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Immune-checkpoint inhibitor plus chemotherapy *versus* conventional chemotherapy for treatment of recurrent or metastatic head and neck squamous cell carcinoma: a systematic review and network meta-analysis

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Abstract

Background: Multiple therapies including immune-checkpoint inhibitors are emerging as effective treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSSC). However, the optimal first-line and second-line treatments remains controversial.

Methods: We systematically searched databases and conducted a systematic review of phase II/III randomized controlled trials (RCTs) that compared two or more treatments for R/M HNSSC. Progression-free survival (PFS), overall survival (OS) and adverse events (AEs) ⩾3 with hazard ratios (HRs) were extracted and synthesized based on a frequentist network meta-analysis.

Results: Twenty-six trials involving 8908 patients were included. Of first-line treatments, pembrolizumab plus cisplatin plus 5-fluorouracil is associated with significantly improved OS (P-score = 0.91) and TPEx ranked first for prolonging PFS (0.91). EXTREME plus docetaxel (0.18) ranked lowest for AEs ⩾3. Of second-line treatments, nivolumab was the highest-ranked treatment for prolonging OS (0.95), while buparlisib plus paclitaxel was the highest-ranked treatment for PFS (0.94). Subgroup analyses suggested that nivolumab was significantly associated with improvement of OS in patients with high PD-L1 expression (HR 0.55, 0.43–0.70), whereas its OS benefit is similar with conventional chemotherapy for those with low PD-L1 expression. Buparlisib plus paclitaxel showed the best OS benefit in subgroups of patients with HPV-negative status, and with oral cavity or larynx as primary tumor sites.

Conclusions: Pembrolizumab plus cisplatin plus 5-fluorouracil is likely to be the best first-line treatment when OS is a priority. Otherwise, TPEx should be the optimal first-line option due to its superior PFS prolongation efficacy, best safety profile, and similar OS benefit with pembrolizumab plus cisplatin plus 5-fluorouracil. Nivolumab appears to be the best second-line option with best OS prolongation efficacy and outstanding safety profile in the overall population. Future RCTs with meticulous grouping of patients and detailed reporting are urgently needed for individualized treatment.

Keywords: chemotherapy, immune-checkpoint inhibitor, network meta-analysis, recurrent or metastatic head and neck carcinoma

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Background

Head and Neck Squamous Cell Carcinoma (HNSCC) is one of the seven most common malignancies.[1] Despite aggressive multi-modality therapies, a significant proportion of patients develop recurrence and metastasis with a poor prognosis.[2] For patients with recurrent or metastatic HNSCC (R/M HNSSC), the EXTREME regimen has been established as standard of care in the first-line treatment for more than 10 years.[3] This regimen is a platinum-based chemotherapy with introduction of cetuximab, followed by maintenance cetuximab, and it confers improved survival benefits and quality of life, with overall response rates between 36% and 44%, median survival over 10 months, and significant reduction in pain. However, the overall survival (OS) in R/M HNSSC patients hardly exceeds 1 year.[4]

Recently, several trials reported promising antitumor activities and safety profiles of immune-checkpoint inhibitors (ICIs) in R/M HNSSC, such as pembrolizumab and nivolumab.[5–7] As a result, the latest National Comprehensive Cancer Network (NCCN) guidelines included ICI therapy as first- and second-line recommended treatment for R/M HNSSC patients.[8] However, no consensus has been reached on the optimal therapies in either first- or second-line treatments, and EXTREME regimen is currently juxtaposed with ICI therapies as preferred first-line regimens according to the NCCN guidelines.[8] In addition, there are many emerging chemotherapies that have shown promising antitumor activity in randomized controlled trials (RCTs). For instance, encouraging survival results of the taxane-based TPEx regimen was observed in the TPExtreme randomized trial.[9] Another recent trial, the BERIL-1 study, demonstrated a manageable safety profile and improved clinical efficacy of buparlisib plus paclitaxel in platinum-pretreated R/M HNSSC.[10]

The diversity of options in the guidelines and many emerging promising therapies have overburdened clinical decision-making. Therefore, we performed a network meta-analysis (NMA) to compare the relative efficacy and safety of different treatment options for advance.[11–13]

Methods

The reporting of this study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMAs (supplemental material Table S1),[14] and our protocol was registered in Prospective Register of Systematic Reviews (CRD42020155865).

Search strategy

We performed searches on PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), using a combination of the following terms: "Squamous Cell Carcinoma of Head and Neck," "Recurrent" or "Metastatic" with the filter of "Randomized Controlled Trial" to find relevant studies from inception to 1 December 2019, with no restriction on language or status. In addition, for including complete and updated outcomes, unpublished research results from Clinicaltrials.gov, abstracts and presentations of ongoing RCTs were inspected, and reference lists of the relevant articles were examined. The detailed search strategy is presented in the supplemental Table S2.

We included published and unpublished phase II/III RCTs assessing first- or second-line treatments in patients with R/M HNSSC. The detailed eligibility criteria and exclusion criteria are as described in the supplemental Methods. If a multi-arm trial compared more than two drugs or two different doses of one drug with another, we treated them as separate pairwise comparisons. Two investigators (ZJ and BZ) independently screened the articles and abstracts according to the eligibility criteria. Disagreements were resolved by consensus.

Data extraction

Details of the study (e.g. study ID, publication year, author, number of patients), patient characteristics (e.g. age, sex, lines of treatment, HPV infection status, PD-L1 expression level), treatments, and outcomes [hazard ratios (HRs) and their 95% credible intervals (CI) for OS and progression-free survival (PFS), and the number of patients experiencing adverse events (AEs) grade $\geqslant$3] were extracted into an Excel sheet. For studies with unclear or unreported data, we assessed the corresponding data reported in ClinicalTrials.gov or contacted the authors. Survival data extracted were double-checked by a third reviewer (LZ) to avoid potential assessment bias by investigators. Two independent reviewers (ZJ and LZ) assessed the risk of bias for all included RCTs using the Cochrane Collaboration's tool.[15] Any disagreements were resolved through consultation by a research team (BZ, LZ, WhH, and SxZ).

Statistical analysis

We conducted NMAs based on a frequentist approach to calculate the pooled effect estimates and uncertainty for all interventions compared with the reference treatment. Comparative efficacy and safety are reported as HR for PFS and OS and odds ratio (OR) for AEs ⩾ grade 3 along with 95% CI. Fixed-effect models were fitted if quantification of heterogeneity was not possible; otherwise, random-effects models were used.[16] Statistical significance was set at a *p*-value of 0.05. Heterogeneity and inconsistency were assessed by the between-study variance τ^2 value, Cochran Q with a *p*-value, and I^2. Overall ranks of treatments were estimated by P-scores which were based solely on the point estimates and standard errors of the network estimates.[17] Treatments with highest and lowest P-scores are considered to be the best and worst treatments, respectively. Additionally, subgroup analyses were based on the patient's primary tumor sites, HPV infection status, PD-L1 expression level, and Eastern Cooperative Oncology Group performance status (ECOG PS). The network meta-analysis was completed using the netmeta package (version 1.2-1, Rűcker *et al.*, 2020[18]) within the R Environment (version 4.0.3, R Core Team, 2020).

Results

Study selection

In total, 431 studies were identified through database search and 186 additional studies were identified through trial registers, international conferences, references of reviews, and other sources. Twenty RCTs[5–7,10,19–34] with full texts and six with abstracts only[9,35–39] met the eligibility for assessment (Figure 1). The amount of evidence included is illustrated using a network diagram (Figure 2A, 3A). Of the 20 trials with full text, seven were double blinded. Fourteen and 12 trials involved first-line and second-line treatments, respectively.

Study characteristics

A total of 8908 patients with 25 different treatments including chemotherapies [cisplatin, methotrexate, taxanes, and platinum-based chemotherapy (PBC)], EGFR inhibitors (cetuximab, gefitinib, and afatinib), PD-1/L1 inhibitors (nivolumab, pembrolizumab, durvalumab), and 18 combinations of these therapies were analyzed. Nearly all trials comprised male-dominated populations with a median age of 60 years. The characteristics of trials are described in the supplemental Table S3. EXTREME regimen (platinum plus cetuximab plus 5-fluorouracil) has been considered as the first-line standard treatment for R/M HNSSC for the past decade, while the second-line standard of care (SOC) includes a monotherapy of any of the following drugs: cisplatin, methotrexate, taxanes, and cetuximab. Therefore, they were used as the reference in our NMAs of first-line and second-line treatments, respectively. Risk of bias assessments of each individual study are summarized in the supplemental Figure S1.

Network meta-analysis of first-line treatments

A total of 14 trials were included for NMA of first-line treatments, with 15 and 14 treatments included for PFS and OS analysis, respectively (Figure 2A). Pooled estimates for each outcome are presented in supplemental Figure S2.

In terms of PFS benefit (Figure 2C), TPEx (HR 0.65, 95% CI 0.48–0.89), platinum plus cetuximab (0.66, 0.42–1.03), and patritumab plus cetuximab plus platinum (0.65, 0.32–1.32) yielded similar efficacy, but the latter two did not achieve statistically significant difference with the EXTREME regimen. Pembrolizumab plus cisplatin plus 5-fluorouracil, EXTREME plus docetaxel, CetuGEX plus cisplatin plus 5-fluorouracil, EXTREME regimen, EXTREME plus motolimod, and EXTREME plus CIL1W shared similar efficacy, as the HRs of their comparisons were equal or close to 1. The efficacy of the remaining treatments were weaker than that of EXTREME regimen, because their HRs exceeded 1.

In terms of OS benefit (Figure 2D), pembrolizumab plus cisplatin plus 5-fluorouracil was the best (HR 0.77, 95% CI 0.66–0.89). TPEx regimen gained the second-best OS benefit (0.84, 0.72–0.98), followed by pembrolizumab (0.85, 0.72–1.00), which was the only monotherapy of the first-line treatments included. However, the remaining treatments showed no superiority over EXTREME regimen in prolonging OS, especially PBC.

Regarding AEs ⩾ grade 3 (supplemental Figure S2), TPEx showed the least toxicity among the comparable treatments (OR 0.64, 95% CI 0.48–0.85), followed by pembrolizumab (0.66, 0.51–0.85). PBC, EXTREME plus CIL1W, patritumab

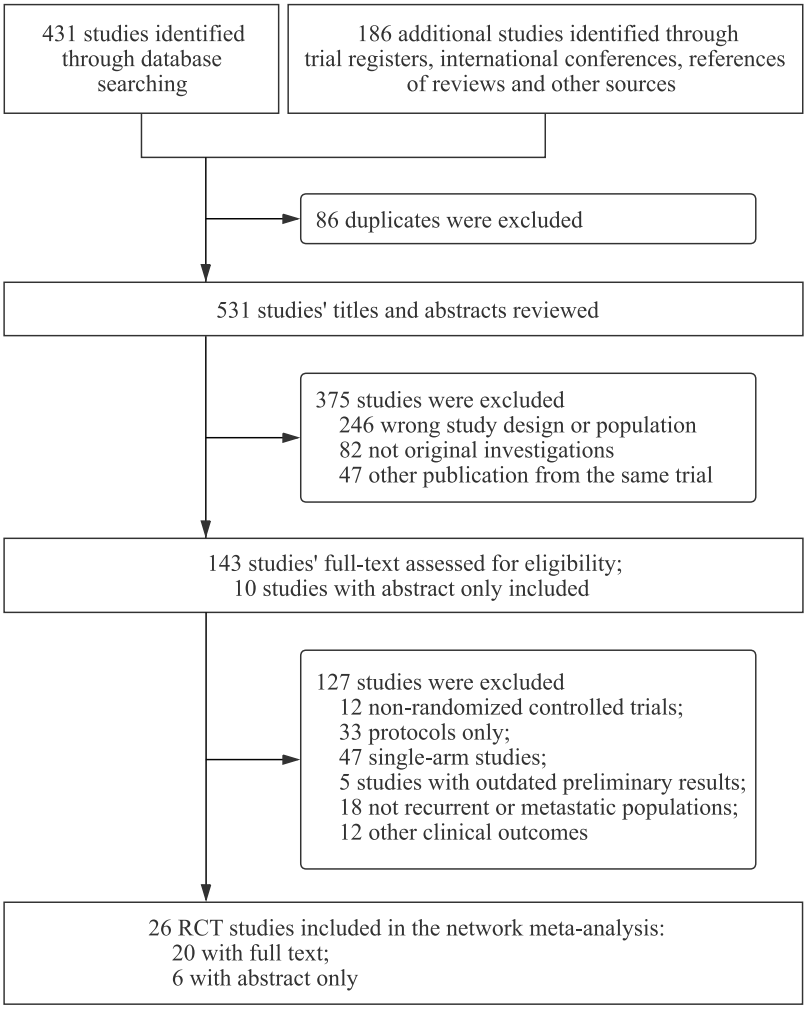


Figure 1. PRISMA flowchart.

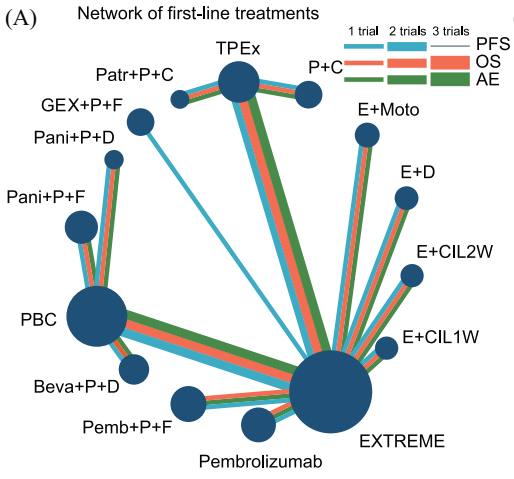
plus cetuximab plus platinum, EXTREME plus motolimod, EXTREME regimen, panitumumab plus cisplatin plus 5-FU, EXTREME plus CIL2W, and pembrolizumab plus cisplatin plus 5-fluorouracil were associated with similar risk of AEs ⩾ grade 3. EXTREME plus docetaxel was associated with the highest risk of AEs ⩾ grade 3 (1.45, 0.71–2.99).

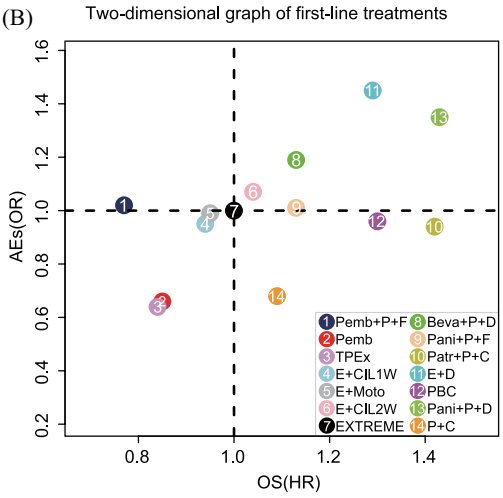
Network meta-analysis of second-line treatments

Twelve trials including a total of 10 and 12 second-line treatments were included for PFS and for OS analysis, respectively (Figure 3A). Pooled estimates for each outcome are presented in the supplemental Figure S3.

In terms of PFS (Figure 3C), buparlisib plus paclitaxel (HR 0.65, 95% CI 0.51–0.83) and afatinib (0.71, 0.63–0.80) yielded significant differences against SOC. However, beyond these two treatments, there were no statistically significant differences with SOC observed among platinum plus cetuximab, PBC, nivolumab, pembrolizumab, durvalumab, EMD1201081 plus cetuximab, and durvalumab plus tremelimumab.

In terms of OS (Figure 3D), nivolumab (HR 0.68, 95% CI 0.58–0.80) not only yielded the best benefit in all monotherapies [*versus* pembrolizumab (0.85, 0.68–1.07), durvalumab (0.77, 0.61–0.98), afatinib (0.73, 0.59–0.90), gefitinib (500 mg) (0.61, 0.44–0.84), and gefitinib (250 mg) (0.56, 0.39–0.79)], but also showed a beneficial trend over other combination treatments [buparlisib plus paclitaxel (0.94, 0.69–1.30), PBC (0.78, 0.63–0.96), gefitinib plus docetaxel (0.73, 0.55–0.98), and durvalumab plus tremelimumab (0.65, 0.50–0.85)].

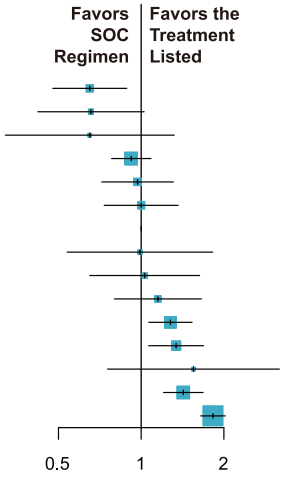




(C) PFS of first-line treatments: other vs 'EXTREME'

Treatment	No. of patients	HR 95%CI	P-score
TPEx	133	0.65 [0.48; 0.89]	0.91
P+C	143	0.66 [0.42; 1.03]	0.89
Patr+P+C	44	0.65 [0.32; 1.32]	0.85
Pemb+P+F	281	0.92 [0.78; 1.09]	0.68
E+D	89	0.97 [0.72; 1.31]	0.60
GEX+P+F	117	1.00 [0.73; 1.36]	0.57
EXTREME	1100	1.00	0.57
E+Moto	100	0.99 [0.54; 1.82]	0.56
E+CIL1W	62	1.03 [0.65; 1.63]	0.53
Pani+P+D	56	1.15 [0.80; 1.66]	0.41
Beva+P+D	203	1.28 [1.07; 1.53]	0.29
Pemb	301	1.34 [1.06; 1.69]	0.24
E+CIL2W	60	1.55 [0.75; 3.18]	0.20
Pani+P+F	327	1.42 [1.21; 1.68]	0.18
PBC	884	1.83 [1.65; 2.02]	0.03

Subtotal τ2 = not estimable; I2 = not estimable; Cochran Q = 0.21; P = 0.6496



(D) OS of first-line treatments: other vs 'EXTREME'

Treatment	No. of patients	HR 95%CI	P-score
Pemb+P+F	281	0.77 [0.66; 0.89]	0.91
TPEx	403	0.84 [0.72; 0.98]	0.82
Pemb	301	0.85 [0.72; 1.00]	0.80
E+CIL1W	62	0.94 [0.61; 1.45]	0.64
E+Moto	100	0.95 [0.52; 1.75]	0.61
EXTREME	1247	1.00	0.57
E+CIL2W	60	1.04 [0.64; 1.69]	0.51
P+C	143	1.09 [0.78; 1.51]	0.45
Beva+P+D	203	1.13 [0.89; 1.44]	0.40
Pani+P+F	327	1.13 [0.91; 1.40]	0.40
Patr+P+C	44	1.42 [0.60; 3.36]	0.27
E+D	89	1.29 [0.86; 1.92]	0.26
Pani+P+D	56	1.43 [0.85; 2.42]	0.19
PBC	884	1.30 [1.13; 1.50]	0.19

Subtotal τ2 = not estimable; I2 = not estimable; Cochran Q = 1.58; P = 0.4533

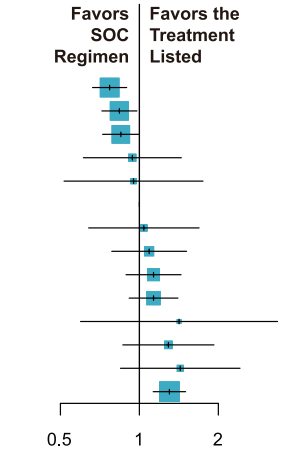
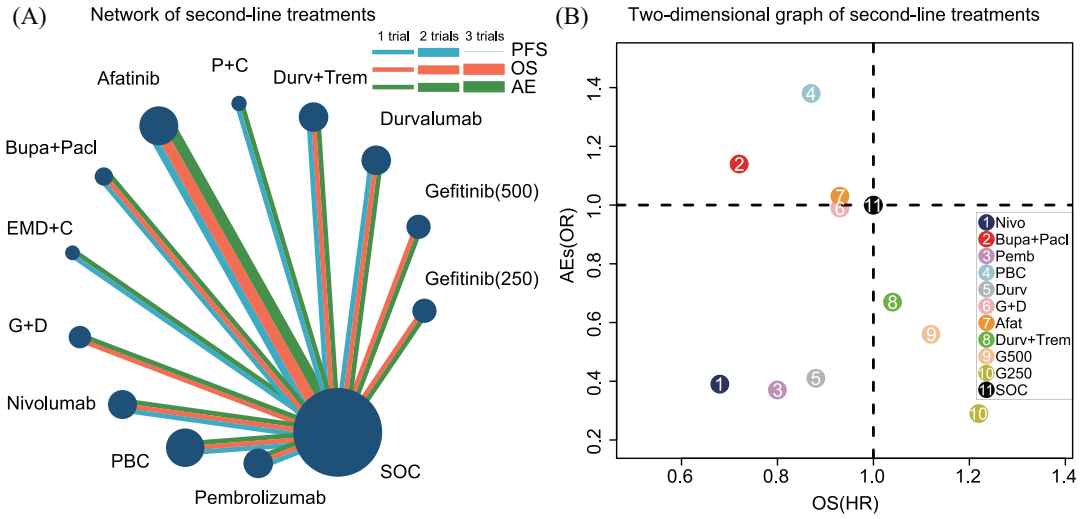


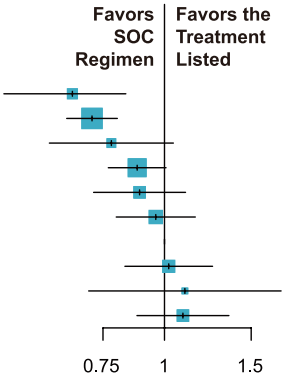
Figure 2. Network and treatment efficacy of first-line treatments.
(A) Comparisons of progression-free survival (PFS) (blue line), overall survival (OS) (orange line), and unacceptable adverse events (green line) among first-line treatments. The node size is proportional to the total number of patients who received treatment. Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. (B) The abscissa value corresponding to a point on the two-dimensional map is the Pooled hazard ratios (95% CI) for OS of a particular treatment, and the ordinate value is the odds ratios (95% CI) for AEs ⩾ grade 3. The more to the left and lower the point is, the longer the OS is and fewer AEs ⩾ grade 3 are associated with the corresponding therapy. (C) Forest plots depicting PFS results of first-line comparisons. (D) Forest plots depicting OS results of first-line comparisons.
AEs, grade ⩾3 adverse events; Beva+P+D, bevacizumab plus cisplatin plus docetaxel; CI, confidence interval; E+CIL1W, EXTREME plus CIL1W; E+CIL2W, EXTREME plus CIL2W; E+D, EXTREME plus docetaxel; E+Moto, EXTREME plus motolimod; GEX+P+F, CetuGEX plus 5-fluorouracil plus cisplatin; HR, hazard ratio; Nivo, nivolumab; P+C, platinum plus cetuximab; Pani+P+D, panitumumab plus cisplatin plus docetaxel; Pani+P+F, panitumumab plus cisplatin plus 5-fluorouracil; Patr+P+C, patritumab plus cetuximab plus platinum; PBC, platinum-based chemotherapy; Pemb, pembrolizumab; Pemb+P+F, pembrolizumab plus cisplatin plus 5-fluorouracil; PFS, progression-free survival; TPEx, cisplatin plus cetuximab plus taxane.



(C) PFS of second-line treatments: other vs 'SOC'

Treatment	No. of patients	HR 95%CI	P-score
Bupa+Pacl	79	0.65 [0.51; 0.83]	0.94
Afat	550	0.71 [0.63; 0.80]	0.88
P+C	57	0.78 [0.58; 1.04]	0.74
PBC	398	0.88 [0.77; 1.01]	0.58
Nivo	240	0.89 [0.72; 1.10]	0.54
Pemb	247	0.96 [0.80; 1.16]	0.39
SOC	1481	1.00	0.29
Durv	240	1.02 [0.83; 1.25]	0.27
EMD+C	53	1.10 [0.70; 1.73]	0.23
Durv+Trem	247	1.09 [0.88; 1.35]	0.16

Subtotal τ2 = not estimable; I2 = not estimable; Cochran Q = 0.63; P = 0.7315



(D) OS of second-line treatments: other vs 'SOC'

Treatment	No. of patients	HR 95%CI	P-score
Nivo	240	0.68 [0.58; 0.80]	0.95
Bupa+Pacl	79	0.72 [0.55; 0.95]	0.87
Pemb	247	0.80 [0.68; 0.94]	0.76
PBC	398	0.87 [0.76; 1.00]	0.61
Durv	240	0.88 [0.74; 1.05]	0.58
G+D	134	0.93 [0.73; 1.19]	0.47
Afat	611	0.93 [0.81; 1.08]	0.46
SOC	1724	1.00	0.29
Durv+Trem	247	1.04 [0.85; 1.28]	0.25
G500	167	1.12 [0.85; 1.48]	0.17
G250	158	1.22 [0.89; 1.66]	0.09

Subtotal τ2 = 0.0212; I2 = 74.4%; Cochran Q = 3.91; P = 0.0481

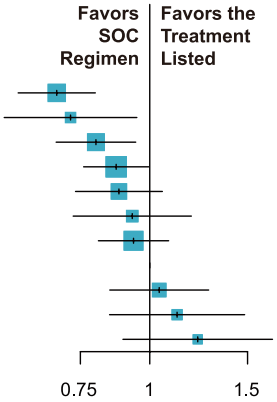


Figure 3. Network and treatment efficacy of second-line treatments.
(A) Comparisons of progression-free survival (PFS) (blue line), overall survival (OS) (orange line), and unacceptable adverse events (green line) among second-line treatments. The node size is proportional to the total number of patients who received treatment. Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. (B) The abscissa value corresponding to a point on the two-dimensional map is the Pooled hazard ratios (95% CI) for OS of a particular treatment, and the ordinate value is the odds ratios (95%CI) for AEs ⩾ grade 3. The more to the left and lower the point is, the longer the OS is and fewer AEs ⩾ grade 3 are associated with the corresponding therapy. (C) Forest plots depicting PFS results of second-line comparisons. (D) Forest plots depicting OS results of second-line comparisons.
AEs, grade ⩾3 adverse events; Afat, afatinib; Bupa+Pacl, buparlisib plus paclitaxel; CI, confidence interval; Durv, durvalumab; Durv+Trem, durvalumab plus tremelimumab; EMD+C, EMD1201081 plus cetuximab; G+D, gefitinib (250 mg) plus docetaxel; G250, gefitinib (250 mg); G500, gefitinib (500 mg); HR, hazard ratio; Nivo, nivolumab; P+C, platinum plus cetuximab; PBC, platinum-based chemotherapy; Pemb, pembrolizumab; PFS, progression-free survival; SOC, standard of care.

Regarding AEs ⩾ grade 3 (supplemental Figure S3), except for gefitinib (250 mg) that showed the least AEs ⩾ grade 3 (OR 0.29, 95% CI 0.16–0.52), ICIs showed less toxicity among the treatments compared, in particular for pembrolizumab (0.37, 0.24–0.57) and nivolumab (0.39, 0.23–0.65) ranking second-least and third-least, respectively. Combination treatments were associated with an increase of AEs ⩾ grade 3 risks in reference to buparlisib plus paclitaxel (1.14, 0.70–1.84), and platinum plus cetuximab (1.24, 0.72–2.14). Furthermore, PBC was likely to produce the most AEs ⩾ grade 3 (1.38, 1.06–1.79).

Subgroup analyses of second-line treatments

Due to data limitation, only OS subgroup analyses of second-line treatments were conducted. The subgroups stratified by HPV infection status, PD-L1 expression level, and ECOG PS each included four treatments, and the subgroup stratified by primary tumor sites included five treatments (supplemental Figures S4–S6).

Nivolumab was the most effective drug in prolonging OS for HPV-positive patients (HR 0.56, 95% CI 0.40–0.78), while buparlisib plus paclitaxel was preferred in HPV-negative patients (0.61, 0.47–0.79) followed by nivolumab. Different standards were adopted to define the expression of PD-L1 in separate trials. Therefore the patients were divided into high- and low-expression subgroups, correlated with the criteria of the original trial.[6,7] Performances of nivolumab and pembrolizumab were consistently different between two groups, showing a promising effect on patients with high expression of PD-L1, [(0.55, 0.43–0.70) and (0.74, 0.62–0.88), respectively], but no statistically significant impact on those with low expression. Nivolumab showed consistent optimal efficacy in both ECOG PS = 0 (0.60, 0.38–0.96) and ECOG PS ⩾ 1 groups (0. 71, 0.57–0.88). Notably, OS benefits of pembrolizumab was no different from SOC in patients with ECOG PS = 0 (0. 87, 0.60–1.27). For patients whose primary tumor site is oral cavity, buparlisib plus paclitaxel showed the most optimal efficacy (0.55, 0.36–0.84). PBC delivers the most significant benefits to patients whose primary tumor site is oral pharynx (0.57, 0.46–0.70). And there was no significant difference in efficacy between the five treatments for those with larynx as their primary tumor site.

Ranking

Ranking profiles of comparable treatments on efficacy and safety are depicted as hot-spot maps according to P-scores which were based solely on the point estimates and standard errors of the network estimates (supplemental Figure S7). Larger P-score indicates the treatment is better than many others. Two-dimensional graphs (Figures 2B and 3B) were drawn to compare the OS benefits and safety of treatments simultaneously. Of first-line treatments, pembrolizumab plus cisplatin plus 5-fluorouracil was most likely to be ranked first in terms of OS (P-score = 0.91). TPEx was the preferred option with respect to PFS (P-score = 0.91) with the least risk of AEs ⩾ grade 3 (P-score = 0.90). EXTREME plus docetaxel was most likely to show the most AEs ⩾ grade 3 (P-score = 0.18). Of second-line treatments, nivolumab was most likely to be ranked first in terms of OS (P-score = 0.95). Buparlisib plus paclitaxel was the preferred option concerning PFS (P-score = 0.94). PBC was most likely to be ranked last in terms of AEs ⩾ grade 3 (P-score = 0.09). Gefitinib (250 mg) had the lowest risk of AEs ⩾ grade 3 (P-score = 0.94), followed by pembrolizumab (P-score = 0.86) and nivolumab (P-score = 0.84).

Discussion

Principal findings and implications

This is the first NMA that assessed the comparative efficacy and safety of first-line and second-line treatments in R/M HNSSC. Our findings should assist clinicians in selecting the most appropriate treatments for R/M HNSSC.

Of first-line treatments, pembrolizumab plus cisplatin plus 5-fluorouracil is likely to be considered as the best choice due to its best OS benefit, which is often used as the primary outcome to measure the efficacy of antineoplastic agents. We observed that regarding PFS benefit of the first-line therapy, the performances of pembrolizumab and PBC were weaker than those of the EXTREME. However, the PFS of pembrolizumab plus cisplatin plus 5-fluorouracil group was significantly better than that of the EXTREME group. It is suggested that the combination of immunotherapy and chemotherapy may have a synergistic effect on patients with HNSSC. Meanwhile, such PFS benefits were also transformed into OS benefits. OS of the

pembrolizumab plus cisplatin plus 5-fluorouracil group was significantly better than that of the EXTREME group, with similar risk of AEs ⩾ grade 3. Moreover, it is apparent that the benefits were greater for OS than for PFS in both nivolumab and pembrolizumab, either as first-line or second-line treatment. A meta-analysis of ICIs in the treatment of nasopharyngeal carcinoma showed consistent results with those of the present study.[40] Several hypotheses may explain this phenomenon: (1) the response patterns of patients treated with ICIs is atypical. Since the RECIST criteria used in these trials had not been modified for this particular situation, it may lead to misjudgment of PFS;[41,42] (2) some studies suggested that the residual efficacy of ICIs could lead to a continuous effect on OS after the treatment discontinuation;[43,44] (3) a hypothesis called pseudoprogression suggests that increased T-cell trafficking might result in initial tumor growth before shrinkage.[45] Given the above consideration, investigators must reconsider the response of progressive disease under RECIST criteria while ICIs are being used, and the actual PFS prolongation efficacy of pembrolizumab plus cisplatin plus 5-fluorouracil may not be as bad as the statistical results seem to suggest.

Another common phenomenon associated with the use of ICIs is that they are more effective in patients with high level of PD-L1 expression, which is determined by their mechanism of action.[46,47] Previous data showed that higher PD-L1 expression was associated with better survival in patients with R/M HNSSC. In the KEYNOTE-48 study,[5] the ability of pembrolizumab monotherapy to improve OS in the group with PD-L1 high expression (HR 0.61, 95% CI 0.45–0.83) was significantly more robust than that in the group with PD-L1 low expression (0.78, 0.64–0.96). Nivolumab included in our subgroup analysis of the second-line therapy showed similar differences between the two groups of patients. Notably, however, there are multiple measures of PD-L1 expression level as previously mentioned. Therefore, future studies are urgently needed to determine a suitable definition criterion of PD-L1 expression level for R/M HNSSC patients, as well as reliable biomarkers to customize ICIs therapy.

In addition to ICIs therapy, the EXTREME regimen and its derivatives are also worthy of consideration. Since the EXTREME regimen has been widely used, many studies have been conducted to improve it by strengthening or optimizing chemotherapy backbone of EXTREME. The results of our study show that adding adjuvant drugs to the EXTREME regimen (such as motolimod, cilengitide, or docetaxel) did not achieve significant OS benefits but increases the risk of more AEs. In contrast, optimizing the backbone of chemotherapy with the EXTREME regimen may be feasible. The TPEx study,[21] in which 5-fluorouracil was replaced with taxane, resulted in a significantly improved PFS, OS and safety benefits among the comparable treatments. Some plausible explanations for this superiority are: (1) previous studies have suggested a synergistic effect when combining taxanes with cetuximab;[48] (2) 5-fluorouracil is not recommended in patients with cardiovascular disease and is considered to be related to mucositis and diarrhea.[3] In addition to the above, studies have shown that TPEx regimen was more cost-effective than immunotherapy.[49] In general, with comprehensive consideration about PFS, OS, safety and cost-effective benefits, TPEx is more likely to be considered as the optimal first-line treatment (Figure 2B).

In our analysis of second-line treatments, nivolumab may be the treatment of choice for overall R/M HNSSC patients due to its most remarkable OS benefit (HR 0.68, 95% CI 0.58–0.80) and lower AEs ⩾ grade 3 (OR 0.37, 95% Cl 0.11–1.22). However, based on the results of our subgroup analysis, we have to be more careful not to overrate this conclusion: although the efficacy of nivolumab on OS prolongation did not differ significantly between patients with different ECOG PS, there was no significant difference between the efficacy of nivolumab and SOC in the HPV-negative subgroup. In subgroup analyses grouped by primary tumor sites, patients in the oral cavity and larynx groups were able to achieve greatest OS benefit from buparlisib plus paclitaxel therapy, and patients in the oropharynx group were able to derive longer OS from PBC treatment, whereas nivolumab achieved the second-best efficacy in all three of these groups. From the overall perspective, the results of our subgroup analysis indicated two facts: (1) nivolumab may not be the most appropriate option for each patients. This does not imply that the results of subgroup analysis contradict the overall findings, and one possible explanation is that the best OS prolongation efficacy of nivolumab in the overall population most likely stems from its better efficacy in each of the subgroups. (2) R/M HNSCC is a complex group of

diseases, and it is crucial to select the most appropriate treatment according to the patient's primary tumor site, molecular phenotype, and other characteristics. However, the principal difficulty lies in that only a few RCTs have reported survival data based on primary tumor site, molecular phenotype etc,[6,7,10,19,30] while the vast majority of RCTs continue the traditional thinking of treating these patients as a whole, which has far-reaching implications for evidence-based clinical decision-making. Now that our findings confirm the need for precision therapy of R/M HNSCC, it is hoped that ongoing and upcoming RCTs will result in more rational and meticulous grouping of patients and detailed reporting of data.

Finally, studies have suggested that the HPV infection status is strongly associated with oral cancer prognosis.[50,51] In our subgroup analysis, patients in the oral cavity group derived a more significant OS benefit from buparlisib plus paclitaxel therapy, which also showed optimal OS benefit in HPV-negative patients, but its effect was not significantly different from SOC in HPV-positive patients. We found a larger proportion of HPV-negative patients (67%) included in the relevant RCTs, which may be related to the greater OS benefit of buparlisib plus paclitaxel therapy in the oral cavity group. Therefore we recommend that this finding be taken with caution and that clinicians pay particular attention to the HPV infection status of patients before adopting buparlisib plus paclitaxel.

Strengths and limitations

Different from other reported NMAs comparing second-line treatments for R/M HNSSC, our present NMA has the following main strengths: (1) it is the first study to establish comparisons among all monotherapies, including the two innovative regimens of pembrolizumab and nivolumab, and combination therapies for R/M HNSCC; (2) we included the previously unpublished or recently updated results to comprehensively assess the efficacy and safety of treatments; and (3) in particular, we separately established four subgroup comparisons to investigate the relative effectiveness of second-line treatments.

There are some limitations to this study. First, although only RCTs were included, and NMA has been used and validated to compare outcomes for most trials indirectly, confounding factors could hardly be eliminated. Second, a selection bias depending on the RCTs was inevitable. Strict inclusion criteria were used to obtain a homogeneous sample; however, underlying changes in patient characteristics among different studies may affect the transitivity of the network. Moreover, despite of a total of 8908 patients included, the included phase II RCTs offer less precise estimates due to small sample sizes, as reflected that only 44 patients who received patritumab plus cetuximab plus platinum,[24] and 53 patients who received EMD1201081 plus cetuximab were evaluated.[27] However, the inclusion of these RCTs provides a comprehensive overview of all possible treatments currently available. Third, the included RCTs are likely to have screened the status of patients by performance status and sufficient organ functions in the enrolling stage. Therefore, efficacy and safety of these treatments in patients who were not covered remain unknown. Fourth, due to limitations in data availability across trials, our subgroup analysis relies on limited published results rather than on individual patients' data. Therefore, the results from subgroup analysis remain merely suggestive. An individual patient data meta-analysis will be important in the future.

Conclusion

Based on our NMAs, pembrolizumab plus cisplatin plus 5-fluorouracil is likely to be considered as the best first-line treatment when OS is a priority. However, with comprehensive consideration, TPEx should be the optimal first-line option due to its superior PFS prolongation efficacy, best safety profile, and OS benefit fairly close to that of pembrolizumab plus cisplatin plus 5-fluorouracil. Nivolumab appears to be the best second-line option due to its best OS prolongation efficacy and outstanding safety profile in the overall population. In addition, the optimal treatment for prolonging OS varies in some subgroups of patients: PBC for patients with oropharynx as primary tumor site; buparlisib plus paclitaxel for patients with HPV-negative, and with oral cavity or larynx as primary tumor sites. Future RCTs with meticulous grouping of patients and detailed reporting are urgently needed for individualized treatment of R/M HNSCC.

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Authors' contributions

ZJ, BZ, LZ, WhH, XkM, and SxZ contributed to study concept and design. All authors selected the articles and extracted the data. QyC, ZzC, MmL, and FW contacted study investigators and pharmaceutical companies to request additional information. ZJ, BZ, and LZ analyzed and interpreted the data. ZJ and BZ wrote the first draft of the report with input from ZL, WhH and SxZ. All authors approved the final version of the report. All authors had full access to all the data, and the corresponding authors were responsible for the decision to submit for publication.

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References

1. Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Gupta B, Johnson NW and Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. *Oncology* 2016; 91: 13–23.
3. Taberna M, Oliva M and Mesia R. Cetuximab-containing combinations in locally advanced and recurrent or metastatic head and neck squamous cell carcinoma. *Front Oncol* 2019; 9: 383.
4. Sacco AG and Cohen EE. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. *J Clin Oncol* 2015; 33: 3305–3313.
5. Burtness B, Harrington KJ, Greil R, *et al*. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019; 394: 1915–1928.
6. Cohen EEW, Soulieres D, Le Tourneau C, *et al*. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 2019; 393: 156–167.
7. Ferris RL, Blumenschein G Jr, Fayette J, *et al*. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016; 375: 1856–1867.
8. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Head and neck cancers. Version 3.2019, https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (2019, accessed 16 September 2019).
9. Guigay J, Fayette J, Mesia R, *et al*. TPExtreme randomized trial: TPEx versus extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *J Clin Oncol* 2019; 37(Suppl. 15): 6002.
10. Soulieres D, Faivre S, Mesia R, *et al*. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Oncol* 2017; 18: 323–335.
11. Cipriani A, Higgins JP, Geddes JR, *et al*. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; 159: 130–137.
12. Lu G and Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23: 3105–3124.
13. Salanti G, Ades AE and Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163–171.

14. Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162: 777–784.

15. Higgins JP and Green S. *Cochrane handbook for systematic reviews of interventions*. Hoboken, NJ: John Wiley & Sons, 2011.

16. Dias S, Sutton AJ, Ades AE, *et al.* Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013; 33: 607–617.

17. Shim SR, Kim SJ, Lee J, *et al.* Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019; 41: e2019013.

18. Rücker G, Krahn U, König J et al. netmeta: Network Meta-Analysis using Frequentist Methods. R package version 1.2-1 ed. 2020.

19. Argiris A, Ghebremichael M, Gilbert J, *et al.* Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2013; 31: 1405–1414.

20. Argiris A, Li S, Savvides P, *et al.* Phase III randomized trial of chemotherapy with or without bevacizumab in patients with recurrent or metastatic head and neck cancer. *J Clin Oncol* 2019; 37: 3266–3274.

21. Bossi P, Miceli R, Locati LD, *et al.* A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol* 2017; 28: 2820–2826.

22. Burtness B, Goldwasser MA, Flood W, *et al.* Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005; 23: 8646–8654.

23. Ferris RL, Saba NF, Gitlitz BJ, *et al.* Effect of adding motolimod to standard combination chemotherapy and cetuximab treatment of patients with squamous cell carcinoma of the head and neck: the Active8 randomized clinical trial. *JAMA Oncol* 2018; 4: 1583–1588.

24. Forster MD, Dillon MT, Kocsis J, *et al.* Patritumab or placebo, with cetuximab plus platinum therapy in recurrent or metastatic squamous cell carcinoma of the head and neck: a randomised phase II study. *Eur J Cancer* 2019; 123: 36–47.

25. Klinghammer K, Gauler T, Dietz A, *et al.* Cetuximab, fluorouracil and cisplatin with or without docetaxel for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CeFCiD): an open-label phase II randomised trial (AIO/IAG-KHT trial 1108). *Eur J Cancer* 2019; 122: 53–60.

26. Machiels JP, Haddad RI, Fayette J, *et al.* Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. *Lancet Oncol* 2015; 16: 583–594.

27. Ruzsa A, Sen M, Evans M, *et al.* Phase 2, open-label, 1:1 randomized controlled trial exploring the efficacy of EMD 1201081 in combination with cetuximab in second-line cetuximab-naive patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). *Invest New Drugs* 2014; 32: 1278–1284.

28. Seiwert TY, Fayette J, Cupissol D, *et al.* A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. *Ann Oncol* 2014; 25: 1813–1820.

29. Stewart JS, Cohen EE, Licitra L, *et al.* Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 2009; 27: 1864–1871.

30. Urba S, van Herpen CM, Sahoo TP, *et al.* Pemetrexed in combination with cisplatin versus cisplatin monotherapy in patients with recurrent or metastatic head and neck cancer: final results of a randomized, double-blind, placebo-controlled, phase 3 study. *Cancer* 2012; 118: 4694–4705.

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

32. Vermorken JB, Peyrade F, Krauss J, *et al.* Cisplatin, 5-fluorouracil, and cetuximab (PFE) with or without cilengitide in recurrent/metastatic squamous cell carcinoma of the head and neck: results of the randomized phase I/II ADVANTAGE trial (phase II part). *Ann Oncol* 2014; 25: 682–688.

33. Vermorken JB, Stohlmacher-Williams J, Davidenko I, *et al.* Cisplatin and fluorouracil with or without panitumumab in patients with

recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. *Lancet Oncol* 2013; 14: 697–710.

34. Wirth LJ, Dakhil S, Kornek G, *et al*. PARTNER: an open-label, randomized, phase 2 study of docetaxel/cisplatin chemotherapy with or without panitumumab as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck. *Oral Oncol* 2016; 61: 31–40.

35. Friesland S, Tsakonas G, Kristensen C, *et al*. Randomised phase II study with cetuximab in combination with 5-FU and cisplatin or carboplatin versus cetuximab in combination with paclitaxel and carboplatin for treatment of patients with relapsed or metastatic squamous cell carcinoma of the head and neck (CETMET trial). *J Clin Oncol* 2018; 36(Suppl. 15): 6032.

36. Guo Y, Ahn M-J, Chan ATC, *et al*. Afatinib versus methotrexate as second-line treatment for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) progressing on or after platinum-based therapy: LUX-Head & Neck 3 phase III trial. *Ann Oncol* 2019; 30: 1831–1839.

37. Keilholz U, Kawecki A, Dietz A, *et al*. Efficacy and safety of CetuGEX in recurrent/metastatic squamous cell carcinoma of the head and neck (RM-HNSCC): results from the randomized phase II RESGEX study. *J Clin Oncol* 2018; 36(Suppl. 5): 59.

38. Licitra LF, Haddad RI, Even C, *et al*. EAGLE: a phase 3, randomized, open-label study of durvalumab (D) with or without tremelimumab (T) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). *J Clin Oncol* 2019; 36(Suppl. 5): 6012.

39. ClinicalTrials.gov. Phase III trial to assess efficacy and safety of cetuximab for the treatment of Chinese participants with head and neck cancer (CHANGE2), https://clinicaltrials.gov/ct2/show/results/NCT02383966?cond=Combination+of+Cetuximab+and++Cisplatin+Plus+5-Fluorouracil+%285-FU%29&rank=2&view=results (2019, accessed 1 November 2019).

40. Gyawali B, Hey SP and Kesselheim AS. A comparison of response patterns for progression-free survival and overall survival following treatment for cancer with PD-1 inhibitors: a meta-analysis of correlation and differences in effect sizes. *JAMA Netw Open* 2018; 1: e180416.

41. Gyawali B, Ota A and Ando Y. Nivolumab in nonsquamous non-small-cell lung cancer. *N Engl J Med* 2016; 374: 493.

42. Hodi FS, Hwu WJ, Kefford R, *et al*. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol* 2016; 34: 1510–1517.

43. Lipson EJ, Sharfman WH, Drake CG, *et al*. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. *Clin Cancer Res* 2013; 19: 462–468.

44. Queirolo P and Spagnolo F. Atypical responses in patients with advanced melanoma, lung cancer, renal-cell carcinoma and other solid tumors treated with anti-PD-1 drugs: a systematic review. *Cancer Treat Rev* 2017; 59: 71–78.

45. Chiou VL and Burotto M. Pseudoprogression and immune-related response in solid tumors. *J Clin Oncol* 2015; 33: 3541–3543.

46. He C, Duan X, Guo N, *et al*. Core-shell nanoscale coordination polymers combine chemotherapy and photodynamic therapy to potentiate checkpoint blockade cancer immunotherapy. *Nat Commun* 2016; 7: 12499.

47. Santarpia M and Karachaliou N. Tumor immune microenvironment characterization and response to anti-PD-1 therapy. *Cancer Biol Med* 2015; 12: 74–78.

48. Rose WC and Wild R. Therapeutic synergy of oral taxane BMS-275183 and cetuximab versus human tumor xenografts. *Clin Cancer Res* 2004; 10: 7413–7417.

49. Tringale KR, Carroll KT, Zakeri K, *et al*. Cost-effectiveness analysis of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 2018; 110: 479–485.

50. Fakhry C, Blackford AL, Neuner G, *et al*. Association of oral human papillomavirus DNA persistence with cancer progression after primary treatment for oral cavity and oropharyngeal squamous cell carcinoma. *JAMA Oncol* 2019; 5: 985–992.

51. Ellington TD, Henley SJ, Senkomago V, *et al*. Trends in incidence of cancers of the oral cavity and pharynx - United States 2007-2016. *MMWR Morb Mortal Wkly Rep* 2020; 69: 433–438.