Comparison of second-line treatments of recurrent and/or metastatic squamous cell carcinoma of the head and neck

Elie El Rassy*1, Tarek Assi1,2, Ziad Bakouny1, Fadi El Karak1, Nicholas Pavlidis3 & Marwan Ghosn1

1Department of Hematology-Oncology, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon
2Department of Medical Oncology, Institut Gustave Roussy, Université Paris-Saclay, Villejuif F-94805, France
3University of Ioannina, Ioannina, Greece

*Author for correspondence: elie.rassy@hotmail.com

Aim: The literature lacks direct evidence comparing the different regimens evaluated in the second-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Methods: We conducted a network meta-analysis (NMA) of the randomized controlled phase reporting on the second-line drug therapy in R/M SCCHN. Results: These eligible trials included 11 regimens among which six targeted therapies, two immune checkpoint inhibitors and three chemotherapy drugs. Only nivolumab has shown statistically significant superiority over methotrexate in terms of overall survival (OS; hazard ratios [HR]: 0.64; 95% CI: 0.43–0.96) and objective response rate (odds ratios [OR]: 2.51; 95% CI: 1.07–5.86). Conclusion: Based on the efficacy and safety outcomes of this network meta-analysis, nivolumab seems the most favorable regimen in the management of R/M SCCHN.

First draft submitted: 29 August 2018; Accepted for publication: 6 December 2018; Published online: 23 January 2019

Keywords: metastatic • platinum refractory • recurrent • second line • squamous cell carcinoma of the head and neck

Head and neck cancers have reached an incidence of nearly 500,000 new cases and 300,000 deaths annually in the last estimates of GLOBOCAN 2012 [1]. Patients with early-stage and locally advanced squamous cell carcinoma of the head and neck (SCCHN) are treated in a curative perspective but the risk of recurrence is not subtle, reaching 20% in early-stage SCCHN and 50% in locally advanced SCCHN [2]. Approximately 10% of patients present with metastatic disease, the overall survival (OS) of whom is usually less than 1 year [3]. The first-line treatment of patients with recurrent or metastatic (R/M) SCCHN has been well established with the EXTREME regimen [4–6]. Patients requiring second-line treatment for R/M SCCHN and platinum-refractory SCCHN are managed similarly [7]. The trials of second-line treatment have allowed any number of prior therapies; and therefore, second-line treatment imply second-line and beyond. The possible treatment options in this setting include chemotherapy, targeted therapy and immune checkpoint inhibitors. Available chemotherapy regimens include methotrexate, docetaxel and paclitaxel monotherapies, with no data showing the superiority of one regimen over the others [8,9]. The CheckMate 141 trial was not designed to compare these regimens but showed a slight numerical superiority of docetaxel over methotrexate and cetuximab in terms of OS [10]. The approved targeted therapies in R/M SCCHN include cetuximab as monotherapy (objective response rate [ORR]: 10–13% and OS: 5–6 months) or in combination with a taxane (ORR: 38–55% and OS: 7.6–10 months) [11–13]. Other targeted therapies, namely panitumumab, gefitinib, erlotinib, lapatinib and afatinib yielded modest results at best and did not offer higher efficacy outcomes [7]. Two immune checkpoint inhibitors, pembrolizumab and nivolumab, are approved for the second-line treatment of R/M SCCHN. The first got accelerated approval based on the Phase I-B trial KEYNOTE-012 of 192 R/M SCCHN patients showing a median OS of 8 months, ORR of 18% and a tolerable safety profile [14]. The second was approved based on the Phase III trial, CheckMate 141, that enrolled 361 platinum-refractory patients and showed an OS of 7.5 months, ORR of 13.3% without major adverse events [10].
Each of the second-line trials in R/M SCCHN tested different drugs with small sample sizes which rendered the evaluation of the relative efficacy of each drug challenging. The current literature lacks direct evidence proving the superiority of one regimen over the other in the absence of direct head-to-head comparisons. Therefore, our aim was to perform a network meta-analysis (NMA) to overcome these limitations by comparing the different drugs according to their efficacy and safety profiles.

Materials & methods

The protocol of our study has not been previously published. This analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Search strategy

We conducted an independent review of the published data in PubMed/Medline until 31 October 2017. The search in the databases was done using combinations of the following keywords ‘head and neck’, ‘metastatic’, ‘therapy’, ‘relapse’, ‘recurrent’, ‘tumor’ and ‘cancer’. Studies with low number of randomized patients (n ≤ 30) were not included. In order to avoid missing data, we did not limit our search to a specific language and we also searched the Cochrane Central Register of Controlled Trials and clinical trials registries (Clinicaltrials.gov and International Clinical Trials Registry Platform of WHO) to obtain additional information on the registered trials on head and neck tumors.

Eligibility criteria & study selection

Randomized controlled Phase II and III trials reporting on the efficacy and safety of second-line drug therapy in R/M SCCHN were included. Eligible studies comparing any chemotherapeutic agent, targeted therapy or immune therapy to the current standard of care (methotrexate, taxanes or cetuximab) in the second-line setting were included in the analysis. Patients were also considered to be in the second-line setting of recurred or metastatic head and neck cancer in the following situations: progression while receiving frontline EXTREME protocol for R/M SCCHN tumors; platinum-refractory patients who progress within 6 months of the last platinum administration. Retrospective, observational, nonrandomized trials or abstracts with incomplete data were excluded from this study. Studies with incomplete or inadequate details of the study design were ineligible for our analysis (Figure 1). Furthermore, abstracts with sufficient outcome data for assessment were included in this review in order to be as exhaustive as possible in evaluating available evidence, which is in accordance with the standard search practices of systematic reviews of the Cochrane collaboration. The independent screening of the articles and abstracts according to the eligibility criteria was performed manually by two investigators (EE Rassy and T Assi) of the review team based on reading the study title and abstract.

Data extraction & evaluation

Two investigators (EE Rassy and T Assi) independently extracted the data from the selected trials to an Excel sheet. Details of the study (year of publication, number of patients, first author and trial design) and patient characteristics (age, sex, Eastern Cooperative Oncology Group [ECOG] performance status, number of previous lines of treatment, primary tumor location, EGFR testing and HPV status) were retrieved. Additional information on the efficacy (OS and ORR) and toxicity (grade 3/4 treatment-related adverse events and treatment discontinuation) were also extracted. Double checking of the extracted data was done by a third reviewer (Z Bakouny). When possible, we used data from intention-to-treat (ITT) populations. Discrepancies were resolved by discussion with all the authors.

Outcomes

The primary outcome was OS defined as the duration in months between the first administration of treatment and the date of patient’s death or last follow-up. Secondary outcomes were ORR and progression-free survival (PFS), defined as the duration in months between the administration of treatment and the date of first tumor progression or death. The percentage of treatment discontinuation due to adverse events, in each treatment arm, was evaluated as a surrogate for drug tolerability.

Quality assessment

An independent assessment of the quality and potential bias for each study was done according to the ‘Cochrane Handbook for Systematic Reviews of Interventions’. Two reviewers (EE Rassy and T Assi) assessed the published
Treatment options of R/M SCCHN Review

Potentially relevant articles screened and identified by title/abstract (n = 2459)

Citations excluded for not meeting eligibility criteria (n = 2409): reviews, commentaries, case reports, non-RCT, non-English articles

Potentially relevant RCT retrieved for detailed review (n = 52)

Trials excluded (n = 42)
- Duplicate data (n = 5)
- Single-arm trial (n = 36)
- Data not adequate for evaluation (n = 1)

Ten potential RCTS were selected for analysis.

RCTS trials excluded (n=2)
- No prior platinum therapy (n = 1; Guardiola et al. 2004)
- Low number of randomized patients (n = 1; Limaye et al. 2013)

Eight RCTS were included in the final analysis.
- Phase III trials (n = 6)
  - Afatinib (n = 1)
  - Nivolumub (n = 1)
  - Pembrolizumab (n = 1)
  - Zalutumumab (n = 1)
  - Gefitinib (n = 1)
  - Gefitinib + docetaxel (n = 1)
- Phase II trials (n = 2)
  - Buparlisib + paclitaxel (n = 1)
  - Afatinib (n = 1)

Figure 1. Flowchart describing the article selection process.
RCT: Randomized controlled trial.
reports of the selected trials for the following information: selection bias, allocation concealment, blinding of the participants and the outcome assessment, incomplete outcome data, selective reporting and baseline characteristics. The studies were ranked as A (low-risk bias) for a score of 4–5, B (intermediate risk of bias) for a score of 2–3 or C (high risk of bias) for a score of 0–1.

**Statistical methods**

We performed a NMA utilizing a frequentist approach with generalized pairwise modeling using MetaXL 5.3 (EpiGear International, Brisbane, Australia). The inverse variance heterogeneity method was used to overcome the previously described limitations of the fixed and random effects models [16]. Succinctly, inverse variance heterogeneity is a model which maintains the inverse variance weights of studies, even when heterogeneity increases (this is in contrast with the random effects model, in which increased heterogeneity tends to render the weights of smaller and larger studies equal). NMA was computed for OS, ORR and grade 3/4 adverse event rates. Results of the NMA of OS were expressed as hazard ratios (HR) and those of grade 3/4 adverse event rates as odds ratios (OR), with their 95% CI. Network plots were generated in which treatments that were directly compared in studies were connected with lines, the widths of which were proportional to the number of studies comparing the two treatments. The sizes of the treatment circles were also proportional to the number of arms in the included studies which corresponded to the treatment. The choice of the common comparator is mainly analytical since it should be chosen in a manner which allows the largest proportion of estimates of comparisons between treatment effects to be based on direct comparisons, which is why methotrexate (the most common treatment arm among included studies) was chosen as the common comparator in this study. However, regardless of the choice of common comparator, the various included agents could be compared among each other by evaluating the distance between point estimates of treatment effects and, in particular, the presence or absence of overlap between the CIs of treatment effect.

When extracting data from studies that had not reported data by treatment subpopulations and in order to allow indirect comparisons between treatments, some simplifications regarding treatment arms were necessary: the control arm of Cohen *et al.* study [17], in which patients had been treated according to the standard of care (docetaxel: 110 patients, methotrexate: 65 patients and/or cetuximab: 73 patients), was considered to be docetaxel instead of standard of care; the control arm of Machiels *et al.* study [18], in which patients had been treated by either methotrexate (68 patients) or best supportive care (27 patients), was considered to be methotrexate; the control arm of Ferris *et al.* study [10], in which patients had been treated according to the standard of care (methotrexate: 52 patients, docetaxel: 54 patients and/or cetuximab: 15 patients), was considered to be methotrexate for the NMA of the ORR and grade 3–5 adverse event rates outcomes. These simplifications were performed by considering the arm containing multiple agents as being only the treatment which had been given to the largest proportion of patients in that treatment arm (e.g., the control arm of the Machiels *et al.* study being considered docetaxel instead of standard of care) [18]. Furthermore, this was done while also taking into account the impact of the simplification on the network plot. In particular, for the study of Ferris *et al.*, methotrexate (and not docetaxel) was chosen to be the simplified comparator arm of nivolumab since it allowed a number of supplementary indirect comparisons with methotrexate, which would have otherwise not been possible (this choice was also made since methotrexate and docetaxel had been administered to a comparable number of patients in that study) [10].

Furthermore, two sensitivity analyses were computed for the primary outcome of this study (OS): by excluding the two studies for which the abovementioned simplifications were necessary [17,18]; by only including data from patients who had progressed under platinum-based therapy (excluding Argiris *et al.* study [19] and extracting the data from the platinum-refractory subpopulation of Stewart *et al.* study [20]).

All NMAs were limited by the incomplete reporting of data within the papers detailing the original studies. Furthermore, when one study was excluded from an analysis, this often entailed exclusion of other studies due to the absence of sufficient connecting nodes to the common comparator (methotrexate).

**Results**

**Study selection process**

A flowchart describing the selection process of reports is presented in Figure 1. The electronic search yielded 2459 potentially relevant articles published in PubMed/Medline until 31 October 2017. Our search in the Cochrane Central Register of Controlled Trials and clinical trials registries did not yield any supplementary articles, which had not been identified in PubMed/Medline. We excluded 2409 articles not meeting our eligibility criteria and ended up with 52 trials that were retrieved for detailed review. After title and abstract screening, 42 articles (five articles...
Table 1. Characteristics of the studies included in the network meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Follow-up (months)</th>
<th>Study population</th>
<th>N</th>
<th>Treatment arm 1 (n)</th>
<th>Treatment arm 2 (n)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart et al.</td>
<td>2008</td>
<td>6.2</td>
<td>R/M with or without platinum</td>
<td>647</td>
<td>Gefitinib (n = 325)</td>
<td>Methotrexate (n = 322)</td>
<td>[21]</td>
</tr>
<tr>
<td>Machiels et al.</td>
<td>2011</td>
<td>6</td>
<td>R/M after platinum therapy</td>
<td>286</td>
<td>Zalutumab (n = 191)</td>
<td>Best supportive care (n = 27) or methotrexate (n = 68)</td>
<td>[18]</td>
</tr>
<tr>
<td>Argiris et al.</td>
<td>2013</td>
<td>35</td>
<td>R/M with or without platinum</td>
<td>270</td>
<td>Docetaxel + gefitinib (n = 134)</td>
<td>Docetaxel (n = 136)</td>
<td>[20]</td>
</tr>
<tr>
<td>Seiwert et al.</td>
<td>2014</td>
<td>NR</td>
<td>R/M after platinum therapy</td>
<td>121</td>
<td>Aflatinib (n = 61)</td>
<td>Cetuximab (n = 60)</td>
<td>[24]</td>
</tr>
<tr>
<td>Machiels et al.</td>
<td>2015</td>
<td>6.7</td>
<td>R/M after platinum therapy</td>
<td>483</td>
<td>Aflatinib (n = 322)</td>
<td>Methotrexate (n = 161)</td>
<td>[22]</td>
</tr>
<tr>
<td>Ferris et al.</td>
<td>2016</td>
<td>5.1</td>
<td>R/M after platinum therapy</td>
<td>361</td>
<td>Nivolumab (n = 240)</td>
<td>Cetuximab (n = 15), methotrexate (n = 52), docetaxel (n = 54)</td>
<td>[10]</td>
</tr>
<tr>
<td>Soulieres et al.</td>
<td>2017</td>
<td>18.1</td>
<td>R/M after platinum therapy</td>
<td>158</td>
<td>Buparlisib + paclitaxel (n = 79)</td>
<td>Paclitaxel (n = 79)</td>
<td>[23]</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>2017</td>
<td>7.3</td>
<td>R/M after platinum therapy</td>
<td>495</td>
<td>Pembrolizumab (n = 247)</td>
<td>Cetuximab (n = 73), methotrexate (n = 65), docetaxel (n = 110)</td>
<td>[17]</td>
</tr>
</tbody>
</table>

N: Number of patients in the trial; n: Number of patients in the treatment arm; NR: Not reported; R/M: Recurrent or metastatic.

for duplicate data, 36 articles for single-arm trial design and one article for insufficient details of study design) were excluded leading to a total of ten articles [18–24]. Two randomized controlled trials were also excluded [9,25]: the first because patients had not received prior platinum therapy and the second due to the low number of randomized patients (n ≤ 30). The remaining studies matched the aforementioned criteria and hence were included in the NMA.

Characteristics of included studies

Eight trials with a total of 2584 patients were finally selected and included in the analysis. The characteristics of the included trials are listed in Table 1. In total, these trials included 11 regimens among which six targeted therapies, two immune checkpoint inhibitors and three chemotherapy drugs: best supportive care (27 patients; 1.0%), afatinib (383 patients; 14.8%), cetuximab (94 patients; 3.6%), docetaxel (177 patients; 6.8%), gefitinib (325 patients; 12.6%), methotrexate (694 patients; 26.9%), nivolumab (240 patients; 9.3%), paclitaxel (79 patients; 3.1%), zalutumumab (191 patients; 7.4%), docetaxel in combination with gefitinib (134 patients; 5.2%) and paclitaxel in combination with buparlisib (79 patients; 3.1%) (Table 1). The most commonly tested treatment arm was methotrexate (five trials) followed by afatinib and cetuximab (two trials each).

The patients and tumor characteristics of the studied populations in each of the trials are reported in Table 2. It is noteworthy that only the study by Stewart et al. reported on the prevalence of EGFR across the study population. However, the prevalence of P16 positivity was more commonly reported: afatinib: 10–14.5%; cetuximab: 12.9%; methotrexate: 11%; nivolumab: 26.2%; paclitaxel: 79%; the combination of paclitaxel and buparlisib: 67% and pembrolizumab: 24.7%.

Risk of bias assessment

The performed quality assessment yielded three studies scoring A (low-risk bias) and five scoring B (intermediate-risk bias). None of the trials was evaluated as C (high-risk bias) (Table 3). All of the eight trials were centralized with identical baseline (except for pembrolizumab) and detailed withdrawal and drop-out (except for pembrolizumab). Two trials had adequate allocation concealment, five were open label and one with unclear concealment. Three of the eight trials were blinded.

Outcome assessment

The primary analysis for the comparison of OS between the included treatments is represented in a network plot in Figure 2, forest plot in Figure 3 and detailed in Supplementary Table 1 in the Supplementary Appendix. Among the evaluated agents, only nivolumab was significantly superior to methotrexate in terms of OS (HR: 0.64; 95% CI: 0.43–0.96). Except for gefitinib, all the evaluated treatments tended to have a positive effect on OS compared with methotrexate, although none of these reached the threshold for statistical significance. These results remained consistent after conducting a sensitivity analysis for the comparison of OS between the included treatments, while
Table 2. The characteristics of the study populations in the trials of second-line treatment of recurrent and/or metastatic head and neck cancers.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of patients</th>
<th>Median age (years)</th>
<th>N age &lt; 65 years</th>
<th>N of women</th>
<th>% one line of previous treatment</th>
<th>N PS 0–1</th>
<th>N PS 2</th>
<th>N larynx</th>
<th>N oral cavity</th>
<th>N pharynx</th>
<th>N other</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>384</td>
<td>58–60</td>
<td>239</td>
<td>54</td>
<td>NR</td>
<td>383</td>
<td>0</td>
<td>74</td>
<td>107</td>
<td>194</td>
<td>9</td>
<td>[22,24]</td>
</tr>
<tr>
<td>Cetuximab†</td>
<td>62</td>
<td>58</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>59</td>
<td>1</td>
<td>12</td>
<td>16</td>
<td>25</td>
<td>9</td>
<td>[24]</td>
</tr>
<tr>
<td>Docetaxel†</td>
<td>136</td>
<td>61.4</td>
<td>72</td>
<td>25</td>
<td>NR</td>
<td>46</td>
<td>71</td>
<td>28</td>
<td>30</td>
<td>36</td>
<td>23</td>
<td>[20]</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>198</td>
<td>NR</td>
<td>72</td>
<td>35</td>
<td>NR</td>
<td>105</td>
<td>72</td>
<td>40</td>
<td>46</td>
<td>61</td>
<td>32</td>
<td>[21]</td>
</tr>
<tr>
<td>Methotrexate†</td>
<td>396</td>
<td>59</td>
<td>144</td>
<td>70</td>
<td>NC</td>
<td>210</td>
<td>144</td>
<td>80</td>
<td>92</td>
<td>122</td>
<td>64</td>
<td>[18,21,22]</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>240</td>
<td>59</td>
<td>NR</td>
<td>43</td>
<td>44.2</td>
<td>238</td>
<td>1</td>
<td>34</td>
<td>108</td>
<td>92</td>
<td>6</td>
<td>[10]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>79</td>
<td>58</td>
<td>NR</td>
<td>11</td>
<td>98</td>
<td>78</td>
<td>1</td>
<td>15</td>
<td>23</td>
<td>35</td>
<td>6</td>
<td>[23]</td>
</tr>
<tr>
<td>Zalutumumab</td>
<td>191</td>
<td>57</td>
<td>161</td>
<td>22</td>
<td>51</td>
<td>157</td>
<td>34</td>
<td>36</td>
<td>64</td>
<td>87</td>
<td>3</td>
<td>[18]</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>495</td>
<td>60</td>
<td>NR</td>
<td>40</td>
<td>57.1</td>
<td>176</td>
<td>71</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>[17]</td>
</tr>
</tbody>
</table>

Combination therapy regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of patients</th>
<th>Median age (years)</th>
<th>N of patients</th>
<th>N of NS 0–1</th>
<th>N of NS 2</th>
<th>N of larynx</th>
<th>N of oral cavity</th>
<th>N of pharynx</th>
<th>N of other</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + gefitinib</td>
<td>134</td>
<td>60.8</td>
<td>85</td>
<td>24</td>
<td>NR</td>
<td>43</td>
<td>29</td>
<td>33</td>
<td>23</td>
<td>42</td>
</tr>
<tr>
<td>Paclitaxel + buparlisib</td>
<td>79</td>
<td>59</td>
<td>NR</td>
<td>14</td>
<td>90</td>
<td>79</td>
<td>0</td>
<td>10</td>
<td>23</td>
<td>39</td>
</tr>
</tbody>
</table>

†These numbers excluded the standard of care arm in Ferris et al. [10] and Cohen et al. [18].
N: Number of patients; NC: Not calculable; NR: Not reported; PS: Performance status.
Table 3. Quality assessment of the studies included in the network meta-analysis.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Method of randomization</th>
<th>Allocation concealment</th>
<th>Blinded</th>
<th>Withdrawal and drop-out</th>
<th>Baseline</th>
<th>Quality level†</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machiels et al. (2011)</td>
<td>Centralized</td>
<td>Open label</td>
<td>No</td>
<td>Detailed</td>
<td>Identical</td>
<td>B</td>
<td>[18]</td>
</tr>
<tr>
<td>Machiels et al. (2014)</td>
<td>Centralized</td>
<td>Open label</td>
<td>No</td>
<td>Detailed</td>
<td>Identical</td>
<td>B</td>
<td>[22]</td>
</tr>
<tr>
<td>Ferris et al. (2016)</td>
<td>Centralized</td>
<td>Open label</td>
<td>No</td>
<td>Detailed</td>
<td>Identical</td>
<td>B</td>
<td>[10]</td>
</tr>
<tr>
<td>Cohen et al. (2017)</td>
<td>Centralized</td>
<td>Open label</td>
<td>No</td>
<td>No details</td>
<td>No details</td>
<td>B</td>
<td>[17]</td>
</tr>
</tbody>
</table>


Figure 2. Network plot for the primary analysis of the overall survival outcome.

Figure 3. Forest plot for the primary analysis of the overall survival outcome with methotrexate as the common comparator (HR: 1). HR: Hazard ratio.
excluding the studies which required simplifications in the analysis of treatment arms [17,18]. This sensitivity analysis is represented in a network plot in Supplementary Figure 1, forest plot in Figure 4 and detailed in Supplementary Table 2 in the Supplementary Appendix.

The sensitivity analysis for the comparison of OS between the included treatments, while only including data from patients who had progressed under platinum-based therapy, is represented in a network plot in Supplementary Figure 2, forest plot in Figure 5 and detailed in Supplementary Table 3 in the Supplementary Appendix. Nivolumab was the only drug that had a statistically significant positive effect on OS compared with methotrexate (HR: 0.64; 95% CI: 0.43–0.96). Zalutumumab had a trend for statistical significance in comparison to methotrexate (HR: 0.77; 95% CI: 0.57–1.05). The other regimens including pembrolizumab as well as the combination of buparlisib and paclitaxel showed numerically superior results in comparison to methotrexate with regards to OS but did not achieve statistical significance. Gefitinib 250 mg (HR: 1.62; 95% CI: 1.13–2.32) and 500 mg (HR: 1.5; 95% CI: 1.06–2.13) were the only two regimens with a significantly negative effect on OS, compared with methotrexate, in patients who had progressed under platinum-based therapy.

The NMA for the comparison of ORR between the included treatments is represented in a network plot in Supplementary Figure 3, in a forest plot in Figure 6, and detailed in Supplementary Table 4 in the Supplementary Appendix. Only nivolumab was found to yield a significantly larger ORR compared with methotrexate (OR: 2.51; 95% CI: 1.07–5.86). Zalutumumab (OR: 6.30; 95% CI: 0.81–49.21), gefitinib 500 mg (OR: 2.18; 95% CI: 0.81–5.88) and afatinib (OR: 1.67; 95% CI: 0.80–3.48) tended to have a better ORR compared with methotrexate, although none of these reached the threshold for statistical significance. The other included treatments, cetuximab
Table 4 reports the prevalence of grade 3/4 adverse events and cites those that are most frequently encountered with second-line treatment of R/M SCCHN. The most commonly reported grade 3/4 adverse events are rash (10–21%), fatigue (2.1–19%), stomatitis (8–10%), diarrhea (13%), hyperglycemia (22%), anemia (6–18%) and neutropenia (5–17%). This table also reports the discontinuation rates secondary to treatment-related adverse events achieving the highest rates with afatinib.

1These numbers excluded the standard of care arm in Ferris et al. [10] and Cohen et al. [18].

AE: Adverse events; NR: Not reported.

(OS: 0.61; 95% CI: 0.15–2.52) and gefitinib 250 mg (OR: 0.67; 95% CI: 0.19–2.42), tended to have negative effects on ORR compared with methotrexate.

Adverse events

Table 4 reports the prevalence of grade 3/4 adverse events and cites those that are most frequently encountered with second-line treatment of R/M SCCHN. The most commonly reported grade 3/4 adverse events are rash (10–21%), fatigue (2.1–19%), stomatitis (8–10%), diarrhea (13%), hyperglycemia (22%), anemia (6–18%) and neutropenia (5–17%). This table also reports the discontinuation rates secondary to treatment-related adverse events achieving the highest rates with afatinib.

The comparison of grade 3/4 adverse events between the included treatments is represented in a network plot in Supplementary Figure 4, in a forest plot in Figure 7, and detailed in Supplementary Table 5 in the Supplementary Appendix. This analysis included only direct evidence from the original studies. Nivolumab (OR: 0.28; 95% CI: 0.16–0.47), gefitinib 250 mg (OR: 0.21; 95% CI: 0.11–0.39), gefitinib 500 mg (OR: 0.46; 95% CI: 0.28–0.76)
resulted in a significantly lower rate of grade 3–5 adverse events compared with methotrexate. Among the included treatments, only afatinib tended to have a higher rate of grade 3–5 adverse events compared with methotrexate (OR: 1.19; 95% CI: 0.80–1.77).

Quality of evidence
For all the NMA reported in this study, except for the one on grade 3–5 adverse events, at least one global treatment effect estimate was based solely on indirect or extended indirect comparisons. In fact, none of the global estimates which were based on indirect or extended indirect comparisons were corroborated by direct evidence. This rendered the calculation of the H-index for consistency impossible [16].

Discussion
The treatment of patients with R/M SCCHN remains a challenge in the daily clinical practice in view of the reduced performance status, low treatment compliance and persistent toxicities from prior treatments [3]. The EXTREME trial showed that the addition of cetuximab to platinum and 5-fluorouracil significantly increased OS from 7.4 to 10.1 months (HR: 0.80; p = 0.034), PFS from 3.3 to 5.5 months (HR: 0.57; p < 0.0001) and ORR from 19.5 to 35.6% (p = 0.0001) [11]. Despite these results, all patients eventually progressed and their prognoses remain dismal [3]. There is currently no established second-line of treatment and the treatment approach is mainly palliative [26]. Combination regimens were more promising than monotherapies but were also more toxic [27]. It is unclear if the historical regimens yield any meaningful improvement in clinically relevant outcomes. Indeed, the clinical benefit of tumor reduction in this setting has never been rigorously studied [28]. Therefore, it is recommended to opt for tailored-individualized decisions in these circumstances, based on the benefits of palliation and the risks of treatment toxicity. In the absence of early evidence of palliation of symptoms or tumor reduction, change or discontinuation of treatment is commonly considered [28]. This NMA highlights these end points in view of an evidence-based optimized management plan for R/M SCCHN.

To our knowledge, this is the first NMA to compare the efficacy and safety outcomes of the second-line regimens evaluated in the management of R/M SCCHN. Our results confirmed that only nivolumab yielded a statistically significant OS benefit compared with methotrexate in the overall population R/M SCCHN patients (Figure 3 and Supplementary Table 1 & 3 in the Supplementary Appendix). The analysis of other efficacy outcomes has demonstrated a significantly larger ORR with nivolumab compared with methotrexate (Figure 6 & Supplementary Table 4 in the Supplementary Appendix). Furthermore, nivolumab and gefitinib 250 mg were associated with the lowest occurrence of treatment-related adverse events but were similar to the other regimens in terms of treatment discontinuation rates secondary to adverse events (Figure 7 & Supplementary Table 5 in the Supplementary Appendix, Table 4).

Over the past decade, patients received palliative care, single-agent chemotherapy, combination regimen or clinical trials. Most recently, two immune checkpoint inhibitors (pembrolizumab and nivolumab) received approvals in August and November 2016, respectively, for use in patients with R/M SCCHN who progress on or after platinum-based chemotherapy, without a requirement of PD-L1 testing. The Checkmate 141 trial showed an OS benefit
with nivolumab in a direct comparison to three different arms (docetaxel, methotrexate and cetuximab) of small samples (54, 52 and 15 patients, respectively). The KEYNOTE-040 trial used a similar population and study design to evaluate the efficacy of pembrolizumab in comparison to the same control arms (docetaxel, methotrexate and cetuximab) in a larger sample sizes (65, 110 and 73 patients, respectively) [17]. In this NMA, pembrolizumab failed short in achieving a significant OS benefit compared with methotrexate. The comparison of Checkmate 141 and KEYNOTE-040 demonstrated higher efficacy outcomes in the comparator arm of the KEYNOTE-040 trial (ORR: 10.1 vs 5.8% and OS: 7.1 vs 5.1 months), probably due to the more prevalent administration of docetaxel, which was associated with a numerically superior efficacy compared with methotrexate and cetuximab (the two other treatments of the control arms of both studies) [10,18]. While this is the rationale used to explain the OS benefit of nivolumab compared with pembrolizumab, this explanation does not seem to hold since our indirect comparisons (which had more than adjusted for this by considering the control arm of the KEYNOTE-040 as being only taxane) favored nivolumab over pembrolizumab. It is noteworthy that the OS outcome in the KEYNOTE-040 trials may also have been affected by the fact that patients’ molecular characteristics may differ between the studies and that more patients in the control arm received immune checkpoint inhibitors upon progression.

The combination of the efficacy and safety results of our NMA favors nivolumab in the second-line treatment of R/M SCCHN. Although the efficacy outcomes (OS and ORR) of nivolumab and pembrolizumab were numerically close but the latter failed to achieve statistically significant superiority over methotrexate. Our analysis also brings to attention two regimens often forgotten. The first includes the combination of buparlisib and paclitaxel that seemed to achieve numerically better efficacy outcomes (OS and ORR) that did not reach statistical significance compared with methotrexate. The second includes zalutumumab that has shown a trend for superiority over methotrexate with regards to OS in platinum-resistant R/M SCCHN. These results should be considered in future clinical trials investigating the treatment of R/M SCCHN. Unfortunately, we were not able to compute the safety outcomes of these two regimens in our NMA.

The small sample sizes and the scarce number of published trials are circumvented by the network design of our analysis, which allowed the best estimate of treatment effects through direct and indirect comparisons. Furthermore, the use of the inverse variance heterogeneity method instead of the conventionally used fixed and random effect models allowed a more adequate approach to dealing with heterogeneity. However, a few limitations of the present study merit discussion. First, our analysis was limited to the published data and the authors did not have access to patient level data. Furthermore, the results are to be interpreted as being observational since the patients had been randomized only at the level of the studies but not between studies. Second, tumor HPV status is a strong prognostic factor for OS among patients with oropharyngeal cancer that is associated with response to treatment [29,30]. Thus, the major limitation inherent to the published data is the discrepancy in the percentage of HPV-induced HNSSC between the different studies (positivity of P16 is reported with nivolumab as being 26.2%; paclitaxel: 79%; paclitaxel and buparlisib: 67%; afatinib 10–14.5%; methotrexate: 11% and cetuximab: 12.9%) and its lack of reporting in the studies investigating gefitinib, zalutumumab and pembrolizumab. Another important feature is the lack of EGFR reporting among all the trials except that of Stewart et al. [20]. A third limitation of our NMA is its inability to include data from single-arm trials, such as those of the cetuximab–taxane combinations, which had shown numerically similar OS (7.5–8 months vs 7.6–10 months) and higher ORR (13.3–18% vs 38–55%) in comparison to immune checkpoint inhibitors [10,12,13]. A fourth limitation is the equivalence between ‘second-line treatment’ and ‘beyond second-line treatment’. Effectively, the evaluated regimens were studied across multiple lines of treatment and not obligatorily in the second-line treatment per se. The percentage of patients that had already received only one line of treatment was 47% for docetaxel, 44.2% for nivolumab, 98% for paclitaxel, 51% for zalutumumab, 90% for the combination paclitaxel and buparlisib, and 57.1% for pembrolizumab [18–24]. These discrepancies may have influenced the efficacy results of the different studies.

**Implications for clinical practice**

This NMA of eight prospective randomized controlled studies investigating 11 different regimens concluded that, based on the current evidence, nivolumab seems to have the best efficacy and safety profiles for the second-line treatment of R/M SCCHN. As such, based on a combination of direct and indirect comparisons and the robustness of the results of the NMA to sensitivity analyses, there is low-to-moderate evidence that nivolumab has a better safety profile as evaluated by the rate of grade 3–5 adverse events and higher efficacy as evaluated by ORR and OS in comparison to methotrexate.
R/M SCCHN remains a challenge in daily clinical practice. Additionally, reduced performance status, low treatment compliance and persistent toxicities from previous treatments are common patient characteristics in this setting. In line with the current clinical and observational evidence in the field, our NMA supports the use of nivolumab in the second-line treatment of R/M SCCHN. It is active and well tolerated in patients who experience disease progression after platinum-based chemotherapy, including those present with resistant disease. However, not all patients are candidates for immune checkpoint inhibitors as those with autoimmune diseases and those on steroids may not be the best candidates. Buparlisib with paclitaxel, pembrolizumab, docetaxel with gefitinib, zalutumumab and taxanes seem to be potentially active regimens in R/M SCCHN patients that are platinum-refractory but further head-to-head trials are required. The cetuximab–taxane combination is a possible regimen in fit patients, since it yielded similar OS and higher ORR in comparison to immune checkpoint patients; which however, were shown to have more their durable responses [10,12,13]. In those ineligible for these regimens, docetaxel may be favored over methotrexate because of the observational superiority of docetaxel in the CheckMate 141 trial [10]. An optimal approach would require an understanding of the previous treatment history and molecular analysis. Testing for PD-L1 expression is insignificant for any of the efficacy outcomes namely with the immune checkpoint inhibitors [10]. On the other hand, testing for P16 to identify HPV-induced SCCHN has its therapeutic implications that manifest in the ORR benefit with immune checkpoint inhibitors, although no survival benefit has been shown [10].

Future perspective
Multiple trials are tackling the second-line treatment of R/M SCCHN including durvalumab monotherapy in the HAWK trial (NCT02207530) and combination with tremelimumab in the EAGLE trial (NCT02369774). The clinical scenario where immune checkpoint inhibitors are the standard of care in only the second-line treatment of R/M SCCHN patients may soon be modified because of the ongoing trials in the first-line setting: nivolumab in combination with ipilimumab in the CheckMate 651 trial (NCT02741570), pembrolizumab monotherapy in the KEYNOTE-048 (NCT02358031).

The molecular advances in the last few decades have led to a growing interest in the development of targeted and immune agents. Moreover, the understanding of pathological and molecular factors affecting the behavior and prognosis of the R/M SCCHN allows a better definition of an optimized therapeutic protocol. As such, the management plan would rely on the tumor characteristics, patient factors and the expertise of the medical team. Future research in this field should focus on defining the prognostic features of responsive patients and to evaluate effective combinations with tolerable toxicity profiles. The platinum drugs seem to constitute the cornerstone in the management of head and neck cancers. Therefore, circumventing platinum resistance would represent a rational approach with the addition of the new targeted and immune agents.

Conclusion
The general approach for R/M SCCHN is palliative, therefore several circumstances need to be taken into consideration, especially with regard to the fact that the aim of the treatment should be symptom control and quality of life improvement. The results of the current study primarily underline the scarcity of data and small sample sizes comparing the different regimens in the second-line treatment of R/M SCCHN and lead to the conclusion that, based on currently available data, nivolumab seems to be the most efficacious and safe treatment in this setting, especially considering the lack of data on other combination regimens. Future randomized controlled studies directly comparing these regimens and including the numerically superior cetuximab–taxane combinations, while taking into consideration the molecular prognostic features, are needed in order to accurately determine the optimal regimen in the management of R/M SCCHN.

Supplementary data
To view the supplementary data that accompany this paper please visit the journal website at:

Acknowledgements
The authors thank JB Vermorken for his valuable comments.
Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
No writing assistance was utilized in the production of this manuscript.

Executive summary
- The second-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) includes chemotherapy, targeted therapy and immune checkpoint inhibitors.
- Each of the second-line trials in R/M SCCHN tested different drugs with small sample sizes which rendered the evaluation of the relative efficacy of each drug challenging.
- The current literature lacks direct evidence proving the superiority of one regimen over the other in the absence of direct head-to-head comparisons.
- We performed a network meta-analysis (NMA) to overcome these limitations by comparing the different drugs according to their efficacy and safety profiles.

Material & methods
- We have reviewed the randomized controlled Phase II and III trials reporting on the efficacy and safety of second-line drug therapy in R/M SCCHN.
- The primary outcome was overall survival (OS). The secondary outcomes were objective response rate (ORR) and progression-free survival. The percentage of treatment discontinuation due to adverse events, in each treatment arm, was evaluated as a surrogate for drug tolerability.
- We performed a NMA utilizing a frequentist approach with generalized pairwise modeling. The inverse variance heterogeneity method was used to overcome the previously described limitations of the fixed and random effects model.
- Results of the NMA of OS were expressed as hazard ratios (HR) and those of grade 3/4 adverse event rates as odds ratios (OR), with their 95% CI.

Results
- A total of eight trials with a total of 2584 patients were finally selected and included in the analysis. None of the trials has a high risk of bias.
- The primary analysis showed that none of the evaluated treatments had statistically significant OS benefit compared with methotrexate. The sensitivity analysis only including data from patients who had progressed under platinum-based therapy showed that nivolumab was the only drug that had a statistically significant positive effect on OS compared with methotrexate.
- The secondary analysis found that nivolumab was the only drug to yield a significantly larger ORR compared with methotrexate. Nivolumab and gefitinib resulted in a significantly lower rate of grade 3–5 adverse events compared with methotrexate.

Conclusion
- This is the first NMA to compare the efficacy and safety outcomes of the second-line regimens evaluated in the management of R/M SCCHN.
- Our results favored nivolumab for OS and ORR benefit as well as tolerability of its safety profile over the other regimens.
- The small sample sizes and the scarce number of published trials are circumvented by the network design of our analysis, which allowed the best estimate of treatment effects through direct and indirect comparisons.
- The use of the inverse variance heterogeneity method instead of the conventionally used fixed and random effect models allowed a more adequate approach to dealing with heterogeneity.

References
Papers of special note have been highlighted as: ● of interest; ●● of considerable interest


**There has been a lack of evidence-based second-line treatment options for squamous cell carcinoma of the head and neck (SCCHN), and the therapies that have been available have shown low response rates and poor survival outcomes.**


**For second-line treatment of SCCHN, several options are currently available: enrolment in clinical trials, single-agent therapy (methotrexate, taxane and cetuximab) and best supportive care.**


- Nivolumab results in longer overall survival than treatment with standard, single-agent therapy.


- New targeted therapy, including the use of antibodies, gives a promising perspective in the management of SCCHN.


