.42)**	0.88 (0.45-1.73)	1.49 (0.81-2.78)
3	1.08 (0.87-1.34)	**0.60 (0.44-0.83)**	1.16 (0.84-1.60)
6	0.84 (0.71-1.00)	**0.48 (0.35-0.65)**	0.99 (0.77-1.26)
9	**0.73 (0.59-0.91)**	**0.41 (0.28-0.63)**	0.90 (0.67-1.21)
12	**0.66 (0.51-0.86)**	**0.37 (0.23-0.63)**	0.84 (0.59-1.20)
15	**0.61 (0.45-0.83)**	**0.35 (0.20-0.63)**	0.80 (0.53-1.20)
18	**0.57 (0.41-0.81)**	**0.33 (0.17-0.63)**	0.77 (0.48-1.21)
21	**0.54 (0.38-0.79)**	**0.31 (0.15-0.64)**	0.74 (0.45-1.22)
24	**0.52 (0.35-0.77)**	**0.30 (0.14-0.64)**	0.72 (0.42-1.23)
27	**0.50 (0.33-0.76)**	**0.28 (0.13-0.64)**	0.70 (0.39-1.24)
30	**0.48 (0.31-0.75)**	**0.27 (0.12-0.65)**	0.68 (0.37-1.25)
33	**0.46 (0.29-0.74)**	**0.26 (0.11-0.65)**	0.67 (0.35-1.26)
36	**0.45 (0.28-0.73)**	**0.26 (0.10-0.65)**	0.65 (0.34-1.27)

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
* The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
† Survival data were available for platinum + 5-FU through month 15 (inclusive).
‡ The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available for platinum + 5-FU through month 36 (inclusive).
5-FU, fluorouracil.

of OS HR favored pembrolizumab with chemotherapy relative to cisplatin+cetuximab (HR, 95% CrI: 0.78, 0.50-1.22) and platinum+cetuximab+paclitaxel (0.72, 0.47-1.12) in the total population, although results were not statistically significant, with similar results in the CPS ≥ 1 and CPS ≥ 20 subgroups. Progression-free survival was comparable to these treatments in the total population and according to CPS subgroups.

The results of these additional comparisons should be interpreted with caution given that two of the three additional trials included in this scenario, i.e., Tsakonas *et al.*, 2020 (CETMET) and Burtness *et al.*, 2005, had smaller sample sizes and allowed for shorter treatment-free durations before study entry compared to KEYNOTE-048, as previously noted.

Network meta-analysis: pembrolizumab monotherapy versus alternative treatments

Network meta-analysis using Tier 1 trials only in the CPS ≥ 1 population

In the CPS ≥ 1 subgroup, OS improvement was observed for pembrolizumab monotherapy versus the EXTREME regimen (HR, 95% CrI: 0.73, 0.60-0.88), platinum+5-FU (0.58, 0.44-0.78) and cisplatin+paclitaxel (0.53, 0.35-0.81). Further, a numerical improvement in OS versus the TPEx regimen was observed (0.84, 0.64-1.10), which was not statistically significant (Table 5). The time-varying HR NMA generally showed improved OS over time across all comparisons. For the comparisons with the EXTREME regimen, platinum+5-FU, and cisplatin+paclitaxel,

increased OS benefit was observed starting at approximately 6-9 months, whereas, for the TPEx regimen, OS benefit improved primarily after month 12. OS improvement was also observed when pembrolizumab was compared to single-agent chemotherapies (cisplatin, 5-FU, and methotrexate).

PFS was improved for pembrolizumab monotherapy in the CPS ≥ 1 subgroup in comparison with platinum+5-FU (HR, 95% CrI: 0.59, 0.45-0.79) and comparable versus other treatments (Table 6). The time-varying HR NMA generally showed PFS improvement over time for pembrolizumab monotherapy versus alternative treatments.

Network meta-analysis using Tier 1 trials only in the CPS ≥ 20 population

In the CPS ≥ 20 subgroup, the OS benefit of pembrolizumab monotherapy relative to the alternative treatments was enhanced compared to the CPS ≥ 1 subgroup (Supplementary Table C5). A slightly more pronounced PFS benefit for pembrolizumab monotherapy was observed compared to alternative treatments in the CPS ≥ 20 subgroup relative to the CPS ≥ 1 subgroup (Supplementary Table C6).

Table 5. Estimated overall survival hazard ratios in the base case analysis (Tier 1 trials) for pembrolizumab monotherapy in the PD-L1 CPS ≥ 1 subgroup relative to alternative interventions from fixed-effects network meta-analysis using constant proportional hazards and time-varying hazard ratios

	EXTREME regimen*	Platinum + 5-FU†	Cisplatin + paclitaxel‡	TPEx regimen§	Cisplatin‖	5-FU¶	Methotrexate**
				Constant Hazard Ratio (95% Credible Interval)			
	0.73 (0.60-0.88)	**0.58 (0.44-0.78)**	**0.53 (0.35-0.81)**	0.84 (0.64-1.10)	**0.47 (0.31-0.72)**	**0.58 (0.38-0.89)**	**0.51 (0.35-0.76)**
Time point (months)				Time-Varying Hazard Ratio (95% Credible Interval)			
1	**1.68 (1.01-2.83)**	1.11 (0.54-2.26)	0.95 (0.31-2.92)	1.53 (0.72-3.25)	1.15 (0.41-3.19)	1.05 (0.37-2.96)	1.43 (0.57-3.63)
3	1.10 (0.81-1.48)	0.81 (0.53-1.23)	0.71 (0.37-1.34)	1.11 (0.71-1.73)	0.74 (0.42-1.33)	0.71 (0.39-1.26)	0.81 (0.48-1.39)
6	0.84 (0.68-1.03)	**0.67 (0.50-0.89)**	**0.59 (0.38-0.90)**	0.90 (0.66-1.22)	**0.56 (0.37-0.86)**	**0.55 (0.36-0.85)**	**0.57 (0.38-0.85)**
9	**0.72 (0.59-0.86)**	**0.59 (0.45-0.78)**	**0.53 (0.35-0.79)**	0.80 (0.60-1.05)	**0.48 (0.31-0.75)**	**0.47 (0.30-0.75)**	**0.46 (0.31-0.70)**
12	**0.64 (0.52-0.79)**	**0.55 (0.41-0.73)**	**0.49 (0.31-0.76)**	**0.73 (0.55-0.98)**	**0.42 (0.26-0.71)**	**0.43 (0.25-0.73)**	**0.40 (0.25-0.63)**
15	**0.59 (0.47-0.74)**	**0.51 (0.37-0.70)**	**0.46 (0.28-0.76)**	**0.69 (0.50-0.94)**	**0.39 (0.22-0.69)**	**0.39 (0.22-0.72)**	**0.35 (0.21-0.60)**
18	**0.55 (0.42-0.71)**	**0.49 (0.34-0.69)**	**0.44 (0.25-0.77)**	**0.65 (0.46-0.92)**	**0.36 (0.19-0.69)**	**0.37 (0.19-0.73)**	**0.32 (0.18-0.58)**
21	**0.52 (0.39-0.68)**	**0.47 (0.31-0.69)**	**0.42 (0.23-0.78)**	**0.62 (0.43-0.91)**	**0.34 (0.17-0.68)**	**0.35 (0.17-0.74)**	**0.30 (0.16-0.56)**
24	**0.49 (0.36-0.66)**	**0.45 (0.29-0.68)**	**0.41 (0.21-0.79)**	**0.60 (0.40-0.90)**	**0.32 (0.15-0.69)**	**0.33 (0.15-0.74)**	**0.28 (0.14-0.55)**
27	**0.47 (0.34-0.64)**	**0.43 (0.27-0.68)**	**0.39 (0.19-0.81)**	**0.58 (0.37-0.90)**	**0.31 (0.14-0.69)**	**0.32 (0.14-0.75)**	**0.26 (0.13-0.54)**
30	**0.45 (0.32-0.63)**	**0.42 (0.26-0.68)**	**0.38 (0.18-0.82)**	**0.56 (0.35-0.89)**	**0.29 (0.13-0.69)**	**0.30 (0.13-0.75)**	**0.25 (0.12-0.53)**
33	**0.43 (0.30-0.62)**	**0.41 (0.24-0.68)**	**0.37 (0.16-0.83)**	**0.54 (0.33-0.89)**	**0.28 (0.12-0.69)**	**0.29 (0.12-0.76)**	**0.23 (0.11-0.52)**
36	**0.42 (0.29-0.61)**	**0.40 (0.23-0.68)**	**0.37 (0.16-0.85)**	**0.53 (0.32-0.89)**	**0.27 (0.11-0.69)**	**0.29 (0.11-0.76)**	**0.22 (0.10-0.52)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
* The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
† Survival data were available for platinum + 5-FU through month 36 (inclusive).
‡ Survival data were available for cisplatin + paclitaxel through month 36 (inclusive).
§ The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 36 (inclusive).
‖ Survival data were available for cisplatin through month 33 (inclusive).
¶ Survival data were available for 5-FU through month 27 (inclusive).
** Survival data were available for methotrexate through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score; PD-L1; program death ligand 1.

Table 6. Estimated progression-free survival hazard ratios in the base case analysis (Tier 1 trials) for pembrolizumab monotherapy in the PD-L1 CPS ≥ 1 subgroup relative to alternative interventions from fixed-effects network meta-analysis using constant proportional hazards and time-varying hazard ratios

	EXTREME regimen*	Platinum + 5-FU†	TPEx regimen‡
	Constant Hazard Ratio (95% Credible Interval)		
	1.10 (0.91-1.32)	**0.59 (0.45-0.79)**	1.25 (0.97-1.62)
Time point (months)	Time-Varying Hazard Ratio (95% Credible Interval)		
1	**2.12 (1.58-2.83)**	1.10 (0.69-1.73)	**2.14 (1.43-3.23)**
3	**1.59 (1.27-2.00)**	0.86 (0.61-1.20)	**1.69 (1.22-2.33)**
6	0.99 (0.83-1.20)	**0.58 (0.43-0.79)**	1.14 (0.88-1.47)
9	**0.68 (0.53-0.86)**	**0.42 (0.27-0.67)**	0.83 (0.61-1.12)
12	**0.49 (0.36-0.68)**	**0.32 (0.17-0.61)**	**0.63 (0.43-0.94)**
15	**0.37 (0.25-0.56)**	**0.26 (0.12-0.57)**	**0.50 (0.31-0.82)**
18	**0.29 (0.18-0.47)**	**0.21 (0.08-0.54)**	**0.41 (0.23-0.73)**
21	**0.24 (0.14-0.40)**	**0.17 (0.06-0.52)**	**0.34 (0.18-0.66)**
24	**0.19 (0.11-0.35)**	**0.15 (0.05-0.49)**	**0.29 (0.14-0.61)**
27	**0.16 (0.08-0.31)**	**0.13 (0.04-0.48)**	**0.25 (0.11-0.56)**
30	**0.14 (0.07-0.28)**	**0.11 (0.03-0.46)**	**0.22 (0.09-0.52)**
33	**0.12 (0.05-0.25)**	**0.10 (0.02-0.45)**	**0.19 (0.07-0.49)**
36	**0.10 (0.04-0.23)**	**0.09 (0.02-0.43)**	**0.17 (0.06-0.46)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
* The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
† Survival data were available for platinum + 5-FU through month 15 (inclusive).
‡ The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available for platinum + 5-FU through month 36 (inclusive). v
5-FU, fluorouracil; CPS, Combined Positive Score; PD-L1; program death ligand 1.

Network meta-analysis using Tier 1 plus Tier 2 trials in the CPS ≥ 1 and CPS ≥ 20 populations

Results were consistent with the Tier 1 NMA results (Supplementary Table D1). For the additional comparisons, the point estimates of OS HR favored pembrolizumab monotherapy relative to cisplatin+cetuximab (HR, 95% CrI: 0.79, 0.51-1.24) and platinum+cetuximab+paclitaxel (0.73, 0.47-1.14) in the CPS ≥ 1 subgroup, although results were not statistically significant, with similar results in the CPS ≥ 20 subgroup. Progression-free survival results favored platinum+cetuximab+paclitaxel in the CPS ≥ 1 subgroup, whereas they were similar for pembrolizumab monotherapy in the CPS ≥ 20 subgroup; results were comparable for cisplatin+cetuximab in both CPS subgroups. As stated earlier, the results of these additional comparisons should be interpreted with caution.

Discussion

Survival outcomes associated with historical 1L treatment options for patients with R/M HNSCC have been poor, highlighting the unmet need in this patient population. The most recent prospective clinical trial demonstrating a significant OS benefit was the EXTREME trial, which reported a median OS of 10.1 months for the EXTREME regimen (Vermorken *et al.*, 2008). Most recently, ICIs with antibodies against PD-1 and PD-L1 have demonstrated durable survival benefits in the R/M HNSCC population (Forster & Devlin, 2018). In the KEYNOTE-048 trial, pembrolizumab as monotherapy and in combination with platinum+5-FU chemotherapy significantly improved OS in the CPS ≥ 1 and total R/M HNSCC populations, respectively, and was approved by the FDA as the 1L

treatment in these patient populations. While the EXTREME regimen has been historically considered the standard of care in 1L treatment of R/M HNSCC, other systemic treatment options primarily consisting of platinum-based combination regimens are also commonly used. However, there is a lack of head-to-head trial comparisons across these treatments.

We synthesized the existing evidence on the efficacy of systemic treatment options in this population with the primary objective of evaluating how pembrolizumab (either with chemotherapy or as monotherapy) compared against alternative platinum-based combination regimens or single-agent chemotherapies regarding OS and PFS outcomes. Results were summarized for the total population, the CPS ≥ 1 and CPS ≥ 20 subgroups for pembrolizumab with chemotherapy, and for the CPS ≥ 1 and CPS ≥ 20 subgroups for pembrolizumab monotherapy versus alternative 1L treatments. Although results have been published for the CPS 1-19 subgroup from KEYNOTE-048 (Burtness *et al.*, 2020), it was not used in the NMA as it was not a pre-specified endpoint in the trial.

The NMA showed OS improvements in the total population with pembrolizumab with chemotherapy relative to other recommended 1L treatments. These OS improvements were enhanced in the NMA within the CPS ≥ 1 and CPS ≥ 20 subpopulations. We reached the same conclusions regarding OS improvements with pembrolizumab monotherapy compared to other treatments within the CPS ≥ 1 subgroup, which were also enhanced in the NMA within the CPS ≥ 20 subgroup. Regarding the PFS outcome, pembrolizumab with chemotherapy and pembrolizumab monotherapy showed improvement relative to platinum+5-FU and was comparable to the EXTREME and the TPEx regimens (*i.e.*, results were not statistically significant). Given the recently published 5-year follow-up KEYNOTE-048 data (data cutoff date: February 21, 2022) (Tahara *et al.*, 2022), a sensitivity analysis incorporating that data cut was also conducted, where NMA results were consistent in terms of the direction and magnitude of the estimated HRs and 95% CrIs of pembrolizumab regimens versus comparator treatments (Supplementary Tables E1-E4). These NMA results could be used in cost-effectiveness analyses comparing the cost outcomes of pembrolizumab with other 1L treatments used in R/M HNSCC.

Results from the current NMA align with the results of the KEYNOTE-048 trial, where considerable OS benefit, with no improvement in PFS, was observed with pembrolizumab compared to the EXTREME regimen (Burtness *et al.*, 2019). The observed survival benefit was explained due to response durability and partially by a subset of patients who remained progression-free at three years. Further, it was hypothesized that early exposure to pembrolizumab might have resulted in durable changes to the tumor microenvironment, which could sensitize the tumor and improve outcomes with subsequent therapies (Burtness *et al.*, 2019).

The trials included in the current NMA were generally of high quality and were similar in study design, although some had relatively small sample sizes. While there were well over 250 patients in each treatment arm of KEYNOTE-048, for other comparator trials, the entire population comprised under 250 patients, which may have likely impacted the comparisons versus pembrolizumab. It also has particular importance when interpreting the results of the NMAs using Tier 1 plus Tier 2 trials, which additionally included Burtness *et al.*, 2005, and Tsakonas *et al.*, 2020 (CETMET), as these trials had smaller sample sizes and allowed for shorter treatment-free durations before study entry compared to KEYNOTE-048. Moreover, while baseline demographics were similarly distributed among the trials, there were some differences in the distribution of potential effect modifiers such as metastatic disease (Cadoni *et al.*, 2017; Leoncini *et al.*, 2015), performance status (Wang *et al.*, 2016) and HPV status (Argiris *et al.*, 2014). Lastly, using ICI as subsequent therapy may improve OS outcomes in patients receiving 1L chemotherapy (Cohen *et al.*, 2019b; Ferris *et al.*, 2016). However, no other trials reported information on ICI subsequent therapies except for KEYNOTE-048 (Burtness *et al.*, 2019) and TPExtreme (Guigay *et al.*, 2021). Of note, Bossi *et al.*, 2017 (a Tier 2 trial) completed patient enrollment in September 2016, which makes it likely to have included a small proportion of patients who received ICIs as subsequent therapy. Overall, the qualitative assessment of trial characteristics, patient eligibility criteria, study populations, and outcome definitions showed that the included trials were sufficiently similar and that no major difference across the studies could subject the NMA results to bias.

Recent trials of 1L immunotherapy in the R/M HNSCC population, such as RESGEX (cisplatin + 5-FU + tomuzotuximab) (Klinghammer *et al.*, 2021), CeFCiD (cisplatin + 5-FU + cetuximab + docetaxel) (Klinghammer *et al.*, 2019), Forster *et al.*, 2019 (platinum + cetuximab + patritumab) (Forster *et al.*, 2019) and CheckMate 651 (nivolumab + ipilimumab) (Argiris *et al.*, 2021), were identified in our SLR. However, as of this publication, these experimental treatments were not recommended for the 1L indication by any of the current treatment guidelines. Therefore, none of these trials were of interest to this NMA.

We identified some published NMAs of 1L treatments in the R/M HNSCC population. In the study by Jin *et al.* (Jin *et al.*, 2020), 1L treatments were evaluated regardless of whether international guidelines recommended them for the target population; as such, trials of non-recommended treatments such as panitumumab, bevacizumab, and patritumab were included in the network in addition to those included in the current NMA. Of note, Jacobs *et al.*, 1992; Forastiere *et al.*, 1992; and Gibson *et al.*, 2005 (E1395) were not included in the analysis by Jin *et al.* The authors concluded that pembrolizumab with chemotherapy was likely to be the best 1L treatment regarding the OS outcome.

In the other NMAs (Al-Showbaki *et al.*, 2021; Botticelli *et al.*, 2021; Wang *et al.*, 2021), KEYNOTE-048, which is an RCT of 1L treatments, was included in the same networks as RCTs of second-line (2L) treatments such as KEYNOTE-040 (Cohen *et al.*, 2019b) and CheckMate 141 (Ferris *et al.*, 2016). Therefore, NMAs were subject to a high risk of bias, as previous treatment experience is an important effect modifier and should be consistent across the analyzed trials. Botticelli *et al.*, 2021 (Botticelli *et al.*, 2021) investigated the efficacy of PD-1 inhibitors versus PD-L1 inhibitors in the R/M HNSCC population (regardless of line of treatment), focusing on treatment classes rather than individual treatments. The authors found no significant difference in OS between PD-1 and PD-L1 inhibitors across different patient subgroups, except for those with metastatic disease in whom PD-1 inhibitor-based treatment was associated with significantly less risk of death. In the study by Wang *et al.* (Wang *et al.*, 2021), only those treatments recommended by the NCCN guidelines were included. Results suggested that OS and PFS were comparable between pembrolizumab and most other therapies; however, these results have limitations given the mentioned heterogeneity in trial populations. Lastly, Al-Showbaki *et al.*, 2021 (Al-Showbaki *et al.*, 2021), investigated the differential efficacy of single-agent PD-1/PD-L1 inhibitors in patients with solid cancers. The target population was substantially heterogeneous regarding disease area (various oncology conditions) and prior treatment experience (1L and 2L treatments), requiring heavy assumptions about the even distributions of these important effect modifiers. Furthermore, a treatment effect was derived between pembrolizumab [KEYNOTE-048 (Burtness *et al.*, 2019)] and nivolumab [CheckMate 141 (Ferris *et al.*, 2016)] even though their corresponding clinical trials did not share a common comparator arm: the control arm was investigator's choice of methotrexate, docetaxel, or cetuximab in CheckMate 141 and the EXTREME regimen in KEYNOTE-048. As such, nivolumab and pembrolizumab could not have been 'connected' within the network, and therefore, the derived comparative efficacy estimate is not valid and is misleading for clinical decision-making.

Our study has several strengths and limitations. Among the strengths is the robust methodology used in the SLR, which aligned with the published guidelines. Risk of bias assessment was performed 'within' each study using the Cochrane Collaboration's Risk of Bias tool (Version 2) (Sterne *et al.*, 2019), which showed that the included publications were of high quality (e.g., low risk of selective reporting). We also searched all possible sources (main databases, proceedings of relevant conferences since 2014, bibliography of published SLRs) to identify associated publications of the included trials that may have reported additional results as well as any smaller studies that may have remained unpublished because their results were not statistically significant, aiming to reduce risk of bias due to non-reporting or under-reporting. Since each pairwise comparison in our network was informed by a single RCT, variability of the observed treatment effects for pairs of interventions could not be assessed, and a formal risk of bias assessment (*e.g.*, tests to examine funnel plots asymmetry) could not be conducted. We acknowledge that publication bias is likely because trials that fail (*i.e.*, do not meet their primary endpoints) are less likely to be published, which is a limitation of all SLRs. Furthermore, while every attempt was made to ensure all relevant trial data were captured by performing a comprehensive search of relevant databases and proceedings of recent conferences, any data published or indexed after the search date may not have been captured in the evidence base, which is another limitation of all SLRs. Lastly, the current SLR was restricted to citations published in English; therefore, publications in other languages may not have been captured.

Another strength of our study was using models for time-varying HRs in the NMA. We used a multivariate treatment-effect measure that described how HR develops over time, in contrast to the constant HR model, a univariate treatment-effect measure. Methods for NMA of survival data using a multi-dimensional or multivariate treatment effect have been presented by Ouwens *et al.* and Jansen as an alternative to synthesizing one treatment effect (e.g., the constant HRs) (Jansen, 2011; Ouwens *et al.*, 2010). The advantage of the resulting NMA model is that it fits more closely to the available data by relaxing the proportional hazards assumption and incorporating additional parameters for the treatment effect.

Another limitation of our NMA was that only one RCT informed each direct pairwise comparison in the network. The small sample size of the trials and the small number of trials informing the direct comparisons led to a relatively small amount of data being available for each comparison; as a result, the estimated HRs had wider CrIs (i.e., higher uncertainty). The location of these small trials within the network is also noteworthy; specifically, the large EXTREME and KEYNOTE-048 trials are directly connected, which leads to precise estimates, while the other comparisons are made across many nodes, which are constructed from the smaller trials. Thus, estimates of relative efficacy are less precise due to both the distance from the pembrolizumab arms and the imprecision inherent in the smaller trials. Since the treatments within the network were only connected via single trials, performing a meta-regression to adjust for the above-mentioned differences was not feasible. Lastly, survival data for comparator treatments had to be extrapolated beyond the last time point at which actual data were available before treatment effects could be derived. Results from the NMAs using the KEYNOTE-048 Final Analysis data were estimated up to month 36 (representing three years of follow-up data for the pembrolizumab regimens). Most comparator treatments had sufficient observed data for these analyses, and OS data only needed to be extrapolated for monotherapies

with cisplatin (beyond month 33) and 5-FU (month 27) (Table 3). On the other hand, in the NMAs incorporating 5-year follow-up KEYNOTE-048 data, where results were estimated up to month 72, OS data had to be extrapolated for longer periods for treatments with shorter available follow-up durations, such as the TPEx regimen (beyond month 42) and monotherapies with 5-FU (month 24), cisplatin (month 30) and methotrexate (month 36) (Supplementary Table C1). This is a limitation of these analyses and time-varying HRs calculated for time points beyond the observed trial data should be interpreted with caution.

Conclusion

Our study showed that pembrolizumab, either with chemotherapy or as monotherapy, improved OS and had comparable PFS outcomes versus alternative 1L treatments for R/M HNSCC, consistent with the efficacy results in the KEYNOTE-048 trial. Future NMAs should consider additional trials of interest, providing more data to the current NMA, potentially leading to a more extensive network of trials, and allowing for some differences in baseline patient characteristics to be accounted for across the included trials.

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Supplementary Material

Supplementary Appendix A. Literature search strategies and study eligibility criteria for the systematic literature review and network meta-analysis

Supplementary Table A1. Search strategy for Embase

Line	Search term	Hits
1	exp head cancer/	1,810
2	exp neck cancer/	4,203
3	((head and neck neoplasms) or (head and neck squamous cell carcinoma) or (head and neck cancer) or HNSCC or HNC or SCCHN).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	90,368
4	or/1-3	93,050
5	exp pembrolizumab/	27,686
6	(pembrolizumab or MK-3475 or MK3475 or SCH-90047 or SCH 900475 or lambrolizumab or keytruda).mp.	29,206
7	exp nivolumab/	29,499
8	(nivolumab or ONO-4538 or ONO4538 or BMS-936558 or BMS936558 or MDX-1106 or MDX 1106 or opdivo).mp.	30,917
9	exp ipilimumab/	20,173
10	(ipilimumab or MDX-CTLA-4 or MDXCTLA4 or BMS-734016 or BMS734016 or MDX-010 or MDX010 or yervoy).mp.	21,010
11	exp durvalumab/	7,339
12	(durvalumab or MEDI-4736 or MEDI4736).mp.	7,658
13	exp tremelimumab/	3,357
14	(tremelimumab or ticilimumab or CP-675 or CP675 or CP-206 or CP206).mp.	3,458
15	exp cetuximab/	31,525
16	(cetuximab or C-225 or C225 or IMC-C225 or erbitux).mp.	33,037
17	exp docetaxel/	67,250
18	(docetaxel or taxotere or docecad or RP 56976).mp.	69,625
19	exp paclitaxel/	122,336
20	(paclitaxel or nab-paclitaxel or abraxane or taxol or onxol).mp.	129,572
21	exp methotrexate/	196,514
22	(methotrexate or rheumatrex or trexall or mtx or amethopterin).mp.	205,943
23	exp bleomycin/	52,404
24	(bleomycin or blenoxane or bleo 15k or bleotex or nisbleo or bledmax or bleocare or bleocel or bleochem or bleocin or bleocip or bleolem or bleonco or tumocin).mp.	55,107
25	exp mitomycin/	23,027
26	(mitomycin or mutamycin or mitocin or almito or mitodus or mitonco or oncocin).mp.	50,409
27	exp ifosfamide/	33,129
28	(ifosfamide or iphosphamide or ifex or celofos or holoxan or ifocip or ifoneon or ifos or ipamide or ipoget).mp.	34,140
29	exp tegafur/	6,931
30	(tegafur or fimer or furil or tefudex or teroful or tegracil or uft or ufur or unitoral).mp.	17,001
31	exp cisplatin/	204,643
32	(cisplatin or cisplatinum or cis-platinum or platamin or neoplatin or cismaplat or cis-maplat).mp.	214,819
33	exp carboplatin/	79,526
34	(carboplatin or paraplatin or paraplatin-aq).mp.	82,306
35	exp 5-FU/	150,511
36	(fluorouracil or adrucil or 5-FU).mp.	56,553
37	exp gemcitabine/	65,979

Line	Search term	Hits
38	(gemcitabine or LY-188011 or LY188011 or gemzar).mp.	68,474
39	exp capecitabine/	34,103
40	(capecitabine or Ro 09-1978 or Ro09-1978 or xeloda).mp.	36,575
41	exp vinorelbine/	4,350
42	(vinorelbine or vinorelbine ditatrate or KW-2307 or KW2307 or navelbine).mp.	20,105
43	exp afatinib/	7,029
44	(afatinib or BIBW-2992-MA2 or BIBW 2992 MA2 or gilotrif).mp.	7,295
45	or/5-44	771,743
46	clinical trial/	1,039,874
47	randomized controlled trial/	718,648
48	randomization/	94,417
49	single blind procedure/	46,932
50	double blind procedure/	196,941
51	crossover procedure/	70,941
52	placebo/	382,943
53	randomi?ed controlled trial$.tw.	290,396
54	rct.tw.	4,767
55	random allocation.tw.	2,385
56	randomly allocated.tw.	41,898
57	allocated randomly.tw.	2,806
58	(allocated adj2 random).tw.	923
59	single blind$.tw.	29,203
60	double blind$.tw.	231,965
61	((treble or triple) adj blind$).tw.	1,609
62	placebo$.tw.	345,771
63	prospective study/	779,647
64	or/46-63	2,570,188
65	case study/	86,833
66	case report.tw.	492,207
67	exp abstract report/	89,378
68	exp letter/	1,158,497
69	or/65-68	1,813,465
70	64 not 69	2,508,461
71	4 and 45 and 70	5,756
72	limit 71 to english language	5,537

Database: Embase 1974 to 2022 July 20
Search executed on July 21, 2022

Supplementary Table A2. Search strategy for MEDLINE

Line	Search term	Hits
1	exp head cancer/	340,509
2	((head and neck neoplasms) or (head and neck squamous cell carcinoma) or (head and neck cancer) or HNSCC or HNC or SCCHN).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	76,904
3	1 or 2	350,176
4	(pembrolizumab or MK-3475 or MK3475 or SCH-90047 or SCH 900475 or lambrolizumab or keytruda).mp.	7,571
5	(nivolumab or ONO-4538 or ONO4538 or BMS-936558 or BMS936558 or MDX-1106 or MDX 1106 or opdivo).mp.	8,403
6	(ipilimumab or MDX-CTLA-4 or MDXCTLA4 or BMS-734016 or BMS734016 or MDX-010 or MDX010 or yervoy).mp.	4,993
7	(durvalumab or MEDI-4736 or MEDI4736).mp.	1,228
8	(tremelimumab or ticilimumab or CP-675 or CP675 or CP-206 or CP206).mp.	443
9	exp cetuximab/	5,132
10	(cetuximab or C-225 or C225 or IMC-C225 or erbitux).mp.	8,738
11	(docetaxel or taxotere or docecad or RP 56976).mp.	19,062
12	exp paclitaxel/	29,860
13	(paclitaxel or nab-paclitaxel or abraxane or taxol or onxol).mp.	44,898
14	exp abraxane/	282
15	exp methotrexate/	44,397
16	(methotrexate or rheumatrex or trexall or mtx or amethopterin).mp.	60, 376
17	exp bleomycin/	16,429
18	(bleomycin or blenoxane or bleo 15k or bleotex or nisbleo or bledmax or bleocare or bleocel or bleochem or bleocin or bleocip or bleolem or bleonco or tumocin).mp.	21,607
19	exp mitomycin/	12,527
20	(mitomycin or mutamycin or mitocin or almito or mitodus or mitonco or oncocin).mp.	21,152
21	exp ifosfamide/	4,984
22	(ifosfamide or iphosphamide or ifex or celofos or holoxan or ifocip or ifoneon or ifos or ipamide or ipoget).mp.	7,797
23	exp tegafur/	5,950
24	(tegafur or fimer or furil or tefudex or teroful or tegracil or uft or ufur or unitoral).mp.	7,005
25	exp cisplatin/	56,786
26	(cisplatin or cisplatinum or cis-platinum or platamin or neoplatin or cismaplat or cis-maplat).mp.	85,324
27	exp carboplatin/	12,698
28	(carboplatin or paraplatin or paraplatin-aq).mp.	19,647
29	exp fluorouracil/	49,903
30	(fluorouracil or adrucil or 5-FU).mp.	41,258
31	(gemcitabine or LY-188011 or LY188011 or gemzar).mp.	19,640
32	exp capecitabine/	5,202
33	(capecitabine or Ro 09-1978 or Ro09-1978 or xeloda).mp.	8,333
34	(vinorelbine or vinorelbine ditatrate or KW-2307 or KW2307 or navelbine).mp.	4,413
35	(afatinib or BIBW-2992-MA2 or BIBW 2992 MA2 or gilotrif).mp.	1,901
36	or/4-35	309,684
37	randomized controlled trials as topic/	157,271
38	randomized controlled trial/	575,113
39	random allocation/	106,871
40	double blind method/	172,721

Line	Search term	Hits
41	single blind method/	32,144
42	clinical trial, phase i.pt.	24,192
43	clinical trial, phase ii.pt.	38,518
44	clinical trial, phase iii.pt.	20,857
45	clinical trial, phase iv.pt.	2,358
46	controlled clinical trial.pt.	94,983
47	randomized controlled trial.pt.	575,113
48	multicenter study.pt.	324,679
49	clinical trial.pt.	535,875
50	exp clinical trials as topic/	376,446
51	or/37-50	1,527,903
52	(clinical adj trial$).tw.	445,012
53	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	190,495
54	placebos/	35,921
55	placebo$.tw.	238,175
56	randomly allocated.tw.	34,144
57	(allocated adj2 random$).tw.	37,764
58	or/52-57	739,200
59	51 or 58	1,845,545
60	case report.tw.	368,322
61	letter/	1,188,825
62	historical article/	368,573
63	or/60-62	1,907,724
64	59 not 63	1,804,075
65	3 and 36 and 64	4,979
66	limit 65 to english language	4,552

Databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to July 20, 2022
Search executed on July 21, 2022

Supplementary Table A3. Search strategy for CENTRAL

Line	Search term	Hits
1	exp "Head and Neck Neoplasms"/	6,632
2	((head and neck neoplasms) or (head and neck squamous cell carcinoma) or (head and neck cancer) or HNSCC or HNC or SCCHN).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	7,388
3	1 or 2	11,450
4	(pembrolizumab or MK-3475 or MK3475 or SCH-90047 or SCH 900475 or lambrolizumab or keytruda).mp.	2,446
5	(nivolumab or ONO-4538 or ONO4538 or BMS-936558 or BMS936558 or MDX-1106 or MDX 1106 or opdivo).mp.	2,495
6	(ipilimumab or MDX-CTLA-4 or MDXCTLA4 or BMS-734016 or BMS734016 or MDX-010 or MDX010 or yervoy).mp.	1,632
7	(durvalumab or MEDI-4736 or MEDI4736).mp.	887
8	(tremelimumab or ticilimumab or CP-675 or CP675 or CP-206 or CP206).mp.	359
9	(cetuximab or C-225 or C225 or IMC-C225 or erbitux).mp.	2,628
10	(docetaxel or taxotere or docecad or RP 56976).mp.	8,199
11	(paclitaxel or nab-paclitaxel or abraxane or taxol or onxol).mp.	11,863
12	(methotrexate or rheumatrex or trexall or mtx or amethopterin).mp.	13,748

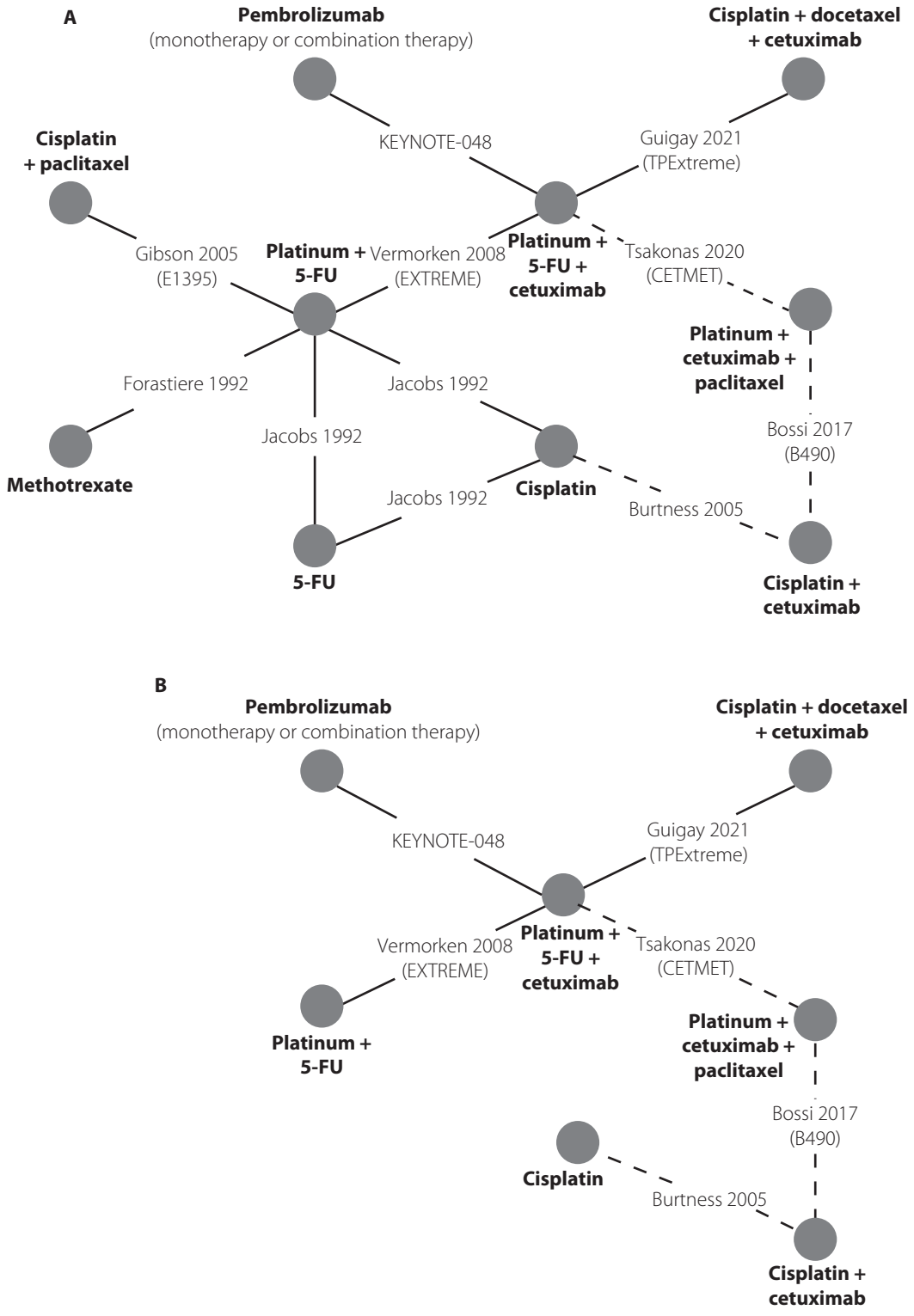
Line	Search term	Hits
13	(bleomycin or blenoxane or bleo 15k or bleotex or nisbleo or bledmax or bleocare or bleocel or bleochem or bleocin or bleocip or bleolem or bleonco or tumocin).mp.	1,722
14	(mitomycin or mutamycin or mitocin or almito or mitodus or mitonco or oncocin).mp.	2,988
15	(ifosfamide or iphosphamide or ifex or celofos or holoxan or ifocip or ifoneon or ifos or ipamide or ipoget).mp.	1,529
16	(tegafur or fimer or furil or tefudex or teroful or tegracil or uft or ufur or unitoral).mp.	1,311
17	(cisplatin or cisplatinum or cis-platinum or platamin or neoplatin or cismaplat or cis-maplat).mp.	15,926
18	(carboplatin or paraplatin or paraplatin-aq).mp.	8,078
19	(fluorouracil or adrucil or 5-FU).mp.	8,051
20	(gemcitabine or LY-188011 or LY188011 or gemzar).mp.	6,718
21	(capecitabine or Ro 09-1978 or Ro09-1978 or xeloda).mp.	4,549
22	(vinorelbine or vinorelbine ditatrate or KW-2307 or KW2307 or navelbine).mp.	1,986
23	(afatinib or BIBW-2992-MA2 or BIBW 2992 MA2 or gilotrif).mp.	470
24	or/4-23	65,497
25	3 and 24	355
26	limit 25 to english language	3,381

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials June 2022
Search executed on July 21, 2022

Supplementary Table A4. Conference proceedings searched as part of the systematic literature review

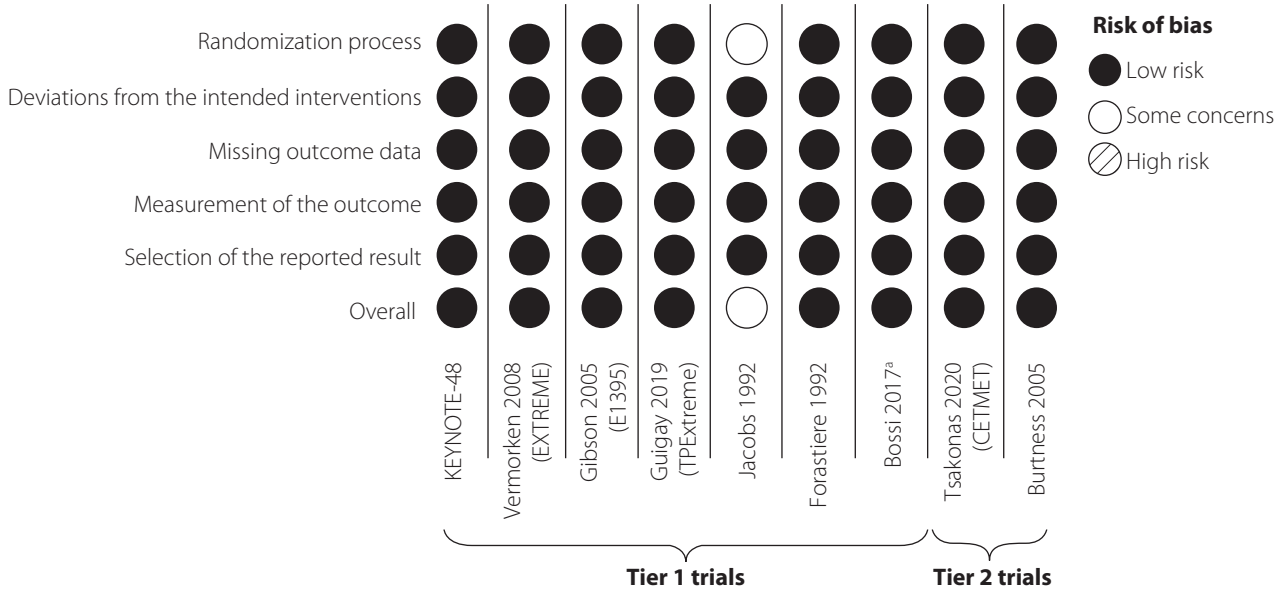
Title	Year(s)
American Association for Cancer Research Annual Meeting (AACR)	2015-2021
American Society of Clinical Oncology Annual Meeting (ASCO)	2015-2022
American Head and Neck Society International Conference (AHNS)	2016-2022
European Cancer Congress (ECCO)	2015-2019
European Society for Medical Oncology Congress (ESMO)	2014-2022
International Conference on Innovative Approaches in Head and Neck Oncology (ICHNO)	2015-2021
National Cancer Research Institute Cancer Conference (NCRI)	2016-2021
British Association of Head & Neck Oncologists Annual Scientific Meeting (BAHNO)	2015-2022

Supplementary Appendix B. Studies included and excluded in the network meta-analysis



Trials connected via dashed lines were additionally included in the analysis using Tier 1 plus Tier 2 trials. Networks of trials were the same for the analyses within the total population; the Combined Positive Score was ≥ 1, and Combined Positive Score was ≥ 20 subgroups.
5-FU, fluorouracil.

Supplementary Figure B1. Network of Tier 1 plus Tier 2 trials for the analysis of the **(A)** overall survival and **(B)** progression-free survival outcomes



[a] Bossi *et al.*, 2017, was a Tier 1 trial that could only be connected to the network via the Tier 2 trials (see **Supplementary Figures B1-A and B1-B**). Therefore, it could only be included in the analysis using Tier 1 plus Tier 2 trials.

Supplementary Figure B2. Risk of bias for randomized controlled trials included in the network meta-analysis

Supplementary Table B1. Eligibility of trials for the network meta-analysis[a]

Study	Interventions	Eligibility
Tier 1 trials		
KEYNOTE-048 (Burtness *et al.,* 2019)	**Pembrolizumab**	Included
	Platinum + 5-FU + pembrolizumab	
	Platinum + 5-FU + cetuximab	
Vermorken *et al.*, 2008 (EXTREME) (Vermorken *et al.*, 2008)	**Platinum + 5-FU**	Included
	Platinum + 5-FU + cetuximab	
Gibson *et al.*, 2005 (E1395) (Gibson *et al.*, 2005)	**Cisplatin + paclitaxel**	Included
	Platinum + 5-FU	
Guigay *et al.*, 2021 (TPExtreme) (Guigay *et al.*, 2021)	**Cisplatin + docetaxel + cetuximab**	Included
	Platinum + 5-FU + cetuximab	
Jacobs *et al.*, 1992 (Jacobs *et al.*, 1992)	**Platinum + 5-FU**	Included
	Cisplatin	
	5-FU	
Forastiere *et al.*,1992 (Forastiere *et al.*, 1992)	**Cisplatin + 5-FU**	Included
	Carboplatin + 5-FU	
	Methotrexate	
Bossi *et al.*, 2017 (Bossi *et al.*, 2017)	**Platinum + cetuximab + paclitaxel**	Included (NMA of Tier 1 + Tier 2 trials)
	Cisplatin + cetuximab	
Airoldi *et al.*, 1987 (Airoldi *et al.*, 1987)	**Methotrexate**	Excluded (could not connect to the network)
	Methotrexate + 5-FU	
Argiris *et al.*, 2021 (CHECKMATE 651) (Argiris *et al.*, 2021)	Nivolumab + ipilimumab	Excluded (could not connect to the network)
	Platinum + 5-FU + cetuximab	
Davis & Kessler, 1979 (Davis & Kessler, 1979)	**Cisplatin**	Excluded (published before 1990)
	Cisplatin + methotrexate + bleomycin	
Eisenberger *et al.*, 1989 (Eisenberger *et al.*, 1989)	**Methotrexate**	Excluded (published before 1990)
	Methotrexate + Carboplatin	
Ferris *et al.*, 2018 (Active8) (Ferris *et al.*, 2018)	Platinum + 5-FU + cetuximab + motolimod	Excluded (could not connect to the network)
	Platinum + 5-FU + cetuximab	
Forastiere *et al.*, 2001 (E1393) (Forastiere *et al.*, 2001)	Cisplatin + paclitaxel + G-CSF	Excluded (could not connect to the network)
	Cisplatin + paclitaxel	
Forster *et al.*, 2019 (Forster *et al.*, 2019)	Platinum + cetuximab + patritumab	Excluded (could not connect to the network)
	Platinum + cetuximab	
Guigay *et al.*, 2019 (ELAN-UNFIT) (Guigay *et al.*, 2019)	**Cetuximab**	Excluded (all patients were ≥70 years old and classified as unfit, i.e., in substantially poorer conditions compared to KEYNOTE-048)
	Methotrexate	
Guo *et al.*, 2021 (CHANGE-2) (Guo *et al.*, 2021)	**Platinum + 5-FU + cetuximab**	Excluded (exclusively conducted in Asian population)
	Platinum + 5-FU	
Hong *et al.*, 1983 (Hong *et al.*, 1983)	**Methotrexate**	Excluded (published before 1990)
	Cisplatin	
Issell *et al.*, 1982 (Issell *et al.*, 1982)	Bleomycin	Excluded (published before 1990)
	Dibromodulcitol + bleomycin	
Keilholz *et al.*, 2018 (RESGEX) (Keilholz *et al.*, 2018)	Cisplatin + 5-FU + tomuzotuximab	Excluded (could not connect to the network)
	Cisplatin + 5-FU + cetuximab	

Study	Interventions	Eligibility
Schornagel *et al.*, 1995 (Schornagel *et al.*, 1995)	Edatrexate	Excluded (could not connect to the network)
	Methotrexate	
Vermorken *et al.*, 2013 (SPECTRUM) (Vermorken *et al.*, 2013)	Cisplatin + 5-FU + panitumumab	Excluded (could not connect to the network)
	Cisplatin + 5-FU	
Vermorken *et al.*, 2014 (ADVANTAGE) (Vermorken *et al.*, 2014)	Cilengitide (once weekly) + cisplatin + 5-FU + cetuximab	Excluded (could not connect to the network)
	Cilengitide (twice weekly) + cisplatin + 5-FU + cetuximab	
	Cisplatin + 5-FU + cetuximab	
Vogl *et al.*, 1982 (Vogl *et al.*, 1982)	Methotrexate + C. Parvum	Excluded (published before 1990)
	Methotrexate	
Williams *et al.*, 1986 (Williams *et al.*, 1986)	**Methotrexate**	Excluded (published before 1990)
	Cisplatin + vinblastine + bleomycin	
Wirth *et al.*, 2016 (PARTNER) (Wirth *et al.*, 2016)	Cisplatin + docetaxel + panitumumab	Excluded (could not connect to the network)
	Cisplatin + docetaxel	
Tier 2 trials		
Tsakonas *et al.*, 2020 (CETMET) (Tsakonas *et al.*, 2020)	**Platinum + cetuximab + paclitaxel**	Included (NMA of Tier 1 + Tier 2 trials)
	Platinum + 5-FU + cetuximab	
Burtness *et al.*, 2005 (Burtness *et al.*, 2005)	**Cisplatin + cetuximab**	Included (NMA of Tier 1 + Tier 2 trials)
	Cisplatin	
Argiris *et al.*, 2017 (E1305) (Argiris *et al.*, 2017)	**Chemotherapy** [b]	Excluded (could not connect to the network)
	Chemotherapy [b] + bevacizumab	
Ham *et al.*, 2020 (COMMENCE) (Ham *et al.*, 2020)	Methotrexate + cetuximab	Excluded (could not connect to the network)
	Methotrexate	
Schrijvers *et al.*, 1998 (Schrijvers *et al.*, 1998)	**Cisplatin + 5-FU**	Excluded (could not connect to the network)
	Cisplatin + 5-FU + IFNα-2b	

Interventions of interest for the NMA are **bolded**. Trials had to evaluate interventions of interest in at least two treatment arms to be considered for the NMA and connect to the network.
[a] Study references can be found in Section 6 of this supplementary appendix.
[b] Investigators' choice of cisplatin + 5-FU, carboplatin + 5-FU, cisplatin + docetaxel, or carboplatin + docetaxel.
5-FU, 5-fluorouracil; G-CSF, granulocyte colony stimulating factor; IFN, interferon; NMA, network meta-analysis.

Supplementary Table B2. Summary of study characteristics of trials included in the NMA using Tier 1 trials only and additional trials included in the NMA using Tier 1 plus Tier 2 trials

Study	Phase	Masking	Eligible patients	Performance status	NPC	Prior chemotherapy
NMA using Tier 1 trials only						
KEYNOTE-048 (Burtness *et al.*, 2019)	III	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 before study entry.
Vermorken *et al.*, 2008 (EXTREME) (Vermorken *et al.*, 2008)	III	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 before study entry.
Gibson *et al.*, 2005 (E1395) (Gibson *et al.*, 2005)	III	--	HNSCC patients ≥ 18 years old who are not curable with surgery or RT.	ECOG 0-1	Excluded	Not allowed for recurrent disease. Allowed if delivered as part of initial curative therapy (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.*, 2021 (TPExtreme) (Guigay *et al.*, 2021)	III	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 before study entry.
Jacobs *et al.*, 1992 (Jacobs *et al.*, 1992)	III	--	HNSCC patients ≥ 18 years old with recurrence after primary therapy or metastatic at diagnosis.	ECOG 0-3	--	Not allowed in any setting.
Forastiere *et al.*,1992 (Forastiere *et al.*, 1992)	III	--	HNSCC patients who are either recurrent after attempted cure with surgery 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 before study entry.
NMA using Tier 1 plus Tier 2 trials						
Bossi *et al.*, 2017 (Bossi *et al.*, 2017)	II	Open-label	R/M HNSCC patients > 18 years old	ECOG 0-1	Excluded	Not allowed for recurrent disease. Allowed if received in the LA setting ≥ 6 months before study entry.
Tsakonas *et al.*, 2020 (CETMET) (Tsakonas *et al.*, 2020)	II	Open-label	R/M HNSCC patients > 18 years old	ECOG 0-1	Excluded	Not allowed in the R/M setting or if completed in the LA setting < 3 months before study entry.
Burtness *et al.*, 2005 (Burtness *et al.*, 2005)	III	Double-blind	HNSCC patients ≥ 18 years old who are recurrent after locoregional therapy or metastatic.	ECOG 0-1	--	Not allowed in the R/M setting. Induction or adjuvant chemotherapy allowed if completed ≥ 3 months before study entry.

5-FU, fluorouracil; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; KPS, Karnofsky performance score; NMA, network meta-analysis; NPC, nasopharyngeal carcinoma; R/M, recurrent and/or metastatic; RT, radiotherapy.

Supplementary Table B3. Summary of baseline patient characteristics for trials connected within the network

Study	Intervention		N	Age, median (range)	Male, n (%)	White, n (%)	ECOG Score, n (%)				HPV, n (%)			Recurrent, n (%)	Metastatic, n (%)
							0	1	2	3	+	-	Missing		
NMA using Tier 1 trials only															
KEYNOTE-048 (Burtness *et al.*, 2019)	Total	P + C	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)
		EXTREME regimen[a]	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)
	CPS ≥ 1	P + C	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)
		EXTREME regimen[a]	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)
	CPS ≥ 20	P + C	126	62 (28-85)	90 (71.4)	95 (75.4)	47 (37.3)	79 (62.7)	0 (0)	0 (0)	27 (21.4)	99 (78.6)	0 (0)	38 (30.2)	87 (69)
		EXTREME regimen[a]	110	60 (24-80)	96 (87.3)	82 (74.5)	47 (42.7)	63 (57.3)	0 (0)	0 (0)	25 (22.7)	85 (77.3)	0 (0)	40 (36.4)	69 (62.7)
	CPS ≥ 1	P	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)
		EXTREME regimen[a]	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)
	CPS ≥ 20	P	133	62 (22-83)	104 (78.2)	98 (73.7)	58 (43.6)	75 (56.4)	0 (0)	0 (0)	24 (18)	109 (82)	0 (0)	42 (31.6)	88 (66.2)
		EXTREME regimen[a]	122	60 (24-81)	108 (88.5)	92 (75.4)	52 (42.6)	70 (57.4)	0 (0)	0 (0)	28 (23)	94 (77)	0 (0)	42 (34.4)	79 (64.8)
Vermorken *et al.*, 2008 (EXTREME) (Vermorken *et al.*, 2008)	EXTREME regimen		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)
Gibson *et al.*, 2005 (E1395) (Gibson *et al.*, 2005)	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.*, 2021 (TPExtreme) (Guigay *et al.*, 2021)	TPEx regimen		269	60 (38-70)	240 (89)	--	86 (32)	183 (68)	0 (0)	0 (0)	20/104 (19.2)[b]	84/104 (80.8)[b]	--	159 (59.1)	175 (65.1)
	EXTREME regimen		270	60 (23-71)	231 (86)		86 (32)	184 (68)			14/76 (18.4)[b]	62/76 (81.6)[b]		152 (56.3)	172 (63.7)
Jacobs *et al.*, 1992 (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)
Forastiere *et al.*, 1992 (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)
NMA using Tier 1 plus Tier 2 trials															
Bossi *et al.*, 2017 (Bossi *et al.*, 2017)[d]	Cisplatin + cetuximab		100	63 (41-83)	74 (74)	--	51 (51)	49 (49)	0 (0)	0 (0)	6 (6)[b]	6 (6)[b]	25 (25)[b]	63 (63)	62 (62)
	Cisplatin + cetuximab + paclitaxel		91	62 (33-77)	75 (82.4)		46 (50.6)	45 (49.5)	0 (0)	0 (0)	7 (7.7)[b]	10 (11)[b]	16 (17.6)[b]	66 (72.6)	46 (50.6)
Tsakonas *et al.*, 2020 (CETMET) (Tsakonas *et al.*, 2020)	EXTREME regimen		42	59.1 (10.1)[c, e]	33 (78.6)	--	14 (34.1)	27 (65.9)	0 (0)	0 (0)	11 (26.2)	24 (57.1)	7 (16.7)	28 (66.7)	30 (71.4)
	Carboplatin + cetuximab + paclitaxel		43	59.1 (7.3)[c, e]	26 (60.5)		15 (34.9)	27 (62.8)	1 (2.3)	0 (0)	15 (34.9)	27 (62.8)	1 (2.3)	32 (74.4)	22 (51.2)
Burtness *et al.*, 2005 (Burtness *et al.*, 2005)	Cisplatin		60	58.3 (32-84)	50 (83.3)	--	24 (40)	36 (60)	0 (0)	0 (0)		--		56 (98.2)	35 (61.4)
	Cisplatin + cetuximab		57	60.6 (40-86)	41 (71.9)		24 (42.1)	33 (57.9)	0 (0)	0 (0)				57 (95)	41 (68.3)

Double dashes indicate that the value was not reported. The EXTREME regimen consists of platinum + 5-FU + cetuximab, and the TPEx regimen consists of cisplatin + docetaxel + cetuximab

[a] In KEYNOTE-048, enrollment in the pembrolizumab with chemotherapy arm was paused for a safety assessment. The protocol was then amended to exclude the 22 participants randomized to cetuximab + platinum + 5-FU (the "standard treatment") during the pause for the comparison between the pembrolizumab with chemotherapy group and the standard treatment group, and according to the intention-to-treat principle. Therefore, the number of participants in the standard treatment group was 278 compared to pembrolizumab with chemotherapy and 300 compared to pembrolizumab monotherapy.

[b] HPV status was evaluated only in those with oropharyngeal cancer.

[c] Mean was reported.

[d] Bossi *et al.*, 2017 was a Tier 1 trial that could only be connected to the network via the Tier 2 trials (see Supplementary Figures B1-A and B1-B). Therefore, it could only be included in the NMA using Tier 1 plus Tier 2 trials.

[e] Standard deviation was reported.

5-FU, fluorouracil; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; IQR, interquartile range; KPS, Karnofsky performance score; NMA, network meta-analysis; P, pembrolizumab monotherapy; P + C, pembrolizumab with chemotherapy.

Supplementary Appendix C. Additional network meta-analyses using Tier 1 trials only

Pembrolizumab with chemotherapy

Overall survival

Supplementary Table C1. Estimated overall survival hazard ratios in the network meta-analysis using Tier 1 trials only for pembrolizumab with chemotherapy in the CPS ≥ 1 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	Cisplatin + paclitaxel[c]	TPEx regimen[d]	Cisplatin[e]	5-FU[f]	Methotrexate[g]
	Constant Hazard Ratio (95% Credible Interval)						
	0.66 (0.54-0.80)	**0.53 (0.39-0.71)**	**0.48 (0.32-0.73)**	0.76 (0.57-1.00)	**0.42 (0.28-0.65)**	**0.52 (0.34-0.80)**	**0.46 (0.31-0.68)**
Time point (months)	Time-Varying Hazard Ratio (95% Credible Interval)						
1	1.10 (0.79-1.52)	0.82 (0.53-1.24)	0.67 (0.35-1.25)	1.08 (0.70-1.74)	0.65 (0.35-1.19)	0.70 (0.37-1.29)	0.79 (0.45-1.37)
3	0.99 (0.74-1.32)	0.76 (0.51-1.10)	0.63 (0.36-1.10)	1.00 (0.68-1.53)	0.61 (0.36-1.04)	0.64 (0.37-1.08)	0.71 (0.43-1.14)
6	0.86 (0.67-1.09)	**0.67 (0.48-0.92)**	**0.57 (0.36-0.92)**	0.89 (0.64-1.27)	**0.56 (0.35-0.87)**	**0.56 (0.35-0.87)**	**0.60 (0.39-0.90)**
9	**0.74 (0.60-0.91)**	**0.60 (0.45-0.78)**	**0.52 (0.35-0.79)**	0.80 (0.60-1.07)	**0.51 (0.33-0.78)**	**0.49 (0.31-0.74)**	**0.50 (0.34-0.73)**
12	**0.64 (0.52-0.78)**	**0.53 (0.40-0.69)**	**0.47 (0.32-0.71)**	**0.71 (0.54-0.93)**	**0.47 (0.29-0.74)**	**0.42 (0.26-0.68)**	**0.42 (0.28-0.64)**
15	**0.55 (0.44-0.68)**	**0.47 (0.35-0.63)**	**0.43 (0.28-0.68)**	**0.63 (0.47-0.84)**	**0.43 (0.25-0.74)**	**0.37 (0.21-0.66)**	**0.36 (0.22-0.59)**
18	**0.48 (0.37-0.61)**	**0.41 (0.29-0.58)**	**0.39 (0.23-0.67)**	**0.56 (0.40-0.78)**	**0.39 (0.21-0.76)**	**0.32 (0.16-0.66)**	**0.30 (0.17-0.55)**
21	**0.41 (0.30-0.56)**	**0.37 (0.24-0.55)**	**0.36 (0.19-0.68)**	**0.50 (0.33-0.74)**	**0.36 (0.17-0.79)**	**0.28 (0.12-0.67)**	**0.25 (0.13-0.53)**
24	**0.35 (0.24-0.51)**	**0.33 (0.20-0.53)**	**0.32 (0.16-0.70)**	**0.44 (0.27-0.71)**	**0.33 (0.13-0.83)**	**0.24 (0.09-0.68)**	**0.21 (0.09-0.51)**
27	**0.31 (0.20-0.47)**	**0.29 (0.16-0.51)**	**0.29 (0.12-0.72)**	**0.40 (0.22-0.69)**	**0.30 (0.10-0.88)**	**0.21 (0.07-0.70)**	**0.18 (0.07-0.49)**
30	**0.26 (0.16-0.43)**	**0.26 (0.13-0.49)**	**0.27 (0.10-0.75)**	**0.35 (0.18-0.66)**	**0.27 (0.08-0.94)**	**0.19 (0.05-0.73)**	**0.15 (0.05-0.48)**
33	**0.23 (0.13-0.40)**	**0.23 (0.11-0.47)**	**0.24 (0.08-0.78)**	**0.31 (0.15-0.65)**	0.25 (0.06-1.01)	**0.16 (0.04-0.75)**	**0.13 (0.04-0.47)**
36	**0.20 (0.10-0.37)**	**0.20 (0.09-0.46)**	**0.22 (0.06-0.82)**	**0.28 (0.12-0.63)**	0.23 (0.05-1.07)	**0.14 (0.03-0.79)**	**0.11 (0.03-0.46)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 36 (inclusive).
[c] Survival data were available for cisplatin + paclitaxel through month 36 (inclusive).
[d] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 36 (inclusive).
[e] Survival data were available for cisplatin through month 33 (inclusive).
[f] Survival data were available for 5-FU through month 27 (inclusive).
[g] Survival data were available for methotrexate through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

Supplementary Table C2. Estimated overall survival hazard ratios in the network meta-analysis using Tier 1 trials only for pembrolizumab with chemotherapy in the CPS ≥ 20 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	Cisplatin + paclitaxel[c]	TPEx regimen[d]	Cisplatin[e]	5-FU[f]	Methotrexate[g]
	Constant Hazard Ratio (95% Credible Interval)						
	0.61 (0.46-0.81)	**0.49 (0.34-0.70)**	**0.45 (0.28-0.71)**	**0.70 (0.50-0.99)**	**0.39 (0.24-0.63)**	**0.48 (0.30-0.78)**	**0.43 (0.27-0.67)**
Time point (months)	**Time-Varying Hazard Ratio (95% Credible Interval)**						
1	**2.21 (1.01-4.92)**	1.45 (0.58-3.72)	1.26 (0.36-4.42)	2.02 (0.77-5.30)	1.53 (0.46-5.00)	1.39 (0.41-4.58)	1.87 (0.63-5.71)
3	1.14 (0.72-1.82)	0.84 (0.49-1.46)	0.74 (0.36-1.52)	1.15 (0.65-2.03)	0.77 (0.39-1.52)	0.74 (0.37-1.46)	0.84 (0.45-1.61)
6	0.75 (0.55-1.03)	**0.60 (0.41-0.87)**	**0.53 (0.32-0.85)**	0.80 (0.55-1.19)	**0.50 (0.31-0.83)**	**0.49 (0.30-0.81)**	**0.51 (0.32-0.81)**
9	**0.59 (0.44-0.79)**	**0.49 (0.34-0.69)**	**0.43 (0.28-0.68)**	**0.65 (0.46-0.94)**	**0.39 (0.24-0.65)**	**0.39 (0.23-0.65)**	**0.38 (0.24-0.60)**
12	**0.49 (0.36-0.68)**	**0.42 (0.29-0.61)**	**0.38 (0.23-0.62)**	**0.56 (0.39-0.83)**	**0.33 (0.19-0.58)**	**0.33 (0.19-0.60)**	**0.31 (0.18-0.52)**
15	**0.43 (0.30-0.61)**	**0.38 (0.24-0.57)**	**0.34 (0.19-0.59)**	**0.50 (0.33-0.77)**	**0.29 (0.15-0.54)**	**0.29 (0.15-0.57)**	**0.26 (0.15-0.47)**
18	**0.39 (0.26-0.57)**	**0.34 (0.21-0.55)**	**0.31 (0.16-0.58)**	**0.46 (0.29-0.73)**	**0.26 (0.12-0.52)**	**0.26 (0.13-0.55)**	**0.23 (0.12-0.44)**
21	**0.35 (0.23-0.54)**	**0.32 (0.19-0.53)**	**0.29 (0.14-0.57)**	**0.42 (0.26-0.70)**	**0.23 (0.11-0.51)**	**0.24 (0.11-0.54)**	**0.20 (0.10-0.41)**
24	**0.33 (0.20-0.51)**	**0.30 (0.17-0.51)**	**0.27 (0.13-0.57)**	**0.40 (0.23-0.68)**	**0.21 (0.09-0.50)**	**0.22 (0.09-0.53)**	**0.19 (0.09-0.39)**
27	**0.30 (0.18-0.49)**	**0.28 (0.15-0.50)**	**0.26 (0.11-0.56)**	**0.37 (0.21-0.67)**	**0.20 (0.08-0.49)**	**0.21 (0.08-0.52)**	**0.17 (0.08-0.38)**
30	**0.29 (0.17-0.48)**	**0.27 (0.14-0.49)**	**0.24 (0.10-0.56)**	**0.35 (0.19-0.65)**	**0.19 (0.07-0.48)**	**0.19 (0.07-0.52)**	**0.16 (0.07-0.37)**
33	**0.27 (0.15-0.46)**	**0.26 (0.13-0.48)**	**0.23 (0.09-0.56)**	**0.34 (0.18-0.64)**	**0.18 (0.06-0.47)**	**0.18 (0.07-0.52)**	**0.15 (0.06-0.36)**
36	**0.26 (0.14-0.45)**	**0.24 (0.12-0.48)**	**0.22 (0.09-0.56)**	**0.32 (0.16-0.63)**	**0.17 (0.06-0.47)**	**0.17 (0.06-0.51)**	**0.14 (0.05-0.35)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 36 (inclusive).
[c] Survival data were available for cisplatin + paclitaxel through month 36 (inclusive).
[d] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 36 (inclusive).
[e] Survival data were available for cisplatin through month 33 (inclusive).
[f] Survival data were available for 5-FU through month 27 (inclusive).
[g] Survival data were available for methotrexate through month 36 (inclusive).

5-FU, fluorouracil; CPS, Combined Positive Score.

Progression-free survival

Supplementary Table C3. Estimated progression-free survival hazard ratios in the network meta-analysis using Tier 1 trials only for pembrolizumab with chemotherapy in the CPS ≥ 1 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	TPEx regimen[c]
	Constant Hazard Ratio (95% Credible Interval)		
	0.82 (0.68-0.99)	**0.44 (0.33-0.59)**	0.93 (0.72-1.21)
Time points (months)	Time-Varying Hazard Ratio (95% Credible Interval)		
1	1.51 (0.96-2.40)	0.84 (0.42-1.71)	1.41 (0.76-2.69)
3	1.01 (0.80-1.27)	**0.56 (0.40-0.79)**	1.07 (0.78-1.51)
6	**0.78 (0.64-0.94)**	**0.44 (0.32-0.60)**	0.91 (0.70-1.18)
9	**0.67 (0.53-0.85)**	**0.38 (0.25-0.57)**	0.82 (0.60-1.12)
12	**0.60 (0.45-0.80)**	**0.34 (0.20-0.57)**	0.76 (0.52-1.11)
15	**0.55 (0.40-0.77)**	**0.31 (0.17-0.57)**	0.72 (0.47-1.11)
18	**0.51 (0.36-0.75)**	**0.29 (0.15-0.57)**	0.69 (0.42-1.12)
21	**0.49 (0.33-0.73)**	**0.28 (0.13-0.57)**	0.66 (0.39-1.13)
24	**0.46 (0.30-0.72)**	**0.26 (0.12-0.58)**	0.64 (0.36-1.13)
27	**0.44 (0.28-0.70)**	**0.25 (0.11-0.58)**	0.62 (0.34-1.14)
30	**0.42 (0.26-0.69)**	**0.24 (0.10-0.58)**	0.61 (0.32-1.15)
33	**0.41 (0.25-0.68)**	**0.23 (0.09-0.58)**	0.59 (0.30-1.16)
36	**0.40 (0.24-0.67)**	**0.23 (0.09-0.58)**	0.58 (0.29-1.16)

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 15 (inclusive).
[c] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available for platinum + 5-FU through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

Supplementary Table C4. Estimated progression-free survival hazard ratios in the network meta-analysis using Tier 1 trials only for pembrolizumab with chemotherapy in the CPS ≥ 20 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	TPEx regimen[c]
	Constant Hazard Ratio (95% Credible Interval)		
	0.75 (0.57-0.99)	**0.40 (0.28-0.58)**	0.85 (0.61-1.18)
Time points (months)	**Time-Varying Hazard Ratio (95% Credible Interval)**		
1	**2.02 (1.07-3.93)**	1.12 (0.49-2.59)	1.89 (0.87-4.23)
3	1.06 (0.75-1.49)	**0.59 (0.39-0.89)**	1.13 (0.75-1.72)
6	**0.70 (0.53-0.92)**	**0.39 (0.27-0.57)**	0.82 (0.59-1.12)
9	**0.55 (0.40-0.76)**	**0.31 (0.19-0.50)**	**0.68 (0.46-0.98)**
12	**0.46 (0.31-0.68)**	**0.26 (0.15-0.47)**	**0.59 (0.37-0.93)**
15	**0.41 (0.26-0.63)**	**0.23 (0.12-0.45)**	**0.53 (0.31-0.89)**
18	**0.36 (0.22-0.60)**	**0.21 (0.10-0.44)**	**0.49 (0.27-0.87)**
21	**0.33 (0.19-0.57)**	**0.19 (0.08-0.43)**	**0.45 (0.24-0.86)**
24	**0.31 (0.17-0.55)**	**0.18 (0.07-0.42)**	**0.43 (0.21-0.85)**
27	**0.29 (0.15-0.53)**	**0.16 (0.07-0.41)**	**0.40 (0.19-0.84)**
30	**0.27 (0.14-0.51)**	**0.15 (0.06-0.41)**	**0.38 (0.18-0.83)**
33	**0.25 (0.13-0.50)**	**0.15 (0.05-0.40)**	**0.37 (0.16-0.82)**
36	**0.24 (0.12-0.49)**	**0.14 (0.05-0.40)**	**0.35 (0.15-0.81)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 15 (inclusive).
[c] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available for platinum + 5-FU through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

Pembrolizumab monotherapy

Overall survival

Supplementary Table C5. Estimated overall survival hazard ratios in the network meta-analysis using Tier 1 trials only for pembrolizumab monotherapy in the CPS ≥ 20 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	Cisplatin + paclitaxel[c]	TPEx regimen[d]	Cisplatin[e]	5-FU[f]	Methotrexate[g]
	Constant Hazard Ratio (95% Credible Interval)						
	0.63 (0.48-0.83)	**0.50 (0.35-0.72)**	**0.46 (0.29-0.73)**	0.72 (0.52-1.02)	**0.40 (0.25-0.65)**	**0.50 (0.31-0.80)**	**0.44 (0.29-0.69)**
Time point (months)	**Time-Varying Hazard Ratio (95% Credible Interval)**						
1	1.59 (0.74-3.45)	1.06 (0.44-2.70)	0.91 (0.25-3.27)	1.47 (0.57-3.72)	1.12 (0.34-3.66)	1.02 (0.31-3.40)	1.38 (0.47-4.10)
3	1.00 (0.64-1.58)	0.74 (0.44-1.28)	0.65 (0.32-1.34)	1.01 (0.58-1.75)	0.69 (0.35-1.35)	0.65 (0.33-1.29)	0.74 (0.40-1.40)
6	0.74 (0.55-1.02)	**0.59 (0.41-0.85)**	**0.52 (0.32-0.85)**	0.80 (0.55-1.16)	**0.50 (0.31-0.82)**	**0.49 (0.30-0.80)**	**0.50 (0.32-0.79)**
9	**0.63 (0.47-0.83)**	**0.52 (0.37-0.73)**	**0.46 (0.29-0.72)**	**0.70 (0.50-0.98)**	**0.42 (0.26-0.69)**	**0.42 (0.25-0.69)**	**0.40 (0.26-0.63)**
12	**0.55 (0.41-0.74)**	**0.47 (0.33-0.68)**	**0.42 (0.26-0.69)**	**0.63 (0.44-0.90)**	**0.37 (0.21-0.64)**	**0.37 (0.21-0.65)**	**0.34 (0.21-0.57)**
15	**0.50 (0.36-0.70)**	**0.44 (0.29-0.65)**	**0.39 (0.23-0.68)**	**0.59 (0.40-0.87)**	**0.33 (0.18-0.62)**	**0.34 (0.18-0.64)**	**0.30 (0.17-0.53)**
18	**0.47 (0.33-0.67)**	**0.41 (0.26-0.64)**	**0.37 (0.20-0.68)**	**0.55 (0.36-0.85)**	**0.31 (0.16-0.61)**	**0.31 (0.16-0.64)**	**0.27 (0.15-0.51)**
21	**0.44 (0.29-0.65)**	**0.39 (0.24-0.63)**	**0.35 (0.18-0.70)**	**0.52 (0.32-0.84)**	**0.29 (0.14-0.60)**	**0.30 (0.14-0.64)**	**0.25 (0.13-0.50)**
24	**0.41 (0.27-0.63)**	**0.37 (0.22-0.63)**	**0.34 (0.16-0.71)**	**0.50 (0.30-0.84)**	**0.27 (0.12-0.60)**	**0.28 (0.12-0.64)**	**0.23 (0.11-0.48)**
27	**0.39 (0.25-0.62)**	**0.36 (0.20-0.63)**	**0.33 (0.15-0.72)**	**0.48 (0.28-0.83)**	**0.26 (0.11-0.60)**	**0.27 (0.11-0.65)**	**0.22 (0.10-0.48)**
30	**0.37 (0.23-0.61)**	**0.35 (0.19-0.63)**	**0.32 (0.14-0.73)**	**0.46 (0.26-0.83)**	**0.25 (0.10-0.60)**	**0.25 (0.10-0.65)**	**0.20 (0.09-0.47)**
33	**0.36 (0.22-0.60)**	**0.34 (0.18-0.63)**	**0.31 (0.13-0.74)**	**0.45 (0.24-0.83)**	**0.24 (0.09-0.60)**	**0.24 (0.09-0.66)**	**0.19 (0.08-0.47)**
36	**0.35 (0.20-0.59)**	**0.33 (0.17-0.63)**	**0.30 (0.12-0.75)**	**0.44 (0.23-0.83)**	**0.23 (0.08-0.61)**	**0.24 (0.09-0.66)**	**0.18 (0.07-0.46)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 36 (inclusive).
[c] Survival data were available for cisplatin + paclitaxel through month 36 (inclusive).
[d] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 36 (inclusive).
[e] Survival data were available for cisplatin through month 33 (inclusive).
[f] Survival data were available for 5-FU through month 27 (inclusive).
[g] Survival data were available for methotrexate through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

Progression-free survival

Supplementary Table C6. Estimated progression-free survival hazard ratios in the network meta-analysis using Tier 1 trials only for pembrolizumab monotherapy in the CPS ≥ 20 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	TPEx regimen[c]
	Constant Hazard Ratio (95% Credible Interval)		
	0.99 (0.76-1.29)	**0.53 (0.38-0.75)**	1.13 (0.82-1.55)
Time points (months)	**Time-Varying Hazard Ratio (95% Credible Interval)**		
1	**3.14 (1.69-5.98)**	1.74 (0.78-3.97)	**2.95 (1.37-6.46)**
3	**1.39 (1.00-1.93)**	0.78 (0.52-1.16)	1.49 (1.00-2.22)
6	0.83 (0.63-1.09)	**0.47 (0.32-0.67)**	0.97 (0.69-1.33)
9	**0.61 (0.44-0.86)**	**0.35 (0.21-0.56)**	0.75 (0.51-1.10)
12	**0.49 (0.33-0.74)**	**0.28 (0.16-0.50)**	0.63 (0.39-1.00)
15	**0.42 (0.26-0.66)**	**0.24 (0.12-0.47)**	**0.55 (0.32-0.94)**
18	**0.36 (0.22-0.61)**	**0.21 (0.10-0.44)**	**0.49 (0.27-0.89)**
21	**0.32 (0.19-0.57)**	**0.19 (0.08-0.42)**	**0.44 (0.23-0.86)**
24	**0.29 (0.16-0.54)**	**0.17 (0.07-0.41)**	**0.41 (0.20-0.83)**
27	**0.27 (0.14-0.51)**	**0.15 (0.06-0.39)**	**0.38 (0.18-0.81)**
30	**0.25 (0.13-0.49)**	**0.14 (0.05-0.38)**	**0.35 (0.16-0.79)**
33	**0.23 (0.12-0.47)**	**0.13 (0.05-0.37)**	**0.33 (0.15-0.77)**
36	**0.22 (0.11-0.45)**	**0.12 (0.04-0.36)**	**0.32 (0.14-0.75)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 36 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 15 (inclusive).
[c] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

Supplementary Appendix D. Network meta-analysis using Tier 1 plus Tier 2 trials in the total, CPS ≥ 1, and CPS ≥ 20 populations

Supplementary Table D1. Summary of estimated overall survival and progression-free survival hazard ratios in the network meta-analysis using Tier 1 plus Tier 2 trials for pembrolizumab with chemotherapy and pembrolizumab monotherapy relative to alternative interventions from fixed-effects model using constant hazard ratios

Population	EXTREME regimen[a]	Platinum + 5-FU	Cisplatin + paclitaxel	TPEx regimen[b]	Cisplatin	5-FU	Methotrexate	Platinum + cetuximab + paclitaxel	Cisplatin + cetuximab
Pembrolizumab with chemotherapy: OS HR (95% CrI)									
Total (FA)	**0.72 (0.60-0.86)**	**0.61 (0.47-0.81)**	**0.56 (0.38-0.84)**	0.83 (0.63-1.08)	**0.56 (0.38-0.83)**	**0.65 (0.44-0.97)**	**0.54 (0.37-0.79)**	0.72 (0.47-1.12)	0.78 (0.50-1.22)
Total (5-year)	**0.72 (0.60-0.86)**	**0.61 (0.47-0.81)**	**0.56 (0.38-0.84)**	0.83 (0.63-1.08)	**0.56 (0.38-0.83)**	**0.65 (0.44-0.97)**	**0.54 (0.37-0.78)**	0.72 (0.47-1.12)	0.78 (0.50-1.21)
CPS ≥ 1	**0.66 (0.54-0.80)**	**0.56 (0.42-0.75)**	**0.52 (0.34-0.78)**	0.76 (0.57-1.00)	**0.52 (0.35-0.76)**	**0.60 (0.40-0.90)**	**0.49 (0.33-0.73)**	0.66 (0.43-1.03)	0.72 (0.45-1.12)
CPS ≥ 20	**0.61 (0.46-0.82)**	**0.52 (0.36-0.75)**	**0.48 (0.30-0.76)**	**0.70 (0.50-0.99)**	**0.48 (0.31-0.75)**	**0.55 (0.35-0.88)**	**0.46 (0.29-0.71)**	0.61 (0.38-1.00)	0.66 (0.40-1.09)
Pembrolizumab with chemotherapy: PFS HR (95% CrI)									
Total (FA)	0.89 (0.75-1.06)	**0.48 (0.36-0.64)**	-- [c]	1.01 (0.79-1.30)	1.04 (0.52-2.07)	-- [c]	-- [c]	1.37 (0.84-2.24)	1.38 (0.77-2.48)
Total (5-year)	0.91 (0.77-1.08)	**0.49 (0.37-0.65)**	-- [c]	1.03 (0.80-1.33)	1.06 (0.53-2.11)	-- [c]	-- [c]	1.40 (0.86-2.29)	1.41 (0.79-2.54)
CPS ≥ 1	**0.82 (0.68-1.00)**	**0.44 (0.33-0.59)**	-- [c]	0.93 (0.72-1.21)	0.95 (0.47-1.92)	-- [c]	-- [c]	1.26 (0.77-2.08)	1.27 (0.70-2.30)
CPS ≥ 20	**0.75 (0.58-0.99)**	**0.41 (0.28-0.58)**	-- [c]	0.85 (0.61-1.18)	0.87 (0.42-1.80)	-- [c]	-- [c]	1.15 (0.68-1.98)	1.16 (0.63-2.18)
Pembrolizumab monotherapy: OS HR (95% CrI)									
CPS ≥ 1 (FA)	**0.73 (0.60-0.88)**	**0.62 (0.47-0.83)**	**0.57 (0.38-0.86)**	0.84 (0.64-1.10)	**0.57 (0.39-0.84)**	**0.66 (0.44-0.99)**	**0.55 (0.37-0.80)**	0.73 (0.47-1.14)	0.79 (0.51-1.24)
CPS ≥ 1 (5-year)	**0.73 (0.61-0.88)**	**0.63 (0.47-0.83)**	**0.57 (0.38-0.86)**	0.84 (0.64-1.11)	**0.58 (0.39-0.84)**	**0.66 (0.44-1.00)**	**0.55 (0.38-0.81)**	0.74 (0.48-1.14)	0.80 (0.51-1.24)
CPS ≥ 20	**0.63 (0.48-0.83)**	**0.54 (0.38-0.76)**	**0.49 (0.31-0.78)**	0.72 (0.51-1.02)	**0.49 (0.32-0.77)**	**0.57 (0.36-0.90)**	**0.47 (0.30-0.73)**	0.63 (0.39-1.03)	0.68 (0.42-1.12)
Pembrolizumab monotherapy: PFS HR (95% CrI)									
CPS ≥ 1 (FA)	1.10 (0.93-1.32)	**0.59 (0.45-0.79)**	-- [c]	1.25 (0.97-1.62)	1.28 (0.64-2.57)	-- [c]	-- [c]	**1.69 (1.03-2.79)**	1.71 (0.95-3.08)
CPS ≥ 1 (5-year)	1.12 (0.94-1.34)	**0.61 (0.46-0.81)**	-- [c]	1.27 (0.99-1.64)	1.30 (0.65-2.61)	-- [c]	-- [c]	**1.73 (1.05-2.83)**	1.74 (0.96-3.13)
CPS ≥ 20	0.99 (0.77-1.29)	**0.53 (0.38-0.76)**	-- [c]	1.13 (0.82-1.55)	1.15 (0.56-2.37)	-- [c]	-- [c]	1.52 (0.90-2.59)	1.54 (0.83-2.86)

Bolded results indicate a statistically meaningful estimate, evidenced by a 95% CrI excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab.
[b] The TPEx regimen consists of cisplatin + docetaxel + cetuximab.
[c] PFS hazard ratio or Kaplan-Meier data were not reported for this trial.
5-FU, fluorouracil; 5-year, 5-year follow-up KEYNOTE-048 data; CPS, Combined Positive Score; CrI, credible interval; FA, final analysis KEYNOTE-048 data; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Supplementary Appendix E. Results from the sensitivity network meta-analysis using Tier 1 trials only incorporating KEYNOTE-048 5-year follow-up data

Pembrolizumab with chemotherapy

Overall survival

Supplementary Table E1. Estimated overall survival hazard ratios in the sensitivity network meta-analysis using Tier 1 trials only incorporating KEYNOTE-048 5-year follow-up data for pembrolizumab with chemotherapy in the total population relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	Cisplatin + paclitaxel[c]	TPEx regimen[d]	Cisplatin[e]	5-FU[f]	Methotrexate[g]
	Constant Hazard Ratio (95% Credible Interval)						
	0.72 (0.60-0.86)	**0.58 (0.43-0.76)**	**0.53 (0.35-0.79)**	0.83 (0.63-1.08)	**0.46 (0.30-0.70)**	**0.57 (0.38-0.87)**	**0.50 (0.35-0.74)**
Time point (months)	Time-Varying Hazard Ratio (95% Credible Interval)						
1	1.35 (0.85-2.16)	0.89 (0.44-1.74)	0.77 (0.25-2.30)	1.23 (0.60-2.52)	0.93 (0.34-2.51)	0.84 (0.30-2.34)	1.15 (0.45-2.83)
6	0.82 (0.68-1.00)	**0.65 (0.49-0.88)**	**0.58 (0.38-0.89)**	0.88 (0.66-1.19)	**0.55 (0.36-0.85)**	**0.54 (0.36-0.83)**	**0.56 (0.38-0.83)**
12	**0.68 (0.57-0.82)**	**0.58 (0.44-0.77)**	**0.52 (0.34-0.80)**	0.78 (0.60-1.02)	**0.45 (0.27-0.75)**	**0.45 (0.27-0.77)**	**0.42 (0.27-0.67)**
18	**0.61 (0.49-0.75)**	**0.54 (0.39-0.76)**	**0.49 (0.28-0.84)**	**0.72 (0.53-0.99)**	**0.40 (0.21-0.76)**	**0.41 (0.22-0.80)**	**0.36 (0.21-0.64)**
24	**0.56 (0.44-0.72)**	**0.51 (0.35-0.77)**	**0.47 (0.24-0.89)**	**0.68 (0.47-0.99)**	**0.37 (0.18-0.78)**	**0.38 (0.18-0.83)**	**0.32 (0.17-0.62)**
30	**0.53 (0.40-0.70)**	**0.49 (0.32-0.78)**	**0.45 (0.21-0.94)**	0.66 (0.43-1.00)	**0.34 (0.15-0.80)**	**0.36 (0.15-0.87)**	**0.29 (0.14-0.62)**
36	**0.50 (0.37-0.68)**	**0.48 (0.30-0.79)**	**0.44 (0.19-0.99)**	0.64 (0.40-1.01)	**0.33 (0.13-0.82)**	**0.34 (0.14-0.90)**	**0.27 (0.12-0.61)**
42	**0.48 (0.35-0.67)**	**0.47 (0.28-0.80)**	0.43 (0.18-1.04)	0.62 (0.37-1.02)	**0.31 (0.12-0.85)**	**0.33 (0.12-0.93)**	**0.25 (0.11-0.61)**
48	**0.47 (0.33-0.66)**	**0.46 (0.26-0.81)**	0.42 (0.16-1.08)	0.60 (0.35-1.03)	**0.30 (0.11-0.86)**	**0.32 (0.11-0.96)**	**0.24 (0.10-0.61)**
54	**0.45 (0.31-0.65)**	**0.45 (0.25-0.82)**	0.41 (0.15-1.11)	0.59 (0.33-1.04)	**0.29 (0.10-0.88)**	**0.31 (0.10-0.98)**	**0.23 (0.09-0.61)**
60	**0.44 (0.30-0.64)**	**0.44 (0.24-0.83)**	0.40 (0.14-1.15)	0.58 (0.32-1.05)	**0.28 (0.09-0.89)**	0.30 (0.09-1.00)	**0.22 (0.08-0.61)**
66	**0.43 (0.29-0.64)**	**0.43 (0.23-0.84)**	0.40 (0.13-1.18)	0.57 (0.30-1.06)	**0.27 (0.09-0.90)**	0.29 (0.09-1.02)	**0.21 (0.08-0.61)**
72	**0.42 (0.28-0.63)**	**0.42 (0.22-0.85)**	0.39 (0.13-1.22)	0.56 (0.29-1.06)	**0.27 (0.08-0.92)**	0.29 (0.08-1.04)	**0.20 (0.07-0.61)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 72 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 54 (inclusive).
[c] Survival data were available for cisplatin + paclitaxel through month 54 (inclusive).
[d] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 42 (inclusive).
[e] Survival data were available for cisplatin through month 30 (inclusive).
[f] Survival data were available for 5-FU through month 24 (inclusive).
[g] Survival data were available for methotrexate through month 36 (inclusive).
5-FU, fluorouracil.

Progression-free survival

Supplementary Table E2. Estimated progression-free survival hazard ratios in the sensitivity network meta-analysis using Tier 1 trials only incorporating KEYNOTE-048 5-year follow-up data for pembrolizumab with chemotherapy in the total population relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	TPEx regimen[c]
	Constant Hazard Ratio (95% Credible Interval)		
	0.91 (0.77-1.08)	**0.49 (0.37-0.65)**	1.03 (0.81-1.32)
Time points (months)	Time-Varying Hazard Ratio (95% Credible Interval)		
1	**1.58 (1.07-2.32)**	0.88 (0.46-1.65)	1.45 (0.82-2.64)
6	0.90 (0.75-1.06)	**0.51 (0.37-0.69)**	1.05 (0.82-1.34)
12	**0.72 (0.57-0.90)**	**0.41 (0.25-0.67)**	0.92 (0.66-1.28)
18	**0.63 (0.47-0.84)**	**0.36 (0.19-0.67)**	0.86 (0.56-1.30)
24	**0.58 (0.41-0.81)**	**0.33 (0.16-0.68)**	0.81 (0.49-1.32)
30	**0.54 (0.37-0.78)**	**0.31 (0.14-0.69)**	0.78 (0.45-1.35)
36	**0.51 (0.34-0.76)**	**0.29 (0.12-0.70)**	0.75 (0.41-1.37)
42	**0.48 (0.31-0.75)**	**0.28 (0.11-0.71)**	0.73 (0.38-1.39)
48	**0.46 (0.29-0.73)**	**0.27 (0.10-0.71)**	0.72 (0.36-1.41)
54	**0.45 (0.28-0.72)**	**0.26 (0.09-0.72)**	0.70 (0.34-1.42)
60	**0.43 (0.26-0.71)**	**0.25 (0.09-0.72)**	0.69 (0.32-1.44)
66	**0.42 (0.25-0.70)**	**0.24 (0.08-0.72)**	0.68 (0.31-1.45)
72	**0.41 (0.24-0.70)**	**0.24 (0.08-0.73)**	0.67 (0.30-1.46)

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 66 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 12 (inclusive).
[c] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available for platinum + 5-FU through month 42 (inclusive).
5-FU, fluorouracil.

Pembrolizumab monotherapy

Overall survival

Supplementary Table E3. Estimated overall survival hazard ratios in the sensitivity network meta-analysis using Tier 1 trials only incorporating KEYNOTE-048 5-year follow-up data for pembrolizumab monotherapy in the CPS ≥1 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regimen[a]	Platinum + 5-FU[b]	Cisplatin + paclitaxel[c]	TPEx regimen[d]	Cisplatin[e]	5-FU[f]	Methotrexate[g]
	Constant Hazard Ratio (95% Credible Interval)						
	0.73 (0.61-0.88)	**0.59 (0.44-0.78)**	**0.54 (0.36-0.81)**	0.84 (0.64-1.10)	**0.47 (0.31-0.72)**	**0.58 (0.38-0.89)**	**0.51 (0.35-0.76)**
Time point (months)	Time-Varying Hazard Ratio (95% Credible Interval)						
1	1.42 (0.88-2.26)	0.94 (0.46-1.83)	0.81 (0.26-2.37)	1.29 (0.64-2.61)	0.98 (0.35-2.60)	0.89 (0.31-2.44)	1.21 (0.48-2.98)
6	0.84 (0.68-1.03)	**0.67 (0.50-0.89)**	**0.59 (0.39-0.90)**	0.90 (0.67-1.21)	**0.56 (0.37-0.86)**	**0.55 (0.36-0.85)**	**0.57 (0.39-0.85)**
12	**0.69 (0.57-0.83)**	**0.59 (0.44-0.78)**	**0.52 (0.34-0.81)**	0.79 (0.60-1.03)	**0.45 (0.28-0.76)**	**0.46 (0.27-0.78)**	**0.43 (0.27-0.68)**
18	**0.61 (0.49-0.76)**	**0.54 (0.38-0.77)**	**0.49 (0.28-0.84)**	0.72 (0.53-1.00)	**0.40 (0.22-0.77)**	**0.41 (0.21-0.81)**	**0.36 (0.21-0.64)**
24	**0.56 (0.43-0.72)**	**0.51 (0.34-0.77)**	**0.47 (0.24-0.89)**	0.68 (0.47-1.00)	**0.37 (0.18-0.78)**	**0.38 (0.18-0.85)**	**0.32 (0.17-0.62)**
30	**0.53 (0.39-0.70)**	**0.49 (0.31-0.78)**	**0.45 (0.21-0.94)**	0.65 (0.43-1.01)	**0.34 (0.15-0.80)**	**0.36 (0.15-0.88)**	**0.29 (0.14-0.61)**
36	**0.50 (0.36-0.68)**	**0.48 (0.29-0.79)**	**0.44 (0.19-0.98)**	0.63 (0.39-1.01)	**0.32 (0.13-0.81)**	**0.34 (0.13-0.91)**	**0.27 (0.12-0.61)**
42	**0.48 (0.34-0.67)**	**0.46 (0.27-0.79)**	0.42 (0.17-1.02)	0.61 (0.37-1.02)	**0.31 (0.12-0.82)**	**0.33 (0.12-0.94)**	**0.25 (0.11-0.60)**
48	**0.46 (0.32-0.66)**	**0.45 (0.26-0.80)**	0.41 (0.16-1.05)	0.59 (0.35-1.03)	**0.30 (0.11-0.84)**	**0.31 (0.11-0.96)**	**0.24 (0.10-0.60)**
54	**0.44 (0.30-0.65)**	**0.44 (0.24-0.81)**	0.41 (0.15-1.09)	0.58 (0.33-1.03)	**0.29 (0.10-0.86)**	**0.30 (0.10-0.99)**	**0.23 (0.09-0.60)**
60	**0.43 (0.29-0.64)**	**0.43 (0.23-0.82)**	0.40 (0.14-1.12)	0.57 (0.31-1.04)	**0.28 (0.09-0.87)**	0.30 (0.09-1.01)	**0.22 (0.08-0.60)**
66	**0.42 (0.27-0.64)**	**0.42 (0.22-0.82)**	0.39 (0.13-1.15)	0.56 (0.30-1.04)	**0.27 (0.09-0.87)**	0.29 (0.09-1.03)	**0.21 (0.08-0.60)**
72	**0.41 (0.26-0.63)**	**0.42 (0.21-0.83)**	0.39 (0.12-1.19)	0.55 (0.28-1.05)	**0.26 (0.08-0.89)**	0.28 (0.08-1.04)	**0.20 (0.07-0.60)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 72 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 54 (inclusive).
[c] Survival data were available for cisplatin + paclitaxel through month 54 (inclusive).
[d] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 42 (inclusive).
[e] Survival data were available for cisplatin through month 30 (inclusive).
[f] Survival data were available for 5-FU through month 24 (inclusive).
[g] Survival data were available for methotrexate through month 36 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

Progression-free survival

Supplementary Table E4. Estimated progression-free survival hazard ratios in the sensitivity network meta-analysis using Tier 1 trials only incorporating KEYNOTE-048 5-year follow-up data for pembrolizumab monotherapy in the CPS ≥ 1 subgroup relative to alternative interventions from fixed-effects model using constant and time-varying hazard ratios

	EXTREME regime [a]	Platinum + 5-FU[b]	TPEx regimen[c]
	Constant Hazard Ratio (95% Credible Interval)		
	1.12 (0.94-1.34)	**0.61 (0.46-0.81)**	1.27 (0.99-1.64)
Time points (months)	**Time-Varying Hazard Ratio (95% Credible Interval)**		
1	**2.69 (1.84-3.99)**	1.52 (0.81-2.84)	**2.44 (1.39-4.38)**
6	0.98 (0.82-1.18)	**0.55 (0.40-0.75)**	1.16 (0.90-1.49)
12	**0.67 (0.52-0.86)**	**0.37 (0.23-0.61)**	0.87 (0.61-1.22)
18	**0.53 (0.38-0.73)**	**0.29 (0.16-0.56)**	0.73 (0.47-1.13)
24	**0.45 (0.31-0.65)**	**0.25 (0.12-0.52)**	0.65 (0.39-1.07)
30	**0.40 (0.26-0.60)**	**0.22 (0.10-0.50)**	0.59 (0.33-1.04)
36	**0.36 (0.23-0.56)**	**0.20 (0.08-0.49)**	0.55 (0.29-1.01)
42	**0.33 (0.20-0.53)**	**0.18 (0.07-0.47)**	**0.51 (0.26-0.99)**
48	**0.31 (0.18-0.50)**	**0.17 (0.06-0.46)**	**0.48 (0.24-0.97)**
54	**0.29 (0.17-0.48)**	**0.16 (0.06-0.45)**	**0.46 (0.22-0.96)**
60	**0.27 (0.15-0.46)**	**0.15 (0.05-0.44)**	**0.44 (0.20-0.94)**
66	**0.26 (0.14-0.45)**	**0.14 (0.05-0.43)**	**0.42 (0.19-0.93)**
72	**0.24 (0.13-0.43)**	**0.13 (0.04-0.43)**	**0.41 (0.18-0.92)**

Bolded results indicate a statistically meaningful estimate at the given time point, evidenced by a 95% credible interval excluding 1.
[a] The EXTREME regimen consists of platinum + 5-FU + cetuximab. Survival data were available through month 72 (inclusive).
[b] Survival data were available for platinum + 5-FU through month 12 (inclusive).
[c] The TPEx regimen consists of cisplatin + docetaxel + cetuximab. Survival data were available through month 42 (inclusive).
5-FU, fluorouracil; CPS, Combined Positive Score.

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