Critical Reviews in Oncology / Hematology 153 (2020) 102984

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Systemic Therapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma- A Systematic Review and Meta-Analysis

Ashley Lau, Wei-fa Yang, Kar-Yan Li, Yu-xiong Su*

Department of Oral and Maxillofacial Surgery, Prince Phillip Dental Hospital, 34 Hospital Road, Sai Ying Pun, Hong Kong Special Administrative Region

ARTICLE INFO

Keywords:
Head and Neck Neoplasms/therapy
Neoplasm Recurrence
Local/therapy
Neoplasms Metastasis
Immunotherapy
Antineoplastic Protocols

ABSTRACT

Background: The most effective regimen is unclear for patients with recurrent or metastatic head and neck squamous cell carcinomas (R/M HNSCC). We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) investigating only systemic therapy for R/M HNSCC.

Methods: This systematic review followed PRISMA and the Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Endpoints included overall survival (OS), progression-free survival (PFS) and overall response rates (ORR).

Results: 55 RCTs from 1990-November 2019 qualified for review ($n = 12132$). Only PD-1/PDL-1 inhibitors increased OS in R/M HNSCC platinum-resistant disease against their control (HR = 0·79, 95%CI 0·70-0.90, $p < 0·001$), especially for PD-L1 ≥ 1% expressing tumours (HR = 0·72, 95%CI 0·60-0·86, $p < 0·001$). PFS was prolonged for anti-EGFR agents against methotrexate when used in a second line setting (HR = 0·74, 95 %CI 0·62-0·87, $p = 0·001$), and when cetuximab (HR = 0·60, 95%CI 0·49-0·72, $p < 0·0001$) and panitumumab (HR = 0·76, 95%CI 0·65-0·89, $p = 0·001$) were introduced to platinum-based regimens for first-line treatment.

Conclusions: PD-1/PD-L1 inhibitors may represent the future of R/M HNSCC treatment. However, EGFR inhibitors may still play improve clinical outcomes.

1. Introduction

Head and neck squamous cell carcinomas (HNSCC) is the sixth most common cancer worldwide (World Health Organization, 2014). Despite diagnostic and therapeutic advances in the past three decades, up to 50-60% of patients with locally advanced disease develop loco-regional relapse and, or distant metastasis within 2 years (Sacco and Cohen, 2015). The prognosis of patients with recurrent or metastatic (R/M) HNSCC is poor (Sacco and Cohen, 2015). A vast majority have unresectable disease and only qualify for palliative treatment with systemic therapy. First-line treatment in R/M HNSCC historically consisted of cytotoxic agents such as methotrexate (MTX), bleomycin, or platinum-based protocols until targeted biological therapies were introduced in the 2000's (Sacco and Cohen, 2015; Blasco et al., 2017). Combination therapy (the EXTREME regimen) of cetuximab, cisplatin and 5-Fluoruracil (5-FU) rapidly became the standard for first-line treatment in 2008 based on its overall survival benefit against standard cytotoxic therapy reported from one phase III RCT (EXTREME) (Sacco and Cohen, 2015; Blasco et al., 2017; Vermorken and Specenier, 2010).

Recent understanding about the role of immune dysfunction in HNSCC has quickly established immunotherapy (IMT) as a promising treatment avenue (Ling et al., 2018). Antagonizing the programmed-cell death (PD-1) immune check-point can disable T-cell suppression by HNSCC cells for re-sensitization of the immune system to clear tumor cells (Ling et al., 2018). PD-1 inhibitor pembrolizumab used in monotherapy or in combination with platinum/5-FU, has recently superseded the EXTREME regimen by the FDA as first-line treatment in R/M HNSCC based on its superior survival data from the KEYNOTE-048 phase III RCT (Brockstein and Vokes, 2020).

Unfortunately, many patients with R/M HNSCC further relapse despite treatment. The choice of subsequent therapy after first-line treatments was initially poorly defined until PD-1 inhibitors nivolumab and pembrolizumab became FDA- licensed for 2nd line treatment of R/M HNSCC for patients who had disease progression on or after platinum-based therapy (Blasco et al., 2017; Brockstein and Vokes, 2020).

Despite these breakthroughs, the most optimum regime for R/M HNSCC is still unclear. Many recommendations are based on single RCT results and there is currently a dearth of efficacious treatment options available when FDA-approved 1st and 2nd line treatments are contraindicated. To address this issue, we will be the first to appraise RCTs

* Corresponding author at: Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, The University of Hong Kong, 34 Hospital Road, Sai Ying Pun, Hong Kong Special Administrative Region.
E-mail address: richsu@hku.hk (Y.-x. Su).

https://doi.org/10.1016/j.critrevonc.2020.102984
Received 2 February 2020; Received in revised form 10 May 2020; Accepted 11 May 2020
Available online 30 May 2020

evaluating systemic treatment in patients with unresectable R/M HNSCC through a systematic review and meta-analysis. The activity of systemic treatment will be assessed through overall survival (OS), progression free survival (PFS), and clinical response (overall response rate, ORR). By reviewing the existing literature, we hope to highlight recommendations towards treatment and the design of future trials.

2. Methods

This systematic review and meta-analysis is registered on PROSPERO (CRD42019127722) and followed the Cochrane Collaboration Handbook of Interventions Systematic Reviews and the PRISMA statement checklist and flowchart.

2.1. Search strategy and selection criteria

A systematic search was performed from peer-reviewed journals published between 1990-May 2018 from MEDLINE via Pubmed, EMBASE via Ovid, The Cochrane CENTRAL, and Web of Science. The search was updated in September 5, 2018 with a final revision on November 23, 2019.

Search queries included MeSH terms for “Head and Neck Neoplasms”, “Neoplasm recurrence”, “metastatic neoplasm”, “mouth neoplasms”, “oropharyngeal neoplasms”, “laryngeal neoplasms”, “hypopharynx neoplasms”, “anti-neoplastic drugs”, “clinical trials”, “anti-neoplastic combined chemotherapy”, in combination with free text phrases such as “randomized controlled trials”, “head and neck cancer”. The syntax input was revised for each database.

ClinicalTrials.gov, Proceedings from ASCO (http://meetinglibrary.asco.org/) and ESMO (http://www.esmo.org/) for abstract conferences, and reference lists from review articles, were additionally screened for any ongoing or missed trials from the search queries. No language restrictions were imposed.

Studies in the review had the following criteria:

1 Patients with histologically confirmed, unresectable R/M HNSCC
2 RCTs
3 Patients receiving only systemic therapy for R/M HNSCC. All types of agents and routes of administration were included.

Exclusion criteria for the review were as follows:

1 Patients receiving surgery or radiotherapy in addition to systemic therapy for R/M HSNCC
2 Second primary HNSCC
3 Studies only investigating R/M nasopharyngeal carcinomas

Two authors independently reviewed databases for studies fulfilling the eligibility criteria. Characteristics of the excluded studies were documented and counterchecked in a standardized chart. Any inconsistencies and disagreements were resolved amongst group discussion.

If there was insufficient data from a trial, attempts were made to contact the corresponding author for information.

2.2. Data analysis

A risk of bias assessment was performed in accordance with the Cochrane Collaboration’s Tool (Cochrane Handbook version 5·1·0). Outcome data was considered complete if less than 20% of patients randomized were excluded from the trial data with reasoning. We did not assess for blinding due to the ethical difficulty of performing a double-blinded trial. If the bias risk was difficult to interpret, the study authors were contacted for clarification.

A study was classified as ‘low risk’ if it met all criteria for ‘low bias’ in the risk assessment domains. If an ‘unclear risk’ was assigned to at least one key category, the study was considered as ‘unclear risk’. A ‘high risk’ study had a high risk of bias determined in one or more domains and was subsequently excluded to maintain data reliability in the systematic review and meta-analysis.

ORR was reported as odds ratio (OR) for the meta-analysis. If there were no (or all) events reported in both treatment groups, the study as excluded from the meta-analysis. OS and PFS were expressed as hazard ratios (HR) for the meta-analysis. All outcomes included the 95% confidence interval (CI). Survival data was pooled by calculating the logHR and its corresponding variance through formulas derived from Parmar et al (Parmar et al., 1998) and Tierney et al (Tierney et al., 2007). Calculations were performed independently by two authors and verified to minimize error. All outcomes included the 95% confidence interval (CI) in the meta-analysis. A significant result was indicated by a p-value of $< 0{\cdot}05$ for any measured outcomes.

The STAT/SE®, version 11 [Stat Crop., College Station, TX, USA] was used for data input. Because most of the included outcomes were relatively rare and the number of the included studies was relatively small, the fixed-effect model was used (the Mantel-Haenszel fixed-effect method for OR; the Inverse Variance fixed-effect model for hazard ratio). To determine whether result variations were by heterogeneity rather than sample error, substantial heterogeneity between studies was quantified using the chi2 test ($\chi 2$) with p-value of $< 0{\cdot}10$ or I-squared statistic of $> 50\%$. If substantial heterogeneity was significant, the random-effects model was performed as a sensitivity analysis.

Role of Funding Source

There was no funding source for this study.

3. Results

Study selection was conducted according to the PRISMA flowchart (Fig. 1). The initial database query retrieved 1981 studies, where 178 full-text articles were screened for eligibility. 57 RCTs met the inclusion criteria. 2 studies were excluded for high bias risk for not reporting all pre-specified outcomes (Fig. 2). 55 trials ($n = 12132$) were included in the systematic review where 23 RCTs ($n = 5737$) were included for meta-analysis. Characteristics of the included studies are described in Table 1. 36 studies were phase II (Bossi et al., 2017; Bourhis et al., 2006; Burtness et al., 2008; Colella et al., 1994; Fayette et al., 2016; Ferris et al., 2018; Gilbert et al., 2012; Gilbert et al., 2015; Guardiola et al., 2004; Harrington et al., 2018; Jimeno et al., 2015; Jimeno et al., 2014; Joshi et al., 2017; Klinghammer et al., 2019; Limaye et al., 2013; Machiels et al., 2016; Paccagnella et al., 1993; Pivot et al., 2003; Ruzsa et al., 2014; Seiwert et al., 2014a; Siu et al., 2019; Soulières et al., 2017; Vermorken et al., 1999; Vermorken et al., 2013a; Vokes et al., 2015; William et al., 2017; Wirth et al., 2016; Fury et al., 2012; Ferrarotto et al., 2018; Friesland et al., 2018; Seiwert et al., 2014b; Amrein and Fabian, 1992; Kushawah et al., 2015; Pivot et al., 2001; Guigay et al., 2019; Adkins et al., 2019) followed by 19 phase III RCTs (Vermorken et al., 2013b; Argiris et al., 2013; Argiris et al., 2017; Clavel et al., 1994; Ferris et al., 2016; Forastiere et al., 2001; Forastiere et al., 1992; Fountzilas et al., 2006; Jacobs et al., 1992; Machiels et al., 2015; Machiels et al., 2011; Stewart et al., 2009; Urba et al., 2012; Vermorken et al., 2008; Schrijvers et al., 1998; Burtness et al., 2005; Cohen et al., 2018; Licitra et al., 2019; Burtness et al., 2019). Oropharyngeal cancers were the predominant diagnosis ($n = 19$) (Burtness et al., 2008; Fayette et al., 2016; Ferris et al., 2018; Guardiola et al., 2004; Klinghammer et al., 2019; Limaye et al., 2013; Seiwert et al., 2014a; Siu et al., 2019; Vermorken et al., 2013a; William et al., 2017; Wirth et al., 2016; Fury et al., 2012; Argiris et al., 2013; Argiris et al., 2017; Forastiere et al., 2001; Jacobs et al., 1992; Machiels et al., 2015; Vermorken et al., 2008; Burtness et al., 2005) followed by oral ($n = 10$) [24,40,41, 43(Vermorken et al., 2013b; Ferris et al., 2016; Machiels et al., 2011; Stewart et al., 2009; Urba et al., 2012; Schrijvers et al., 1998) laryngeal ($n = 5$) (Bourhis et al., 2006; Colella et al., 1994; Paccagnella et al.,

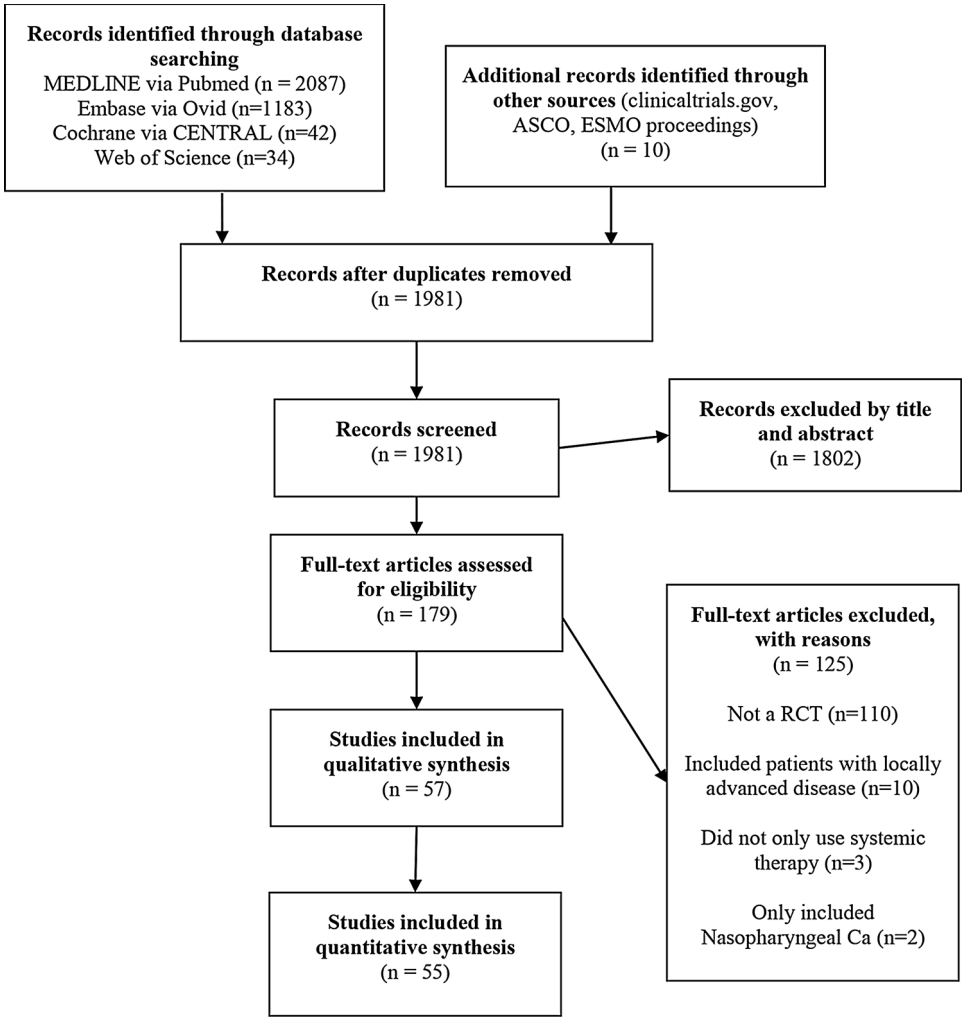

Fig. 1. Literature search according to the PRISMA statement for RCTs studying systemic therapy in R/M HNSCC.
The initial database query found 1981 studies, where 179 full-text articles were screened for eligibility. 55 RCTs met the inclusion criteria for systematic review.

1993; Clavel et al., 1994; Fountzilas et al., 2006), hypopharynx (n = 1) (Pivot et al., 2003) and others but not specified ($n = 4$) (Bossi et al., 2017; Gilbert et al., 2012; Gilbert et al., 2015; Pivot et al., 2001) cancers. 1 study (Soulières et al., 2017) had both larynx and hypopharynx as the highest proportion of cancers. 15 studies did not publish the proportions of tumor site origins (Harrington et al., 2018; Jimeno et al., 2015; Jimeno et al., 2014; Joshi et al., 2017; Ruzsa et al., 2014; Vermorken et al., 1999; Vokes et al., 2015; Ferrarotto et al., 2018; Friesland et al., 2018; Seiwert et al., 2014b; Adkins et al., 2019; Forastiere et al., 1992; Cohen et al., 2018; Argiris et al., 2013; Argiris et al., 2013; Argiris et al., 2017; Clavel et al., 1994; Ferris et al., 2016; Forastiere et al., 2001; Forastiere et al., 1992; Fountzilas et al., 2006; Jacobs et al., 1992; Machiels et al., 2015; Machiels et al., 2011; Stewart et al., 2009; Urba et al., 2012; Vermorken et al., 2008; Schrijvers et al., 1998; Burtness et al., 2005; Cohen et al., 2018; Licitra et al., 2019; Burtness et al., 2019) 29 RCTs evaluated first-line therapy (Bossi et al., 2017; Bourhis et al., 2006; Colella et al., 1994; Ferris et al., 2018; Guardiola et al., 2004; Harrington et al., 2018; Klinghammer et al., 2019; Paccagnella et al., 1993; Pivot et al., 2003; Vermorken et al., 1999; Vermorken et al., 2013a; William et al., 2017; Wirth et al., 2016; Friesland et al., 2018; Seiwert et al., 2014b; Amrein and Fabian, 1992; Guigay et al., 2019Argiris et al., 2013; Clavel et al., 1994; Forastiere et al., 2001; Forastiere et al., 1992; Fountzilas et al., 2006; Jacobs et al., 1992; Urba et al., 2012; Vermorken et al., 2008; Schrijvers et al., 1998; Burtness et al., 2005; Burtness et al., 2019), 25 for second-line treatment (Burtness et al., 2008; Fayette et al., 2016; Gilbert et al., 2012; Gilbert et al., 2015; Jimeno et al., 2015; Jimeno et al., 2015; Jimeno et al., 2014; Joshi et al., 2017; Limaye et al., 2013; Machiels et al., 2016; Ruzsa et al., 2014; Soulières et al., 2017; Vokes et al., 2015; Fury et al., 2012; Ferrarotto et al., 2018; Kushawah et al., 2015; Pivot et al., 2001; Ferris et al., 2016; Machiels et al., 2015; Machiels et al., 2011; Stewart et al., 2009; Cohen et al., 2018; Licitra et al., 2019) and 1 RCT (Argiris et al., 2017) included both R/M HNSCC treatment naïve and previously treated patients.

No trial had low bias risk (Fig. 2). All RCTs were classified as 'unclear risk' since many had an 'unclear risk' assigned to at least one domain. Many RCTs failed to specify how randomization sequencing and allocation were performed leading to an 'unclear risk' in the 'selection bias' category. Likewise, the involvement of pharmaceutical companies precluded an 'unclear risk' to be allotted towards the 'other bias' category.

3.1. First-line treatment

3.1.1. Cytotoxic chemotherapy

3.1.1.1. Single agents. Three trials compared the activity of single cytotoxic agents (Table 1.1a) (Guardiola et al., 2004; Pivot et al., 2003; Vermorken et al., 1999). MTX against taxane therapy found ORR favouring taxanes (OR = 3·16, 95% CI 1·26-7·97 $p = 0·01$) (Fig. 3a) (Guardiola et al., 2004; Vermorken et al., 1999). RCTs reporting for survival noted no difference between OS for MTX and taxane therapy (Guardiola et al., 2004; Vermorken et al., 1999) with the exception of

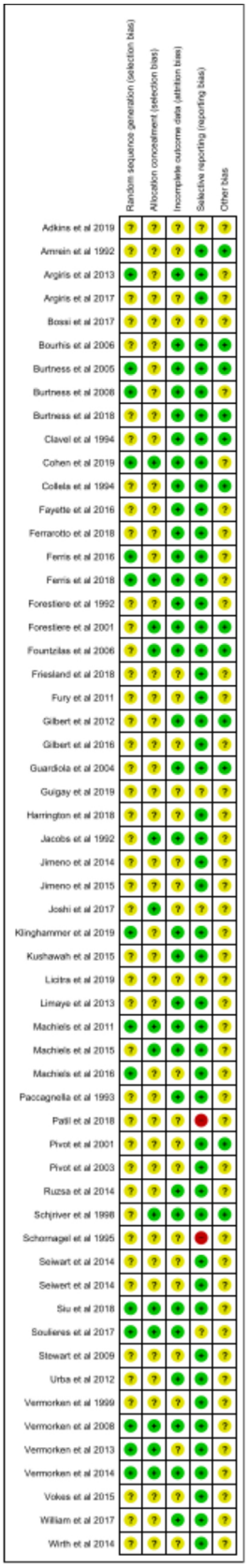

Fig. 2. Risk of Bias Summary of RCTs evaluating systemic treatment for R/M HNSCC.
There were no studies with a low risk of bias. 2 studies had high risk whilst the remaining majority were categorized as an unclear risk.

Table 1
Characteristics of RCTs evaluating systemic treatment for R/M HNSCC – *Summary of patient demographics, intervention and control groups.*

ghcJgAU

increased PFS when paclitaxel given over 24 hours at the expense of higher toxicity (Vermorken et al., 1999).

No other single agents increased ORR, PFS and OS in the remaining studies from Table 2.1a.

3.1.1.2. Combination agents. Ten RCTs tested cytotoxic agents used in combination (Table 1.1b) (Colella et al., 1994; Paccagnella et al., 1993; Amrein and Fabian, 1992; Clavel et al., 1994; Forastiere et al., 2001; Forastiere et al., 1992; Fountzilas et al., 2006; Jacobs et al., 1992; Urba et al., 2012; Schrijvers et al., 1998). Meta-analysis of two RCTs (Clavel et al., 1994; Jacobs et al., 1992) demonstrated a superior ORR with cisplatin-5-FU compared to cisplatin alone (OR = 2·44, 95% CI 1·50-3·95, $p < 0·0003$) (Fig. 3b). Both studies found no OS advantage with the addition of 5-FU to cisplatin (Clavel et al., 1994; Jacobs et al., 1992).

When cisplatin-5-FU was assessed against other cytotoxic combinations, only the addition of bleomycin and MTX to cisplatin-5-FU increased ORR (Amrein and Fabian, 1992). No cytotoxic combination improved OS over cisplatin-5-FU. Regarding the choice of platinum agent used with 5-FU, an indirect analysis from one RCT (Forastiere et al., 1992) demonstrated a higher ORR with cisplatin over carboplatin with no survival difference between the two drugs (Table 2.1b).

No other chemotherapy combination from Table 1.1b increased survival over their control (Joshi et al., 2017; Forastiere et al., 2001; Fountzilas et al., 2006; Urba et al., 2012).

3.1.2. Targeted therapy

3.1.2.1. EGFR combination. 12 RCTs studied the addition of EGFR inhibitors to cytotoxic agents (Table 1.1c) (Bossi et al., 2017; Bourhis et al., 2006; Klinghammer et al., 2019; Vermorken et al., 2013a; William et al., 2017; Wirth et al., 2016; Friesland et al., 2018; Guigay et al., 2019; Adkins et al., 2019; Vermorken et al., 2013b; Vermorken et al., 2008; Burtness et al., 2005). The addition of cetuximab to platinum-based therapy (Vermorken et al., 2008; Burtness et al., 2005) increased ORR (OR = 2.36, 95%CI 1.59-3.51, $p < 0.0001$) (Fig. 3c) and PFS (HR = 0.60, 95% CI 0.49-0.72, $p < 0·0001$) (Fig. 4a) without improving OS (HR = 0.83, 95% CI 0.69-1.00, $p = 0.11$) (Fig. 5a). Regarding the preferred platinum agent paired with cetuximab, cisplatin had better OS over carboplatin from an indirect analysis in one RCT (Vermorken et al., 2008) whereas another (Bourhis et al., 2006) reported no difference to ORR and OS between the two drugs (Table 2.1c).

Similarly, panitumumab included into a platinum-combination (Wirth et al., 2016; Vermorken et al., 2013b) found ORR (OR = 1.49, 95%CI 1.07-3.51, $p = 0.02$) (Fig. 3d) and PFS (HR = 0.76, 95% CI 0.65-0.89, $p = 0.001$) (Fig. 4b) to be increased without prolonging OS (HR = 0·93, 95% CI 0·74-1·16, $p = 0·51$) (Fig. 5b).

The addition of a taxane to a cetuximab-platinum based regime did not improve ORR (OR = 0.86, 95% CI 0.57-1.31, p = 0.48) (Fig. 3e) (Bossi et al., 2017; Klinghammer et al., 2019), PFS (HR = 0.91, 95%CI 0.75-1.11, p = 0.34) (Fig. 4c) (Bossi et al., 2017; Klinghammer et al., 2019; Seiwert et al., 2014b) and OS (HR = 1.29, 95% CI 0.95-1.75, p = 0.23) (Fig. 5c) (Bossi et al., 2017; Klinghammer et al., 2019; Friesland et al., 2018; Guigay et al., 2019). Similarly, the addition other-EGFR inhibitors (excluding cetuximab and panitumumab) to taxane therapy increased ORR (OR = 1.97, 95% CI 1.10-3.51, $p = 0.02$) (Fig. 3e) (Limaye et al., 2013; William et al., 2017; Argiris et al., 2013) without increasing OS (HR = 0.85, 95% CI 0.68- 1.07, p = 0.17) (Fig. 5d) (William et al., 2017; Argiris et al., 2013).

Other EGFR combinations from Table 2.1c did not report increases

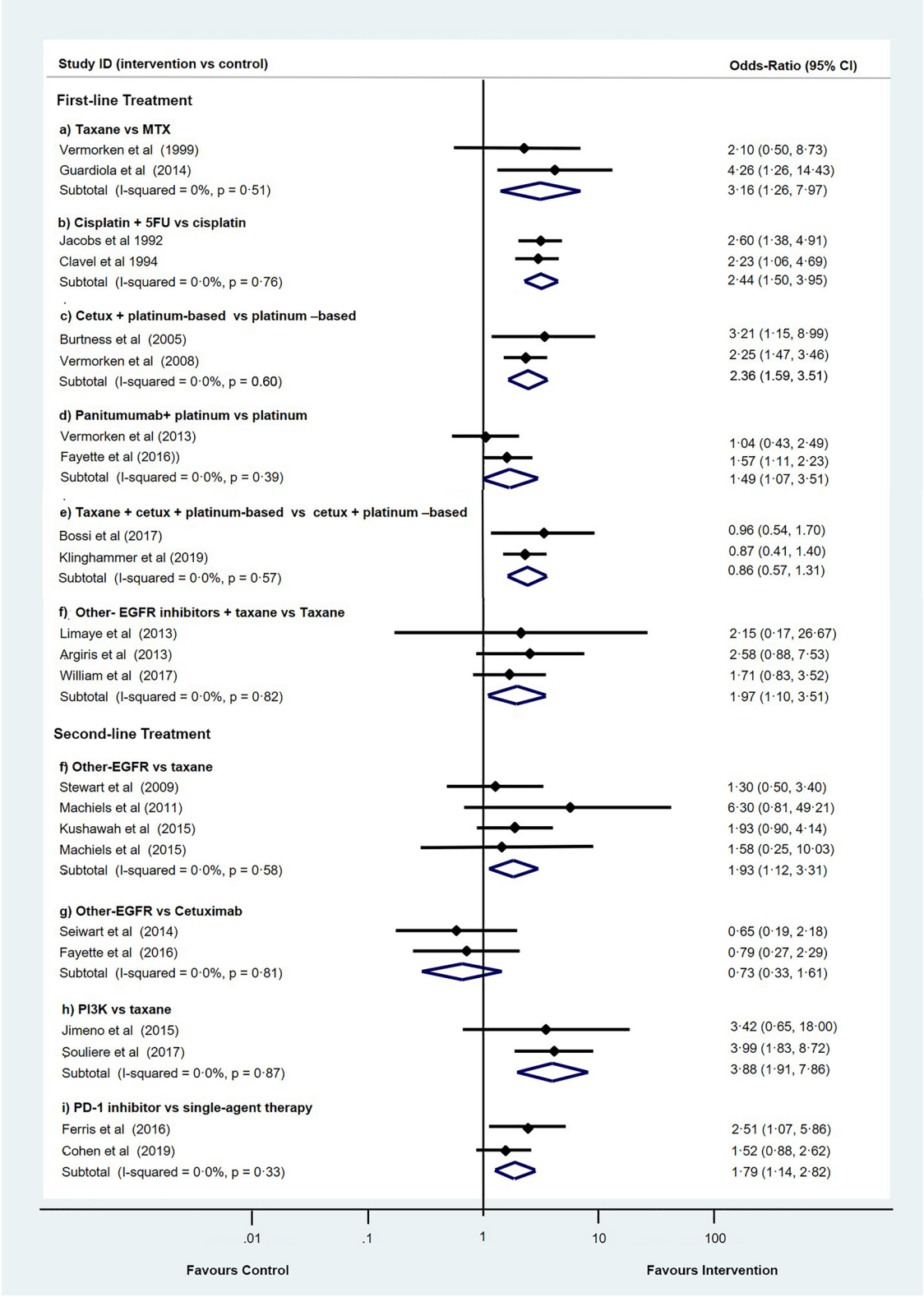

Fig. 3. Overall Response amongst RCTs evaluating systemic therapy for R/M HNSCC.
Overall response rates were increased in most interventions over their control.

Table 2
Results from RCTs evaluating systemic therapy for R/M HNSCC – *Summary of response and survival results of RCTs included in the review.*

jhzgcUAJS

to ORR, PFS and OS over their control cohort.

3.1.2.2. VEGF inhibitors. Bevacizumab was the only VEGF inhibitor evaluated for first-line therapy (Table 1.1d) (Argiris et al., 2017). Whilst the inclusion of bevacizumab to platinum-doublet chemotherapy

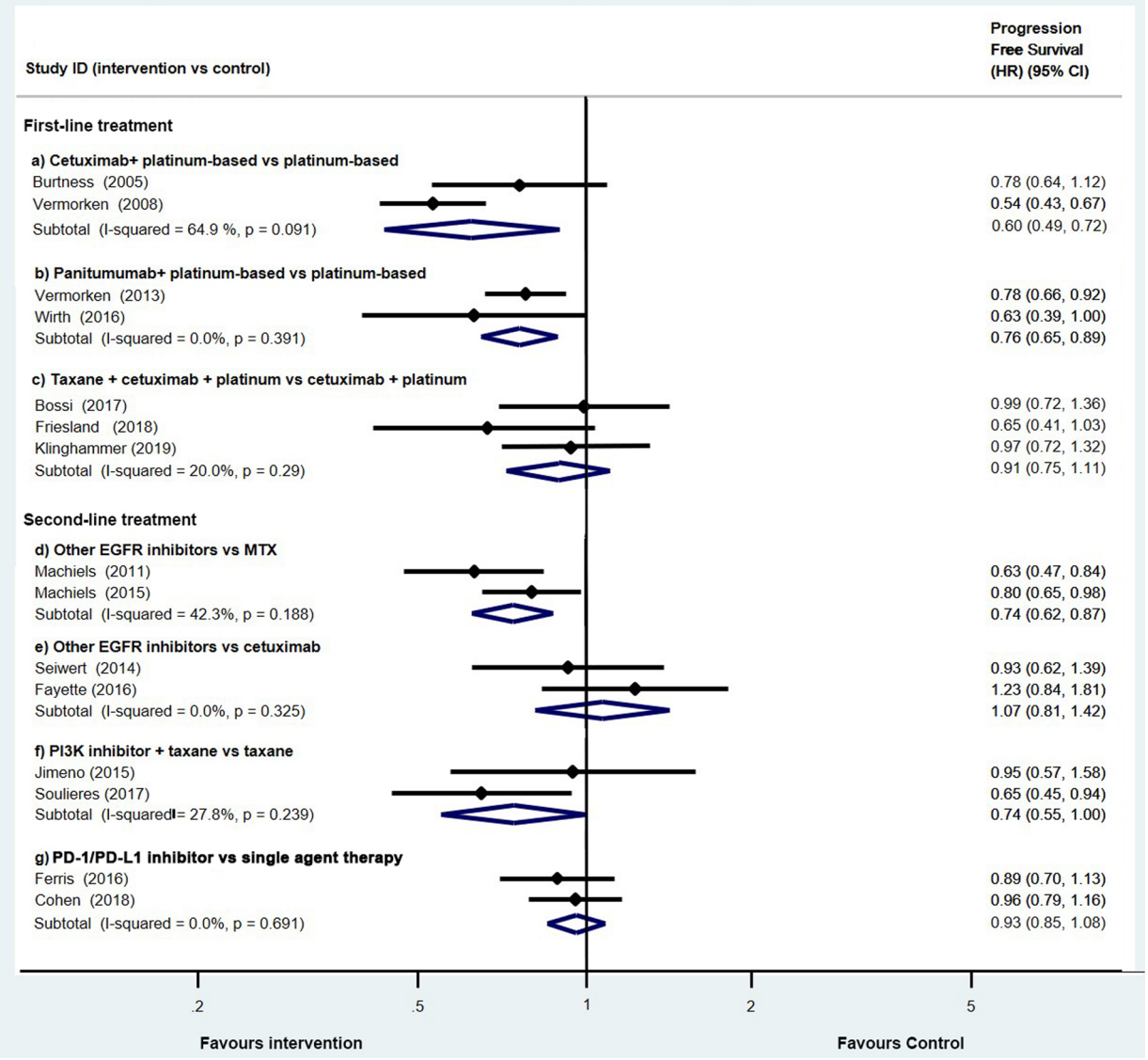

Fig. 4. Progression Free Survival amongst RCTs evaluating systemic therapy for R/M HNSCC.
Progression free survival was increased with EGFR agents against methotrexate and when panitumumab or cetuximab was added to a platinum-based therapy over platinum-based therapy alone.

reported significant improvements to ORR and PFS over chemotherapy alone, OS was not prolonged (Argiris et al., 2017) (Table 2.1d).

3.1.2.3. Other targeted agents. Other targeted agents tested in combination with cetuximab-platinum based therapies did not provide additional benefit to response or survival (Harrington et al., 2018; Vermorken et al., 2013a) (Table 2.1e).

3.1.3. Immunotherapy

3.1.3.1. PD-1/PD-L1 inhibitors. The combination of pembrolizumab-platinum-5-FU (Burtness et al., 2019) was found to increase ORR and OS compared to cetuximab-platinum-5-FU (Table 1.1f). Pembrolizumab alone did not increase OS in overall population but was found to improve OS for those who had a combined positive score of ≥1. No significant difference was found for PFS in both pembrolizumab monotherapy and combination therapy (Table 2.1f).

3.1.3.2. Toll-like receptor (TLR) agonists. Motolimod added to the EXTREME regime found no improvement to PFS and OS but was noted to provide significant improvements to PFS and OS for those with HPV positive oropharyngeal cancer (Ferris et al., 2018) (Table 2.1g).

3.2. Second line-treatment

3.2.1. Cytotoxic agents

3.2.1.1. Single agents. Four trials compared the activity of single cytotoxic agents (Table 1.2a) (Burtness et al., 2008; Joshi et al., 2017; Machiels et al., 2016; Pivot et al., 2001). No cytotoxic agent demonstrated a superior clinical benefit over their control arms.

3.2.2. Targeted therapy

3.2.2.1. EGFR monotherapy. EGFR inhibitor monotherapy was studied in seven RCTs (Table 1.2b) (Fayette et al., 2016; Seiwert et al., 2014a; Fury et al., 2012; Kushawah et al., 2015; Machiels et al., 2015; Machiels et al., 2011; Stewart et al., 2009). EGFR inhibitors demonstrated a higher ORR (OR = 1·93, 95% CI 1·12-3·31, $p = 0·02$) (Fig. 3f) (Kushawah et al., 2015; Machiels et al., 2015; Machiels et al., 2011; Stewart et al., 2009) and PFS (HR = 0·74, 95% CI 0·62-0·87, $p = 0·001$) (Fig. 4d) (Machiels et al., 2015; Machiels et al., 2011) with minimal impact on OS (HR = 1·00, 95% CI 0·89-1·13, $p = 0·83$) (Fig. 5e) (Kushawah et al., 2015; Machiels et al., 2015; Machiels et al., 2011; Stewart et al., 2009) when compared to MTX. Other EGFR inhibitors namely duligotuzumab and afatinib, both had comparable activity to

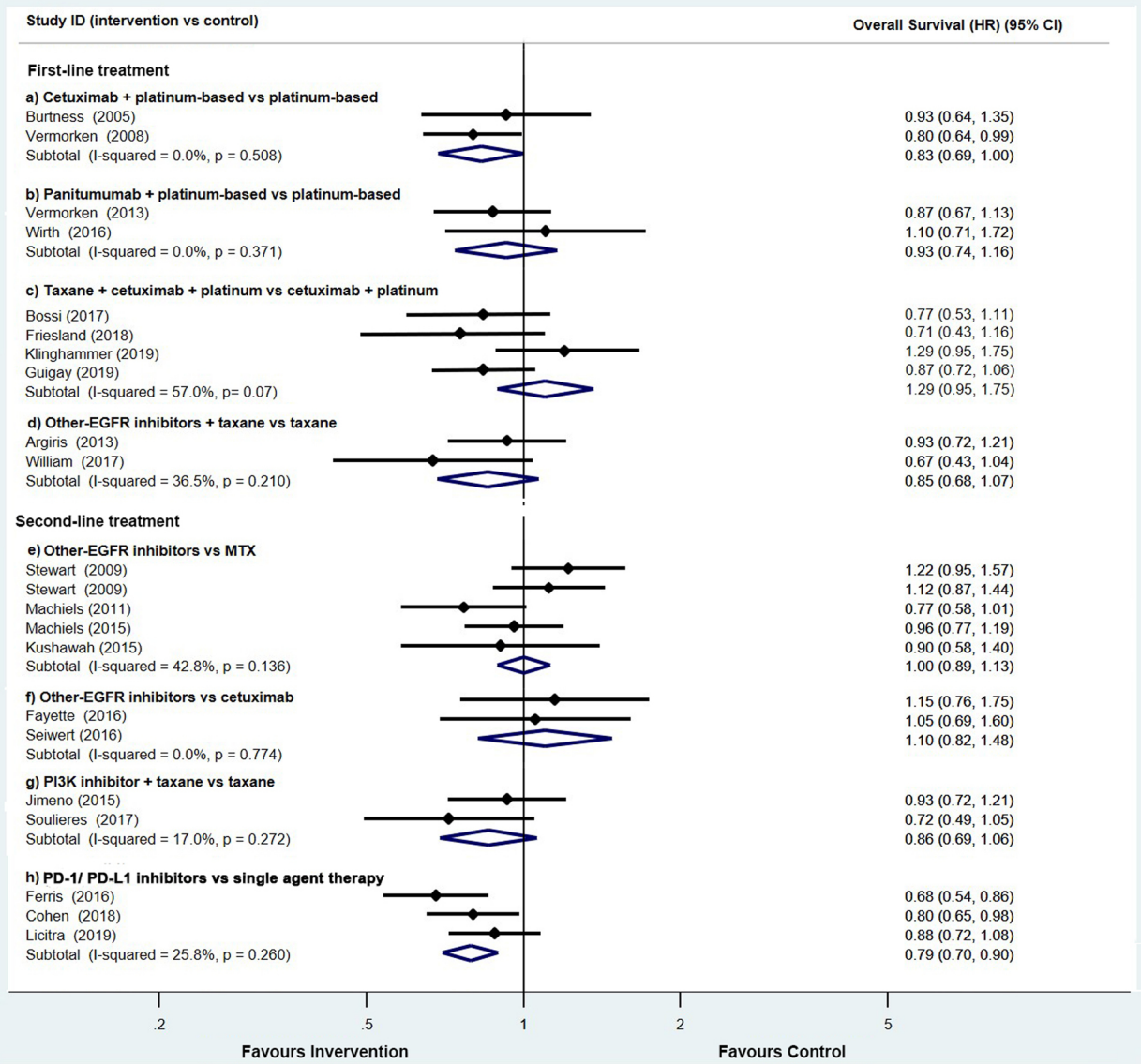

Fig. 5. Overall Survival amongst RCTs evaluating systemic therapy for R/M HNSCC.
Increased overall survival was only observed when PD-1/PD-L1 was investigated against investigator's choice of single agent therapy.

cetuximab (Fayette et al., 2016; Seiwert et al., 2014a) yielding similar ORR (OR = 0.73, 95% CI 0.33-1.61, p = 0.43) (Fig. 3d), PFS (HR = 1.07, 95% CI 0.81-1.42, p = 0.61) (Fig. 4d) and OS (HR = 1.10, 95%CI 0.82-1.48, p = 0.17) (Fig. 5f). Cetuximab at escalating doses made no difference for ORR, PFS and OS (Fury et al., 2012).

3.2.2.2. EGFR Combination therapy. Cixutuxumab with or without cetuximab demonstrated limited benefit to PFS and OS despite the increased ORR observed with cixutuxumab and cetuximab combination (Table 1.2c) (Ferrarotto et al., 2018). The addition of gefitinib to docetaxel also had limited activity without improvements to ORR, PFS, and OS (Argiris et al., 2013) (Table 2.2c). However, this trial recruited both previously treated and those who progressed from R/M HNSCC (Table 1.2c) (Argiris et al., 2013).

3.2.2.3. PI3K inhibitors. Three studies assessed PI3K inhibitors (Table 1.2d) (Jimeno et al., 2015; Jimeno et al., 2014; Soulières et al., 2017). PX-866 added to cetuximab did not improve ORR, PFS and OS over cetuximab alone20]. Although ORR bordered significance (OR = 3·88, 95% CI 1·91-7.86, $p = 0·05$) (Fig. 3h) when PI3K inhibitor was added to taxane therapy (Jimeno et al., 2015; Soulières et al., 2017), PFS (HR = 0·74, 95% CI 0·55-1·00, $p = 0·183$) (Fig. 4f) and OS (HR = 0·86, 95% CI 0·69-1·06, $p = 0·16$) (Fig. 5g) did not improve.

3.2.2.4. VEGF inhibitors. VEGF inhibitor Sorafenib (Table 1.2e) administered with cetuximab did not provide additional clinical benefit over cetuximab alone (Gilbert et al., 2015).

3.2.2.5. Other targeted agents. Other targeted therapies in Table 1.2f did not increase ORR, PFS, and OS over their control arms (Gilbert et al., 2012; Limaye et al., 2013; Vokes et al., 2015; Seiwert et al., 2014b) (Table 2.2f)

3.2.3. Immunotherapy

3.2.3.1. PD-1 /PD-L1 inhibitors. Immune-checkpoint inhibitors targeting PD-1 signaling were tested in four RCTs (Table 1.2g) (Ferris et al., 2016; Cohen et al., 2018; Licitra et al., 2019). Meta-analysis against standard single agent therapies (SOC) including MTX, docetaxel and cetuximab as second-line agents (Ferris et al., 2016; Cohen et al., 2018; Licitra et al., 2019) highlighted increases to ORR with PD-1/PD-L1 inhibitors (OR = 1·79, 95% CI 1·14-2·82, p < 0·01) (Fig. 3j) and OS

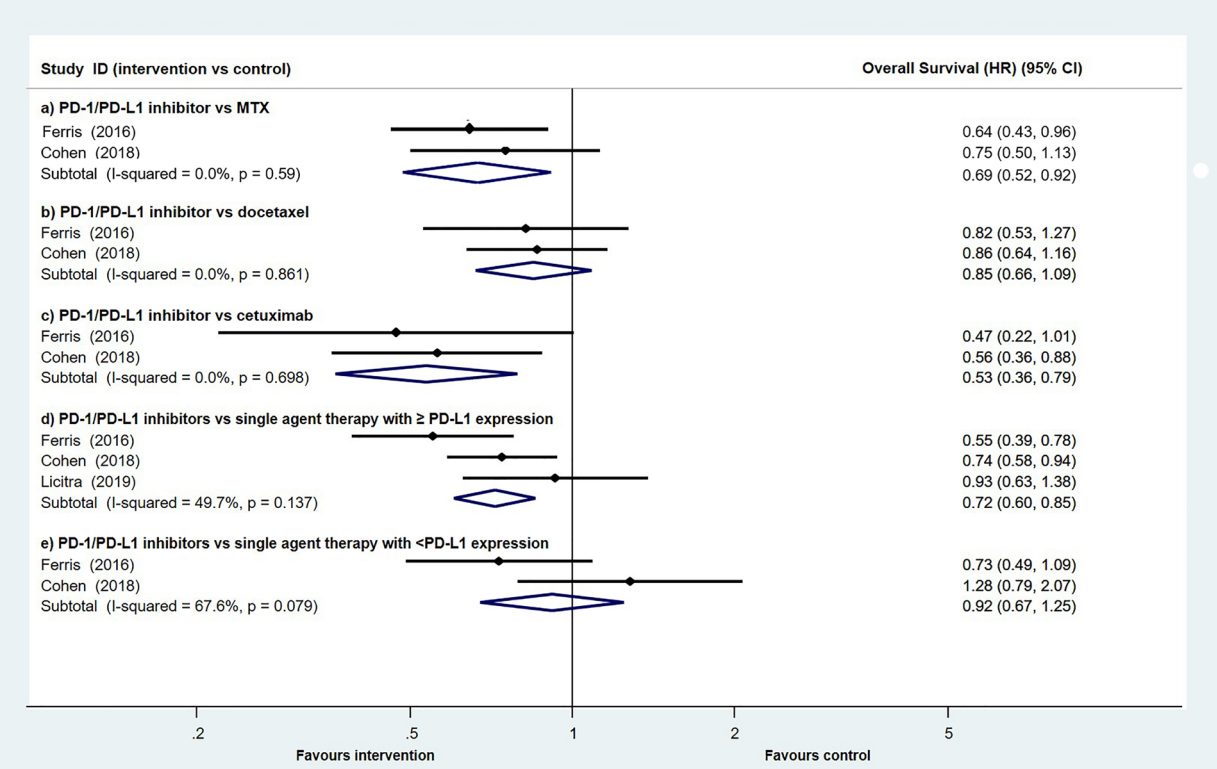

Fig. 6. Subset analysis of PD-1 inhibitors against SOC in R/M HNSCC treatment.
PD-1 inhibitors had a greater magnitude of benefit for patients with a PD-L1 expression ≥1 and also against patients who received cetuximab therapy.

(HR = 0·79, 95% CI 0·70-0·90, $p < 0·001$) (Fig. 5h) especially amongst tumors with high PD-L1 expression (HR = 0·72, 95% CI 0·60-0·85, $p < 0·001$) (Fig. 6d). However, tumors with PD-L1 expression < 1% did not derive the same OS benefits (HR = 0.92, 95% CI 0·67-1·25, $p = 0·58$) (Fig. 6e). Interestingly, greater survival with PD-1/ PD-L1 inhibitors was attained over cetuximab (HR = 0·53, 95% CI 0·36-0·79, $p = 0·002$) compared to MTX (HR = 0·69, 95% CI 0·52-0·92, $p = 0·01$) and docetaxel (HR = 0·85, 95% CI 0·66-1·09, $p = 0·19$) (Fig. 6a, b, c). PD-1/PD-L1 inhibitors did not prolong PFS (HR = 0·96, 95% CI 0·85-1·09, $p = 0·36$) (Fig. 4f).

3.2.3.2. TLR-agonists. TLR-9 agonist EMD 1201081 added to cetuximab did not improve PFS over cetuximab monotherapy (Table 1.2h) (Ruzsa et al., 2014). OS for the control group was not reported as its survival results were confounded by the trial's cross-over design (Ruzsa et al., 2014) (Table 2.2h).

3.2.3.3. IMT Combination therapy. Two trials evaluated the activity of PD-L1 inhibitor durvalumab in combination with anti-CTLA-4 tremelimumab (Table 1.2 g) (Siu et al., 2019; Licitra et al., 2019). The CONDOR study tested the efficacy of durvalumab and tremelimumab combination against durvalumab or tremelimumab monotherapy (Siu et al., 2019). ORR was highest with combination therapy followed by durvalumab and tremelimumab monotherapy. Although the study was not powered to compare survival, PFS and OS were comparable between all three arms. In the EAGLE trial, durvalumab in combination with tremelimumab did not improve ORR, PFS or OS over SOC of either taxane, cetuximab, MTX or a 5-FU-based regimen. However, there was an imbalance of patients with a better ECOG performance score in the control arm with subsequent IMT also provided in the SOC arm (Licitra et al., 2019) (Table 2.2g).

3.3. Heterogeneity analysis

Substantial heterogeneity was located amongst the PFS endpoint for studies testing cetuximab added to platinum-based chemotherapy (Vermorken et al., 2008; Burtness et al., 2005) (Fig. 4b), and for the OS endpoint in trials evaluating taxane added to a cetuximab-platinum regime (Bossi et al., 2017; Klinghammer et al., 2019; Friesland et al., 2018; Guigay et al., 2019) (Fig. 5c) and the effect of PD-1 inhibitors with low PD-L1 expression (Fig. 6e). Sensitivity analysis using the random-effects model did not change the benefit of introducing cetuximab to platinum-based therapy to PFS (HR = 0·63, 95% CI 0·44-0·90, $p = 0·01$) whilst OS for trials evaluating taxane added to a cetuximab-platinum combination (HR = 0.91, 95% CI 0.71-1.16, p = 0.45) and those with low PD-L1 expression (HR = 0.95, 95%CI 0.55-1.65, p = 0.86) remained non-significant.

4. Discussion

Our paper is the first to collate response and survival data from RCTs investigating systemic therapy in R/M HNSCC. In our meta-analysis, only immune checkpoint inhibitors targeting PD-1 signaling demonstrated a significant increase to OS amongst patients with R/M HNSCC refractory to platinum-based therapy despite multiple first and second-line agents capable of increasing ORR. PFS was prolonged when panitumumab or cetuximab was added to platinum-based therapy as first-line agents and when EGFR inhibitors were evaluated against MTX in a second-line setting.

Our results appear to strongly support the paradigm shift towards IMT in R/M HNSCC treatment. Not only have PD-1/PD-L1 inhibitors improved OS for second-line treatment in our meta-analysis, the KEYNOTE-048 trial (Burtness et al., 2019) has established pembrolizumab plus platinum-5FU as the new gold-standard for front-line therapy given its superiority over the EXTREME regime. Unfortunately, not all IMT agents appear to be equivalent in delivering improved

survival outcomes. Although our analysis demonstrated PD-1 blockade to be successful in prolonging survival, PD-L1 inhibitor durvalumab from the EAGLE trial included in the meta-analysis did not actually increase OS over SOC unlike their PD-1 inhibitor counterparts nivolumab and pembrolizumab. In the same EAGLE study, no survival advantage was found with a durvalumab and tremelimumab combination (Licitra et al., 2019). Whether survival data in the EAGLE study was confounded by subsequent IMT and an imbalance in ECOG favouring the control arm, these disappointing findings also suggest that IMT is not 'one-size-fits all'. To identify patients who can maximize from IMT, prognostic biomarkers such as PD-L1 expression have been proposed as multiple trials (Chow et al., 2016) including our own meta-analysis have observed better OS outcomes in R/M HNSCC tumours exhibiting a higher PD-L1 expression compared to those with a lower expression. However, other meta-analyses have also found no association with PD-L1 expression and treatment response in R/M HNSCC (Yang et al., 2018; Li et al., 2017). Such inconsistencies may reflect the intrinsic challenges of utilizing PD-L1 expression as a biomarker since its expression can be fluctuant (Vareki et al., 2017; Suresh and Burtness, 2017) and the lack of a standardized assay can make it difficult to detect on tumour surfaces (Vareki et al., 2017; Suresh and Burtness, 2017). Further research still required to validate the role of IMT especially in a first-line setting as recommendations for management are only based on one trial. Furthermore, KEYNOTE-048 (Burtness et al., 2019) does not address survival amongst those with lower PD-L1 expression indicating other effective first-line alternatives still need to be sought for those who are less likely to respond to PD-1 inhibitor treatment. Understanding which classes of IMT can contribute to survival and the role of biomarkers are equally important to better rationalize treatment strategies.

The success of PD-1 inhibitors does not necessarily preclude the relevance of EGFR-inhibitors in R/M HNSCC treatment. Although our meta-analysis challenges the effectiveness of the EXTREME regimen as cetuximab added to platinum chemotherapy did no improve OS, differences in cetuximab dosing and the platinum-based regime between the EXTREME (Vermorken et al., 2008) and ECOG (Burtness et al., 2005) study could have influenced the accuracy of our assessment. Furthermore, the increase in PFS without the same findings for OS in certain EGFR-inhibitor regimes raises whether cross-over or intervention re-allocation that had occurred in the EXTREME (Vermorken et al., 2008), SPECTRUM (Vermorken et al., 2013b) and PARTNER (Wirth et al., 2016) diluted OS data to the extent of pushing it towards non-significance. As PFS data extrapolates survival figures at an earlier follow-up (Savina et al., 2018; Sherrill et al., 2012), its endpoint may be more representative of drug efficacy as its statistics are less likely to be confounded by cross-over or treatment re-allocation. PFS has already been used as a surrogate endpoint in locally advanced HNSCC (Sherrill et al., 2012). However, validating its role in R/M HNSCC could expand the limited repertoire of treatments available for R/M HNSCC patients especially for those not eligible to receive PD-1/PD-L1 inhibitors. In such circumstances, regimes that increased PFS in our meta-analysis such as cetuximab or panitumumab-platinum combination as first-line and EGFR inhibitor monotherapy as second-line agents could still be viable treatment options to consider.

Conversely, PD-1 inhibitors improved OS without the same benefits observed in PFS. Unlike cytotoxic agents, PD-1 inhibitors can cause tumours to exhibit an initial progressive-like phenomena or a delayed but enduring response, making PFS difficult to define using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Gyawali et al., 2018). The limitations of RECIST to describe PFS in IMT may account for the lack of advantage in PFS vs OS amongst PD-1 inhibitors, as the RECIST guidelines were used in all the currently published PD-1 inhibitor trials for R/M HNSCC. The IMT-specific RECIST (iRECIST) criteria developed to accommodate for the atypical response patterns in IMT (Seymour et al., 2017) should be used in future trial designs to improve survival interpretation.

There are several limitations to our paper. Firstly, the quality of many studies could not be extensively appraised lending to a low number of high-quality studies included in the review. Secondly, median follow-up times were either not reported or varied between trials which could have resulted a less ideal comparability for HR values in OS, and PFS since they used different time points. Finally, our analysis only evaluated survival without considering patient-specific parameters. Whilst interpreting survival data helps to stratify the best drugs available, it is also important to individualize systemic therapy according to prognostic factors such as performance status and therapeutic goals to maximize survival and quality of life.

In summary, IMT appears to be paving the frontier of R/M HNSCC treatment but its routine use is hindered by its expense and the challenge of selecting patients who will truly benefit. EGFR inhibitors may remain a reasonable choice for those not eligible for IMT; however systemic therapy should ultimately employ an individualized approach to optimize treatment outcomes. Refinement to the definition or predictive biomarkers and the position of PFS in cancer trials can further improve the continuum of care in R/M HNSCC. Yet there is a need for more high-quality studies to solidify the role of IMT and to confirm whether other targeted therapies can still contribute to survival.

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate

None required.

Consent for publication

Yes to all participating authors.

CRediT authorship contribution statement

Ashley Lau: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft. **Wei-fa Yang:** Investigation, Formal analysis, Writing - review & editing. **Kar-Yan Li:** Data curation, Writing - review & editing. **Yu-xiong Su:** Conceptualization, Project administration, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors have declared no conflicts of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.102984.

References

Adkins, D., Lin, J.C., Sacco, A.G., Ley, J., Oppelt, P., Shen, Q., et al., 2019. Palbociclib plus cetuximab versus placebo plus cetuximab in platinum-resistant, cetuximab-naive, HPV-unrelated head and neck cancer: A double-blind randomized phase II trial (PALATINUS). In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2019 June; Chicago, USA. J Clin Oncol 37 (15_suppl).

Amrein, P.C., Fabian, R.L., 1992. Treatment of Recurrent Head and Neck Cancer with Cisplatin and 5-Fluorouracil vs the Same Plus Bleomycin and Methotrexate. Laryngoscope 102 (8), 901–906.

Argiris, A., Ghebremichael, M., Gilbert, J., Lee, J.W., Sachidanandam, K., Kolesar, J.,

et al., 2013. 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. 31 (11), 1405–1414.
Argiris, Li, Savvides, et al., 2017. Phase III randomized trial of chemotherapy with or without bevacizumab (B) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Survival analysis of E1305, an ECOG-ACRIN Cancer Research Group trial. In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2017 May; Chicago, USA. J Clin Oncol 35 (15_suppl).
Blasco, M., Svider, P., Raza, S., Jacobs, J., Folbe, A., Saraf, P., et al., 2017. Systemic therapy for head and neck squamous cell carcinoma: Historical perspectives and recent breakthroughs. Laryngoscope. 127 (11), 2565–2569.
Bossi, P., Miceli, R., Locati, L.D., Ferrari, D., Vecchio, S., Moretti, G., et al., 2017. 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. Annals of Oncology. 28 (11), 2820–2826.
Bourhis, J., Rivera, F., Mesia, R., Awada, A., Geoffrois, L., Borel, C., et al., 2006. Phase I/II Study of Cetuximab in Combination With Cisplatin or Carboplatin and Fluorouracil in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck. J Clin Oncol. 24 (18), 2866–2872.
Brockstein, B., Vokes, E., 2020. Treatment of Metastatic and Recurrent Head and Neck Cancer. In: UpToDate [database on the internet]. [cited Feburary 2020]. Available from:. UpToDate, Altham (MA). https://www.uptodate.com/contents/treatment-of-metastatic-and-recurrent-head-and-neck-cancer#H1.
Burtness, B., Goldwasser, M., Flood, W., Mattar, B., Forastiere, A., 2005. 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. 23 (34), 8646–8654.
Burtness, B.A., Manola, J., Axelrod, R., Argiris, A., Forastiere, A., 2008. A randomized phase II study of ixabepilone (BMS-247550) given daily 3 5 days every 3 weeks or weekly in patients with metastatic or recurrent squamous cell cancer of the head and neck: an Eastern Cooperative Oncology Group study. Annals of Oncology. 19 (5), 977–983.
Burtness, B., Harrington, K., Greil, R., Soulières, D., Tahara, M., deCastro, G., et al., 2019. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomized, open label, phase III study. The Lancet 394 (10212), 1915–1928.
Chow, Haddad, Gupta, Mahipal, Mehra, Tahara, 2016. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol. 34, 3838–3845.
Clavel, M., Vermorken, J.B., Cognetti, F., Cappelaere, P., deMulder, P.H., Schornagel, J.H., Tueni, E.A., et al., 1994. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. J Clin Oncol. 5 (6), 521–526.
Cohen, E.E., Soulières, D., Le Tourneau, C., Dinis, J., Licitra, L., Ahn, M.J., et al., 2018. 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 Oncol. 393 (10167), 156–167.
Colella, E., Merlano, M., Blengio, F., Angelini, F., Ausili Cefaro, G.P., Scasso, F., et al., 1994. Randomized Phase II study of Methotrexate (MTX) versus Methotrexate Plus Lonidamine (MTX+LND) in Recurrent and/or Metastatic Carcinoma of the Head and Neck. Eur J Cancer. 30A (7), 928–930.
Fayette, J., Wirth, L., Oprean, C., Udrea, A., Jimeno, A., Rischin, D., et al., 2016. Randomized Phase II Study of Duligotuzumab (MEHD7945A) vs. Cetuximab in Squamous Cell Carcinoma of the Head and Neck (MEGHAN Study). Frontiers in Oncology. 6, 232.
Ferrarotto, R., William, W., Tseng, J., Marur, S., Shin, D., Murphy, M., Cohen, E., et al., 2018. Randomized phase II trial of cixutumumab alone or with cetuximab for refractory recurrent/metastatic head and neck squamous cell carcinoma. Oral Oncology. 82, 83–90.
Ferris, R.L., Blumenschein, G., Fayette, J., Guigay, J., Colevas, D., Licitra, L., et al., 2016. Nivolumab for Recurrent Sqaumous-Cell Carcinoma of the Head and Neck. N Engl J Med. 375, 1856–1867.
Ferris, R., Saba, N., Gitlitz, B., Haddad, R., Sukari, A., Neupane, P., Morris, J., et al., 2018. 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. 4 (11), 1583–1588.
Forastiere, A.A., Metch, B., Schuller, D.E., Ensley, J.F., Hutchins, L.F., Triozzi, P., et al., 1992. Randomized Comparison of Cisplatin Plus Fluorouracil and Carboplatin Plus Fluorouracil Versus Methotrexate in Advanced Squamous-cell Carcinoma of the Head and Neck: A Southwest Oncology Group Study. J Clin Oncol. 10, 1245–1251.
Forastiere, A.A., Leong, T., Rowinsky, E., Murphy, B.A., Vlock, D.R., DeConti, R.C., Adams, G.L., 2001. Phase III Comparison of High Dose Paclitaxel + Cisplatin + Granulocyte Colony-Stimulating Factor versus Low-dose Paclitaxel + Cisplatin in Advanced Head and Neck Cancer: Eastern Cooperative Oncology Group Study E1393. J Clin Oncol. 19 (4), 1088–1095.
Fountzilas, G., Papakostas, P., Dafni, U., Makatsoris, T., Karina, M., Kalogera-Fountzila, A., et al., 2006. Paclitaxel and gemcitabine vs. paclitaxel and pegylated liposomal doxorubicin in advanced non–nasopharyngeal head and neck cancer. An efficacy and cost analysis randomized study conducted by the Hellenic Cooperative Oncology Group. Annals of Oncology. 17, 1560–1567.
Friesland, S., Tsakonas, G., Kristensen, C., Herlestam, M., Moren, C., Haugen, H., Soderstrom, K., et al., 2018. 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). In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2018 June; Chicago, USA. J Clin Oncol 36 (15_suppl).
Fury, M., Sherman, E., Lisa, D., Agarwal, N., Algazy, K., Brockstein, B., et al., 2012. A Randomized Phase II Study of Cetuximab Every 2 Weeks at Either 500 or 750 mg/m2 for Patients With Recurrent or Metastatic Head and Neck Squamous Cell Cancer. J Natl Compr Canc Netw. 10, 1391–1398.
Gilbert, J., Lee, J., Argiris, A., Haigentz, M., Feldman, L., Jang, M., et al., 2012. Phase II 2-arm trial of the proteasome inhibitor, PS-341 (bortezomib) in combination with irinotecan or PS-341 alone followed by the addition of irinotecan at time of progression in patients with locally recurrent or metastatic squamous cell carcinoma of the head and neck (E1304): A trial of the Eastern Cooperative Oncology Group. Head and Neck. 35 (7), 942–948.
Gilbert, J., Schell, M., Zhao, X., Murphy, B., Tanvetyanon, T., Leon, M., Hayes, D., et al., 2015. A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma. Oral Oncol. 51 (4), 376–382.
Guardiola, E., Peyrade, F., Chaigneau, L., Cupissol, D., Tchiknavorian, X., Bompas, E., et al., 2004. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer. 40 (14), 2071–2076.
Guigay, J., Fayette, J., Mesia, R., Lafond, C., Saada-Bouzid, E., Geoffrois, L., et al., 2019. TPExtreme randomized trial: TPEx versus Extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2019 June; Chicago, USA. J Clin Oncol 37 (15_suppl).
Gyawali, B., Phillips, S., Kesselheim, A.S., 2018. 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. 1 (2), e180416.
Harrington, K., Forster, M., Tourneau, C., Ariza, J., Chen, S., Greenberg, J., et al., 2018. Randomized phase 2 trial of patritumab (P) or placebo (PBO) + cetuximab (C) + cisplatin (CIS) or carboplatin (CAR) for recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). In: Proceedings of the American Society of Clinical Oncology Annual Meeting; 2018 May; Chicago, USA. J Clin Oncol 36 (15_suppl).
Jacobs, C., Lyman, G., Velez-Garcai, E., Sridhar, K., Knight, W., Hochster, H., et al., 1992. A Phase III Randomized Study Comparing Cisplatin and Fluorouracil as Single Agents and in Combination for Advanced Squamous Cell Carcinoma of the Head and Neck. J Clin Oncol. 10, 257–263.
Jimeno, A., Shirai, K., Choi, M., Laskin, J., Kochenderfer, M., Spira, A., et al., 2014. A randomized, phase II trial of cetuximab with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. Annals of Oncology. 26 (3), 556–561.
Jimeno, A., Bauman, J., Weissman, C., Adkins, D., Schnadig, I., Beauregard, P., et al., 2015. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. Oral Oncol. 51 (4), 383–388.
Joshi, Patil, Noronha, et al., 2017. Results of a phase II randomized controlled clinical trial comparing efficacy of cabazitaxel versus docetaxel as second-line or above therapy in recurrent head and neck cancer. In: Oncology ASoC, editor. American Society of Clinical Oncology Annual meeting.
Klinghammer, K., Gauler, T., Dietz, A., Grünwald, V., Stöhlmacher, J., Knipping, S., et al., 2019. Cetuximab, fluouracil and cisplatin with or without docetaxel for patients with recurrent and /or metasatic squamous cell carcinoma of the head and neck (CeFCiD): an open-label phase II randomised trial (AIO/IAG-KHT trial 1108). Eur J Cancer. 122, 53–60.
Kushawah, V., Gupta, S., Husain, N., Khan, H., Negi, M., Jamal, N., et al., 2015. Gefitinib, Methotrexate and Methotrexate plus 5-Fluorouracil as palliative treatment in recurrent head and neck squamous cell carcinoma. Cancer Biology & Therapy. 16 (2), 346–351.
Li, J., Wang, P., Xu, Y., 2017. Prognostic value of programmed cell death ligand 1 expression in patients with head and neck cancer: a systematic review and meta-analysis. PLoS ONE.
Licitra, L., Haddad, R., Even, C., Tahara, M., Dvorkin, M., Ciuleanu, T., et al., 2019. EAGLE: A phase 3, randomized, open-label study of durvulumab (D) with or without tremelimumab (T) in (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2019 May; Chicago, USA. J Clin Oncol 37 (15_suppl).
Limaye, S., Riley, S., Zhao, S., O'Neill, A., Posner, M., Adkins, D., et al., 2013. A randomized phase II study of docetaxel with or without vandetanib in recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN). Oral Oncology. 49 (8), 835–841.
Ling, D., Bakkenist, C., Ferris, R., Clump, A., 2018. Role of Immunotherapy in Head and Neck Cancer. Semin Radiat Oncol. 28 (1), 12–16.
Machiels, J.P., Subramanian, S., Ruzsa, A., Repassy, G., Lifirenko, I., Flygare, A., et al., 2011. Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomised phase 3 trial. Lancet Oncol. 12, 333–343.
Machiels, J.P., Haddad, R., Fayette, J., Licitra, L., Tahara, M., Vermorken, J., et al., 2015. 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. 16 (5), 583–594.
Machiels, J.P., Maanen, A., Vandenbulcke, J.-M., Filleul, B., Seront, E., Henry, S., D'Hondt, L., et al., 2016. Randomized Phase II Study of Cabazitaxel Versus Methotrexate in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With Platinum-Based Therapy. The Oncologist. 21 (12) 1416-e1417.
Paccagnella, A., Pappagallo, G.L., Segati, R., Zorat, P., Cavaniglia, G., Lunghi, F., Migliorini, V., et al., 1993. Epirubicin, Methotrexate, and Bleomycin in the Management of Recurrent Squamous Cell Head and Neck Cancer. A GSTTC Randomized Phase II Study. Eur J Cancer. 29A (5), 704–708.
Parmar, M.K., Torri, V., Stewart, L., 1998. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 17 (24), 2815–2834.
Pivot, X., Wadler, S., Kelly, C., Ruxer, R., Tortochaux, J., Stern, J., et al., 2001. Result of two randomized trials comparing nolatrexed (Thymitaq™) versus methotrexate in patients with recurrent head and neck cancer. Annals of Oncology. 12 (11), 1595–1599.
Pivot, X., Awada, A., Gedouin, D., Kerger, J., Rolland, F., Cupissol, D., et al., 2003. Results of randomised phase II studies comparing S16020 with methotrexate in patients with recurrent head and neck cancer. Annals of Oncology. 14 (3), 373–377.
Ruzsa, A., Sen, M., Evans, M., Lee, L.W., Hideghety, K., Rottey, S., et al., 2014. Phase 2, open-label, 1:1 randomized controlled trial exploring the efficacy of EMD 1201081 in combination with cetuximab in second-line cetuximab-naïve patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Invest New Drugs. 32 (6), 1278–1284.
Sacco, A., Cohen, E., 2015. Current Treatment Options for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 33 (29), 3305–3313.
Savina, M., Gourgou, S., Italiano, A., Dinart, D., Rondeau, V., Penel, N., et al., 2018. Meta-analyses evaluating surrogate endpoints for overall survival in cancer randomized trials: A critical review. Critical Reviews in Oncology/Hematology 123, 21–41.
Schrijvers, D., Johnson, J., Jiminez, U., Gore, M., Kosmidis, P., Szpirglas, H., et al., 1998. Phase III Trial of Modulation of Cisplatin/Fluouracil Chemotherapy of Interferon Alfa-2b in Patients with Recurrent or Metastatic Head and Neck Cancer. J Clin Oncol. 16, 1054–1059.
Seiwert, T.Y., Fayette, J., Cupissol, D., DelCampo, J.M., Clement, P., Hitt, R., et al., 2014a. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. Annals of Oncology. 25 (9), 1813–1820.
Seiwert, T.Y., Adkins, D., Worden, F., Wade, J.L., Hu, S., Price, K., et al., 2014b. Activity of Temsirolimus Added to Cetuximab in Patients With Cetuximab-Resistant, Recurrent/Metastatic Head-and-Neck Cancer: Results of the Randomized Phase 2 Maestro-HN Study Molecular Biology and Therapeutics. International Journal of Radiation Oncology Biology Physics: American Society of Radiation Oncology 88 (2), 510.
Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L., Mandrekar, S., et al., 2017. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 18 (3), 143–152.
Sherrill, B., Kaye, J., Sandin, R., Cappelleri, J., Chen, C., 2012. Review of meta-analyses evaluating surrogate endpoints for overall survival in oncology. Onco Targets Ther. 5, 287–296.
Siu, L., Even, C., Mesia, R., Remenar, E., Daste, A., Delord, J.P., et al., 2019. Safety and Efficacy of Durvalumab With or Without Tremelimumab in Patients With PD-L1–Low/Negative Recurrent or Metastatic HNSCC. The Phase 2 CONDOR Randomized Clinical Trial. JAMA Oncol. 5 (2), 195–203.
Soulières, D., Faivre, S., Mesía, R., Remenár, É, Li, S., Karpenko, A., et al., 2017. 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. 18 (3), 323–325.
Stewart, J.S., Cohen, E., Licitra, L., Van Herpen, C., Khorprasert, C., Soulieres, D., et al., 2009. Phase III Study of Gefitinib Compared With Intravenous Methotrexate for Recurrent Squamous Cell Carcinoma of the Head and Neck. J Clin Oncol. 27 (11), 1864–1871.
Suresh, T., Burtness, B., 2017. Immunotherapy in Head and Neck Squamos Cell Cancer. American Journal of Hematology/Oncology 13 (6), 20–27.
Tierney, J., Stewart, L., Ghersi, D., Burdett, S., Sydes, M., 2007. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 8, 16.
Urba, S., Herpen, V., Sahoo, T., Shin, D., Licitra, L., Mezei, K., et al., 2012. 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 118 (19), 4694–4705.
Vareki, S., Garrigós, C., Duran, I., 2017. Biomarkers of response to PD-1/PD-L1 inhibition. Critical Reviews in Oncology/Hematology 116, 116–124.
Vermorken, J.B., Specenier, P., 2010. Optimal treatment for recurrent/metastatic head and neck cancer. Annals of Oncology. 21 (Suppl7) vii252-261.
Vermorken, J.B., Catimel, G., deMulder, D., et al., 1999. Randomized Phase II trial of Weekly Methotrexate (MTX) Versus Two Schedules of Triweekly Paclitaxel (Taxol) in Patients with Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). In: Proceedings of the American Society of Clinical Oncology Annual Meeting; 1999 May; Atlanta, USA. J Clin Oncol p395.
Vermorken, J.B., Mesia, R., Rivera, F., Remenar, E., Kawecki, A., Rottey, S., et al., 2008. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. N Engl J Med. 359, 1116–1127.
Vermorken, J.B., Peyrade, F., Krauss, J., Mésia, R., Remenar, E., Gauler, T.C., et al., 2013a. 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). Annals of Oncology. 25 (3), 682–688.
Vermorken, J.B., Stohlermacher-Williams, J., Davidenko, I., Licitra, L., Winquist, E., et al., 2013b. 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. 14 (8), 697–710.
Vokes, E., Worden, F., Adkins, D., Bauman, J., Lim, D., Sukar, A., et al., 2015. A randomized phase II trial of the MET inhibitor tivantinib + cetuximab versus cetuximab alone in patients with recurrent/metastatic head and neck cancer. In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2015 May; Chicago, USA. J Clin Oncol 33 (15_suppl).
William, W., Feng, L., Kies, M., Ahmed, S., Blumenschein, G., Glisson, B., et al., 2017. Randomized, double-blind, placebo-controlled, phase II trial of first-line platinum/docetaxel with or without erlotinib (E) in patients (pts) with recurrent and/or metastatic (R/M) head and neck squamous cell carcinomas (HNSCCs). In: Proceeding of the American Society of Clinical Oncology Annual Meeting; 2017 May; Chicago, USA. J Clin Oncol 35 (15_suppl).
Wirth, L.J., Dakhil, S., Kornek, G., Axelrod, R., Adkins, D., Pant, S., et al., 2016. 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 Oncology. 61, 31–40.
World Health Organization, 2014. Locally Advanced Squamous Carcinoma of the Head and Neck. Webpage [Internet]. [cited 2019 Sept]. Available from:. World Health Organization, Union for International Cancer Control. https://www.who.int/selection_medicines/committees/expert/20/applications/HeadNeck.pdf?ua=1.
Yang, W., Wong, M., Thomson, P., Li, K.-Y., Su, Y.X., 2018. The prognostic role of PD-L1 expression for survival in head and neck squamous cell carcinoma: A systematic review and meta-analysis. Oral Oncol. 86, 81–90.

Dr. Ashley Lau is a doctor currently based in London with qualifications in medicine from the University of London and dentistry from the University of Hong Kong. Her research interest is in head and neck oncology which she has presented her findings at various international conferences such as ICOMs and EACMFS.

Dr. Wei-Fa Yang received his undergraduate dental degree at Sun-Yat Sen University and is currently pursuing a PhD in at the University of Hong Kong in the Faculty of Dentistry. He has published over 17 research articles in relation to oral and maxillofacial surgery.

Kar-Yan Li is a senior technical officer at the University of Hong Kong with extensive practical working experience in dental research, in particular on statistical analysis, interpretation and presentation with over 39 published research articles to date. She is also involved in teaching and supervision of undergraduate and post-graduate students at the Faculty of Dentistry in the University of Hong Kong.

Dr. Richard Yu-Xiong Su is a Clinical Associate Professor in Oral and Maxillofacial Surgery at the University of Hong Kong. He received his undergraduate and postgraduate education and Oral & Maxillofacial Surgery resident training in Sun Yat-sen University. He has worked in the Department of Maxillofacial Surgery, University of Luebeck, Germany, in 2009, and the Department of Head and Neck Surgery, MD Anderson Cancer Center, TX, US, in 2011-2012. Dr Su specializes in oral and maxillofacial oncology, head and neck reconstruction, and salivary gland diseases.