Systemic Therapy for Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck

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Abstract
This article summarizes the systemic treatment options for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck, with an emphasis on recommendations based on phase II and III comparison trials of commercially available agents. Many single-agent and combination regimens have activity against these cancers, but improvement in overall survival remains a challenge, and median survivals in this population with best available therapy remain less than 1 year. The major recent advancement has been the introduction of epidermal growth factor receptor inhibitors, with mixed success. Although single-agent treatment with methotrexate, paclitaxel, docetaxel, or 5-fluorouracil remains one standard for many patients, the use of cisplatin- or carboplatin-based multidrug regimens that include cetuximab has become more popular, primarily based on one randomized study demonstrating a modest survival improvement of approximately 3 months associated with the addition of cetuximab. The burdensome adverse event profile of multidrug regimens makes appropriate patient selection for such aggressive treatment challenging, and consideration should include factors such as need for palliation, performance status of the patients, history of prior treatment, convenience, and cost. Genetically targeted and immunologically mediated treatments are promising but remain experimental. Given the worrisome prognosis for these patients, innovative clinical trials are a good option for many patients and deserve support. (J Natl Compr Canc Netw 2015;13:e37–e48)

The global burden of squamous cell carcinoma of the head and neck (SCCHN) is substantial. In 2014, an estimated 55,000 new cases were diagnosed in the United States and 500,000 globally, accounting for approximately 5% of the domestic and 8% of the global burden of new cancers.1,2 A substantial portion of these cancers are preventable through tobacco consumption interdiction and reduction in exposure to indoor smoke from sources such as such as wood burning stoves.3 In the United States, for example, a decline has already occurred in the incidence of most upper aerodigestive cancers, including SCCHN.1 One notable exception to this is the exponential increase in the incidence of oropharyngeal SCCHNs, related to an increase in human papillomavirus (HPV)–associated oropharyngeal SCCHNs.4 HPV-related SCCHNs may also be preventable through vaccination strategies analogous to those for the prevention of uterine cervix cancers.

Despite this long-range optimism regarding prevention of many SCCHNs through vaccination against HPV and reduction of tobacco consumption domestically and globally, the burden of incurable disease remains high and is likely to remain so for the next few decades. Approximately half of all patients with SCCHN eventually die of their cancer, either because they have incurable metastatic disease at diagnosis or they experience disease relapse after attempts at curative treatment.5

Several randomized controlled trials have been performed in patients with recurrent or metastatic SCCHN over the past 30 years, with the most common design comparing a single agent with combination therapy. However, these randomized comparisons of different drug options are far from exhaustive, and data from uncontrolled clinical trials and expert clinician experience are regularly considered in clinical decision-making. It can be difficult to compare the clinical benefit of dif-
ferent options because patient characteristics and history of prior therapy can vary widely among studies, and therapies used when a patient comes off a study are typically not reported, which confounds the interpretation of an overall survival (OS) end point. In addition, legacy studies were performed in an era during which the methodological standards for studies were both different and at times less rigorous compared with those of more modern studies. For example, many older studies have not used what are accepted now as rigorous criteria for response assessment, such as the RECIST system.\(^6\) Many studies only report response rates (RR) or progression-free survival (PFS), not both. Patients who experience disease relapse soon after chemoradiation are unlikely to derive substantial benefit from treatment using agents incorporated into the original chemoradiation regimen. Clinical trial reports are often vague about prior treatments, prior treatment responses, and time from prior treatment to the development of recurrent and/or metastatic SCCHN. Therefore, there can be considerable uncertainty concerning the anticancer activity that can be expected for an individual patient based on these reports.

Today most experts agree that the most clinically meaningful and robust outcome measurements are OS and PFS rather than tumor response rates. In the absence of analyses supporting a strong association between response rates and quality of life, one must be cautious about the assumption that higher RRs are associated with clinical benefit, especially because the higher RRs for cytotoxic agents are obtained at the price of a more burdensome adverse event profile, and improvement in OS compared with better-tolerated single agents has proved elusive. Therefore, whether patients with recurrent or metastatic disease are best served by concurrent multidrug treatment or sequential administration of individual chemotherapy agents is unclear.

Randomized trials that demonstrate improvement in survival compared with best supportive care or other drug therapy are rare,\(^7,8\) and the demonstrated survival advantage is a modest 2 to 3 months. Therefore, hope for OS improvement in the presence of recurrent or metastatic disease alone is not sufficient to justify routine immediate treatment with systemic agents in all patients, because most patients will experience a decrease in well-being unless those agents can relieve existing tumor-related symptoms.

Comparisons among treatments whose outcome differences in terms of OS and quality of life are modest, even though the costs of the compared therapy vary substantially, are fertile ground for cost-effectiveness and related value assessments. These circumstances are applicable to patients receiving treatment for recurrent or metastatic SCCHN. Finally, despite average or median outcomes, it is clear that a significant minority of patients experience unquestionable benefit from systemic treatments for their recurrent or metastatic disease. Until better predictors for who will benefit become available, clinicians and patients must often make decisions with significant uncertainty regarding benefit of these choices, but clinicians should be vigilant with respect to avoiding a default position of therapeutic nihilism for all of these incurable patients.

**Single-Agent Uncontrolled Studies**

Several agents have demonstrated robust anticancer activity in patients with recurrent and/or metastatic SCCHN. In the past few years several reviews and overviews have been published concerning systemic treatments for patients with recurrent or metastatic SCCHN.\(^9,15\) The most robustly studied agents are cisplatin, carboplatin, methotrexate, 5-fluorouracil (5-FU), ifosfamide, paclitaxel, and docetaxel (Table 1). Response rates typically range from 10% to 30%, with some outlier reports of higher response rates, typically in older, smaller studies in which patients had received no prior treatment. The choice between cisplatin and carboplatin is largely driven by one study that favored cisplatin over carboplatin when used in combination with 5-FU, based on superior response rates (32% vs 21%, respectively) without significant survival differences.\(^16\) Carboplatin is widely regarded as the more tolerable of these 2 platinum compounds. Other agents occasionally used and less well studied include bleomycin, vinorelbine, cyclophosphamide, hydroxyurea, and gemcitabine, which are typically associated with response rates of 10% to 20%.\(^17-20\)

Epidermal growth factor receptor (EGFR) inhibitors, both anti-EGFR monoclonal antibodies and small molecule tyrosine kinase inhibitors, have recently been studied in patients with recurrent and/or metastatic SCCHN. When used alone, these agents generally have low levels of activity, with response
## Table 1  Selected Single-Agent Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Prior Treatments for Most</th>
<th>RR (%)</th>
<th>Median OS (mo)</th>
<th>Median PFS or TTP (mo)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>26</td>
<td>S, R, C</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>240 mg/m² day 1 and 5, surgery day 12–15</td>
<td>58</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>30</td>
<td>None; neoadjuvant trial</td>
<td>77*</td>
<td>NA</td>
<td>NA</td>
<td>Intravenous and oral, various doses</td>
<td>59</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>44</td>
<td>Mixed</td>
<td>66</td>
<td>NA</td>
<td>NA</td>
<td>Dose levels 5000, 500, 50 mg/m²</td>
<td>60</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>58</td>
<td>Mixed</td>
<td>50, 21,31</td>
<td>NA</td>
<td>NA</td>
<td>1250 mg/m² days 1, 8 q21d</td>
<td>61</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>10</td>
<td>S, R, C</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
<td>250 mg/m² q21d</td>
<td>62</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30</td>
<td>S, R, C (13% prior C)</td>
<td>40</td>
<td>9.2</td>
<td>TTP, 3.4</td>
<td>100 mg/m² weekly</td>
<td>63</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>74</td>
<td>S, R, C (76% prior platinum)</td>
<td>29</td>
<td>14.3</td>
<td>TTP, 3.4</td>
<td>100 mg/m² weekly</td>
<td>64</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>30</td>
<td>S, R, C (63% prior platinum)</td>
<td>7</td>
<td>3.9</td>
<td>PFS, 1.8</td>
<td>35 mg/m² weekly, 3/4 weeks</td>
<td>65</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>23</td>
<td>S, R, C (100% prior platinum)</td>
<td>13</td>
<td>6.9</td>
<td>TTP, 2.1</td>
<td>30 mg/m² weekly, 4/5 weeks</td>
<td>66</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>38</td>
<td>S, R, C (45% prior platinum)</td>
<td>42</td>
<td>11.3</td>
<td>Response duration; median, 8.4</td>
<td>30 mg/m² weekly</td>
<td>67</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>31</td>
<td>S, R, C (32% neoadjuvant platinum)</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>100 mg/m² q21d</td>
<td>68</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>43</td>
<td>S, R, C (2% neoadjuvant cisplatin)</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>100 mg/m² q21d</td>
<td>69</td>
</tr>
<tr>
<td>Zalutumumab</td>
<td>90</td>
<td>Platinum-refractory</td>
<td>5.7</td>
<td>5.3</td>
<td>PFS, 2.1</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>103</td>
<td>Platinum-refractory</td>
<td>13</td>
<td>5.9</td>
<td>TTP, 2.3</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>35</td>
<td>Neoadjuvant</td>
<td>29*</td>
<td>NA</td>
<td>NA</td>
<td>Rash predicted response; EGFR expression did not</td>
<td>70</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>115</td>
<td>Neoadjuvant</td>
<td>4.3</td>
<td>6</td>
<td>PFS, 2.2</td>
<td>PS and rash predict response and OS</td>
<td>23</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>52</td>
<td>S, R, C</td>
<td>10.6</td>
<td>8.1</td>
<td>TTP, 3.4</td>
<td>Dose escalation titrated to rash</td>
<td>24</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>44</td>
<td>S, R, C</td>
<td>7</td>
<td>5.1</td>
<td>PFS, 1.9</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>24</td>
<td>S, R, C (24% prior PF)</td>
<td>22</td>
<td>Response duration, 5.8</td>
<td></td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>16</td>
<td>S, R, C (94% prior platinum)</td>
<td>6</td>
<td>4.3</td>
<td>TTP, 1.9</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>S1</td>
<td>26</td>
<td>NA</td>
<td>46.2</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>UFT</td>
<td>42</td>
<td>S, R, C</td>
<td>21</td>
<td>8.7</td>
<td>NA</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>40</td>
<td>S, R, C (65% prior platinum)</td>
<td>24</td>
<td>7.3</td>
<td>TTP, 4.8</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>298</td>
<td>NA</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>5-FU</td>
<td>118</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>17</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>36</td>
<td>S, R, no prior C</td>
<td>28</td>
<td>6.8</td>
<td></td>
<td></td>
<td>76</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; C, chemotherapy; EGFR, epidermal growth factor receptor; NA, not available; OS, overall survival; PF, cisplatin plus 5-FU; PFS, progression-free survival; PS, performance status; R, radiation; RR, response rate; S, surgery; TTP, time to progression; UFT, uracil and foltarif.  
*Neoadjuvant means no prior treatment.
rates of 5% to 10% and correspondingly short PFS and OS intervals.\textsuperscript{21–25} Trials designed to escalate dose to acneiform rash as a surrogate pharmacodynamics marker have demonstrated no improvement in clinical activity beyond what was previously reported in trials using fixed-dose regimens, suggesting that dose optimization according to titration to rash is not beneficial.\textsuperscript{25,26}

**Single-Agent Randomized Trials**

Table 2 summarizes the data from selected randomized trials for patients with recurrent and/or metastatic SCCHN. Outcomes reported from these clinical trials are summarized herein.

Only 2 studies have compared any of these agents to a best supportive care (BSC) arm. In 1985, Morton et al\textsuperscript{7} published a 2 x 2 factorial design study of BSC versus bleomycin versus cisplatin versus bleomycin plus cisplatin. In this 116-patient study, no statistically significant differences in RR or OS were observed, except in the pooled analysis of cisplatin-containing arms versus the others, in which the median OS was 4.3 months with cisplatin versus 1.8 months without. This early study established cisplatin as the standard (alone or in combination) drug against which many subsequent agents have been tested. Machiels et al\textsuperscript{26} compared zalutumumab, an experimental anti-EGFR monoclonal antibody, with BSC in 286 patients who had prior platinum exposure. The RR to zalutumumab was low at 6.3%, and the median OS (6.7 months) was not statistically different from that of BSC. This response rate approximates that of other anti-EGFR tyrosine kinase inhibitors and monoclonal antibodies (Table 1), suggesting a minor role, if any, for EGFR-targeted therapy alone.

Direct comparison of methotrexate versus cisplatin has yielded no clear winner, with modestly powered studies demonstrating numerical superiority of either cisplatin or methotrexate in terms of RR and median survival, depending on the study. No consistent pattern of superiority has been seen for either agent.\textsuperscript{16,27–29} A large trial comparing methotrexate with 2 dosage regimens of gefitinib in patients either unsuitable for or who experienced disease relapse after treatment with cisplatin similarly failed to demonstrate superiority for either therapy, with all arms’ RR less than 10% and median survival approximately 6 months.\textsuperscript{10} Additionally, a large study comparing cisplatin with 5-FU demonstrated no response or survival superiority for either agent.\textsuperscript{31} One small trial of methotrexate versus docetaxel in the first-line recurrent setting demonstrated no differences in RR, PFS, or OS.\textsuperscript{12}

Therefore, when deciding among these agents for single-agent treatment, data concerning antitumor efficacy does not offer much guidance. The most consistent and robust data are for cisplatin, methotrexate, and 5-FU, but the taxanes also probably should be considered. Although cetuximab is FDA-approved as a single agent in this setting, a 13% response rate, no evidence of superiority, and a dramatically higher price suggest that this agent should not be chosen over the others.

**Multiagent Randomized Trials**

A few dozen trials of multiagent chemotherapy have been performed in patients with recurrent and/or metastatic SCCHN. Tables 2 and 3 provide a summary of controlled and uncontrolled trials. Most of the randomized trials are small studies that have compared a methotrexate- or cisplatin-containing arm with something else. A major weakness with many of these studies is that they were inadequately powered to detect survival improvements. For example, to detect a 3-month (6 vs 9 months) difference in survival between 2 arms accruing over 2 years with a power of 0.9, more than 130 patients would need to be enrolled on each arm. Most randomized controlled trials of systemic chemotherapy fail to meet this adequate sample size criterion. Notably, of the 7 trials in Table 2 that have at least 130 patients per arm, only 1 yielded a statistically significant OS result. Subsequent therapy when a patient comes off study is typically not documented, which may also contribute to the lack of significant impact on OS.

Generally, response rates to combinations are higher than to single agents, but these higher response rates are associated with worse adverse event profiles and, with one exception, have not translated into survival improvement. The doublets of cisplatin plus methotrexate (PM), cisplatin plus 5-FU (PF), and cisplatin plus paclitaxel (PT) are all roughly equivalent in terms of response rates and survival.\textsuperscript{29,33,34} The comparison of PF and PM demonstrated approximately numerically similar adverse...
### Table 2 Selected Randomized Trials

<table>
<thead>
<tr>
<th>Agents</th>
<th>N</th>
<th>Prior Treatments for Most</th>
<th>RR (%)</th>
<th>Median TTP or PFS (mo)</th>
<th>Median OS (mo)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX vs CDDP</td>
<td>44</td>
<td>S, R</td>
<td>24 vs 29</td>
<td>2.8 vs 3.0</td>
<td>6.1 vs 6.3</td>
<td>87% emesis with CDDP</td>
<td>27</td>
</tr>
<tr>
<td>MTX vs CDDP + vincristine + B</td>
<td>61</td>
<td>S, R</td>
<td>33 vs 41</td>
<td>5.5 vs 4.0</td>
<td>Cost per course plus $197 vs $852</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>MTX vs CDDP</td>
<td>100</td>
<td>S, R, no prior C</td>
<td>16 vs 8</td>
<td>Response duration 4.5 vs 2.0</td>
<td>4.6 vs 4.0</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>MTX vs MTX + B + CDDP</td>
<td>163</td>
<td>S, R</td>
<td>35 vs 48</td>
<td>5.0 vs 5.8</td>
<td>5.6 vs 5.6</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>MTX vs CDDP + vinblastine + B</td>
<td>191</td>
<td>S, R</td>
<td>16 vs 24</td>
<td>4.6 vs 3.4</td>
<td>7.1 vs 6.7</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>CDDP vs CDDP + MTX</td>
<td>80</td>
<td>S, R</td>
<td>18 vs 33</td>
<td>6.3 vs 6.9</td>
<td>More AEs in combination, especially leucopenia and mucositis</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>MTX vs CDDP vs MTX vs CDDP + 5-FU</td>
<td>124</td>
<td></td>
<td>19 vs 40 vs 31 vs 33</td>
<td>2.7 vs 8.7 vs 5.3 vs 6.7</td>
<td>OS significantly different only MTX vs CDDP</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Control vs B vs CDDP vs CDDP + B</td>
<td>116</td>
<td>S, R</td>
<td>NA vs 14 vs 24 vs 13</td>
<td>No significant difference except CDDP vs control, 4.3 vs 1.8</td>
<td>2 x 2 trial design</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>CDDP + 5-FU vs CBCDA + 5-FU vs MTX</td>
<td>277</td>
<td>S, R</td>
<td>32 vs 21 vs 10</td>
<td>6.6 vs 5.0 vs 5.6</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX vs MTX + 5-FU</td>
<td>48</td>
<td>S, R</td>
<td>25 vs 58</td>
<td>6.2 vs 8.1</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDDP vs CDDP + vincristine + MTX + B</td>
<td>209</td>
<td>S, R</td>
<td>15 vs 30</td>
<td>No significant difference</td>
<td>No significant difference</td>
<td>CDDP arm much better tolerated</td>
<td>81</td>
</tr>
<tr>
<td>CDDP vs MTX vs CDDP + MTX vs CDDP + 5-FU</td>
<td>200</td>
<td>S, R</td>
<td>14 vs 6 vs 12 vs 11</td>
<td>7.2 vs 4.0 vs 5.0 vs 5.0 (from graph)</td>
<td>CDDP superior to MTX OS; P=.025</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>CDDP + 5-FU vs CDDP + 5-FU + B + MTX</td>
<td>62</td>
<td>S, R</td>
<td>38 vs 61</td>
<td>FFS, 2.3 vs 4.5</td>
<td>7.8, no significant difference in arms</td>
<td>Underpowered study</td>
<td>82</td>
</tr>
<tr>
<td>CDDP vs CDDP + 5-FU vs CABO</td>
<td>382</td>
<td>S, R</td>
<td>15 vs 31 vs 34</td>
<td>TTP, 3 vs 4.3 vs 4.8</td>
<td>6.7, no significant difference in arms</td>
<td>TTP significant only for CDDP vs other arms</td>
<td>83</td>
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<tr>
<td>MTX vs edatrexate</td>
<td>264</td>
<td>S, R</td>
<td>16 vs 21</td>
<td>TTP, 6.4 vs 6.1</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX vs nolatrexed</td>
<td>139</td>
<td>S, R, C</td>
<td>11 vs 3</td>
<td>TTP, 11.5 vs 1.9</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDDP + 5-FU vs CDDP + T</td>
<td>218</td>
<td>S, R</td>
<td>27 vs 26</td>
<td>8.7 vs 8.1</td>
<td>More high-grade AEs with CDDP + 5-FU</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>MTX vs gefitinib (500) vs gefitinib (250)</td>
<td>486</td>
<td>Prior platinum or ineligible for platinum</td>
<td>3.9 vs 7.6 vs 2.7</td>
<td>6.7 vs 6.0 vs 5.6</td>
<td>In platinum-naive patients, MTX OS superior to gefitinib; HRs 1.5 and 1.6</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Zalutumumab vs BSC</td>
<td>286</td>
<td>S, R, C</td>
<td>6.3 vs 1.1</td>
<td>2.3 vs 1.9</td>
<td>6.7 vs 5.2</td>
<td>6% of controls used MTX</td>
<td>26</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; B, bleomycin; BSC, best supportive care; C, chemotherapy; CABO, cisplatin, methotrexate, bleomycin, and vincristine; CBCDA, carboplatin; CDDP, cisplatin; CTZ, cetuximab; D, docetaxel; FFS, failure-free survival; G, gemcitabine; HR, hazard ratio; L, liposomal doxorubicin; MTX, methotrexate; NA, not available; OS, overall survival; PB, cisplatin plus bleomycin; PD, progressive disease; P, paclitaxel plus 5-FU; PFS, progression-free survival; TG, paclitaxel plus gemcitabine; TL, paclitaxel plus liposomal doxorubicin; R, radiation; RR, response rate; S, surgery; T, paclitaxel; TTP, time to progression.

*Bold signifies a statistically significant difference cited in manuscript.*
## Table 2  Selected Randomized Trials (cont.)

<table>
<thead>
<tr>
<th>Agents</th>
<th>N</th>
<th>Prior Treatments for Most RR (%)</th>
<th>Median TTP or PFS (mo)</th>
<th>Median OS (mo)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib vs methotrexate</td>
<td>483</td>
<td>S, R, C (all platinum-exposed)</td>
<td>10 vs 6</td>
<td>2.6 vs 1.7</td>
<td>6.8 vs 6.0</td>
<td>95</td>
</tr>
<tr>
<td>Afatinib v CTZ</td>
<td>121</td>
<td>S, R, C (all platinum refractory)</td>
<td>8.1 vs 9.7 by central review</td>
<td>NA</td>
<td>NA</td>
<td>86</td>
</tr>
<tr>
<td>CDDP vs CDDP + 5-FU vs 5-FU</td>
<td>249</td>
<td></td>
<td>17 vs 32 vs 13</td>
<td>TTP 2.0 vs 2.4</td>
<td>5.7, no difference among arms</td>
<td>31</td>
</tr>
<tr>
<td>CDDP vs CDDP + 5-FU + CTZ</td>
<td>442</td>
<td>S, R, 38% prior C</td>
<td>20 vs 36</td>
<td>3.3 vs 5.6</td>
<td>7.4 vs 10.1</td>
<td>8</td>
</tr>
<tr>
<td>CDDP vs CDDP + CTZ</td>
<td>117</td>
<td>S, R</td>
<td>10 vs 26</td>
<td>2.7 vs 4.2</td>
<td>8.0 vs 9.2</td>
<td>35</td>
</tr>
<tr>
<td>CDDP + 5-FU vs CDDP + 5-FU + panitumumab</td>
<td>657</td>
<td>S, R, 81% prior C</td>
<td>26 vs 37</td>
<td>4.6 vs 5.8</td>
<td>9.0 vs 11.1</td>
<td>36</td>
</tr>
<tr>
<td>D vs D + gefitinib</td>
<td>270</td>
<td>S, R, C</td>
<td>6 vs 13</td>
<td>2.1 vs 3.5</td>
<td>6.0 vs 7.3</td>
<td>87</td>
</tr>
<tr>
<td>D vs D + vandetanib</td>
<td>29</td>
<td>R, C</td>
<td>7 vs 13</td>
<td>0.8 vs 2.1</td>
<td>6.4 vs 5.7</td>
<td>88</td>
</tr>
<tr>
<td>T + G vs T + L</td>
<td>166</td>
<td>S, R, no C</td>
<td>20 vs 29</td>
<td>4.4 vs 6.0</td>
<td>8.6 vs 11.5</td>
<td>39</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; B, bleomycin; BSC, best supportive care; C, chemotherapy; CABO, cisplatin, methotrexate, bleomycin, and vincristine; CB/CDCA, carboplatin; CDDP, cisplatin; CTZ, cetuximab; D, docetaxel; FFS, failure-free survival; G, gemcitabine; HR, hazard ratio; L, liposomal doxorubicin; MTX, methotrexate; NA, not available; OS, overall survival; PB, cisplatin plus bleomycin; PD, progressive disease; PF, paclitaxel plus 5-FU; PFS, progression-free survival; TG, paclitaxel plus gemcitabine; TL, paclitaxel plus liposomal doxorubicin; R, radiation; RR, response rate; S, surgery; T, paclitaxel; TTP, time to progression.

*Bold signifies a statistically significant difference cited in manuscript.*

event rates, but when PF was compared with PT, substantially more high-grade adverse events occurred in the PF arm. Therefore, the choice among these doublets should be based on patient-specific characteristics related to the adverse event profiles, such as hearing and kidney function and factors such as cost and complexity of treatment administration and supportive care.

Only one trial of multiagent chemotherapy has demonstrated statistically significant survival superiority versus another multiagent regimen in recurrent and/or metastatic SCCHN. In the EXTREME study, Vermorken et al randomized 442 patients in the first-line recurrent setting to either PF or PF plus cetuximab (PFC). The platinum agent used was either cisplatin or carboplatin, based on investigator choice. All patients received up to 6 cycles of PF or PFC. Patients continued indefinitely on cetuximab until disease progression. A statistically significant improvement was seen in response rates (20% vs 36%), median PFS (3.3 vs 5.6 months), and median OS (7.4 vs 10.1 months), favoring the PFC arm. Adverse event profiles suggested that the addition of cetuximab was tolerable. These positive data are supported by a small randomized phase II study of cisplatin versus cisplatin plus cetuximab, which demonstrated similar hazard ratios favoring the addition of cetuximab to cisplatin but was not powered to demonstrate an OS difference. However, how generalizable these results are for EGFR inhibitors in combination with cisplatin is unclear. A subsequent 657-patient study (SPECTRUM) investigating the addition of panitumumab to a chemotherapy backbone of PF demonstrated improvement in RR and PFS, but not OS. Whether the outcome differences between EXTREME and SPECTRUM were because the anti-EGFR monoclonal antibodies had a different effect or were due to differences in the clinical trial designs is unclear. More patients in the SPECTRUM
study had chemotherapy exposure before enrollment (81% vs 38%), and the use of the anti-EGFR agent after chemotherapy completion was mandated in the EXTREME study but optional in SPECTRUM.

Whether the benefit seen with the addition of cetuximab to chemotherapy is platinum-specific is unknown. In a recent uncontrolled phase II study of paclitaxel and cetuximab in patients with prior platinum exposure, Hitt et al\textsuperscript{37} reported a 54% RR with a median OS of 8 months. Although this uncontrolled study does not prove that the clinical benefit of cetuximab in combination can be extended to nonplatinum regimens, this atypically high RR suggests that this question should be prioritized for subsequent trials. In regard to the EXTREME and SPECTRUM trials and their use of 5-FU as part of the backbone control regimen, it is also worth noting that taxanes were not approved for this indication in Belgium at the time EXTREME was conducted (J. Vermorken, personal communication). In the United States, the combination of PT plus cetuximab, therefore, although not formally studied or sanctioned by the FDA, is often substituted for PF plus cetuximab because of easier administration and the perceived better adverse event profile of PT.

### Cost-Effectiveness

Because only one trial has demonstrated modest (2.7 months) survival improvement with the use of chemotherapy in the recurrent, metastatic setting, clinicians should consider other factors, such as the regimen’s adverse event profile, patient convenience, and cost to the patient. Table 4 summarizes typical wholesale drug prices for 28 days of treatment based on the agents most commonly used in the United States, demonstrating a remarkable range from a low of $11 for methotrexate to a high of $12,227 for cetuximab. Using these estimates, drug cost alone for PF plus cetuximab for 6 cycles of treatment would be $74,328 for a typical patient and $95,796 if docetaxel were used instead of 5-FU in this combination.

Overall costs are difficult to compare when so few large randomized trials have been performed, but some reports of randomized clinical trials have incorporated cost into the data analysis. An early randomized clinical trial comparing methotrexate with a combination of cisplatin, vincristine, and bleomycin (COB) found that costs associated with one cycle of treatment were 4.3 times higher with COB despite no difference in response or survival rates.\textsuperscript{38} Although this analysis only included costs of administration, subsequent attempts at cost and efficacy analysis have become more sophisticated. Fountzilas et al\textsuperscript{39} performed a cost analysis of paclitaxel and gemcitabine versus paclitaxel plus pegylated liposomal doxorubicin in the first-line treatment of recurrent and/or metastatic SCCHN and found that the latter arm was more costly by 3649 EU ($5042).
when including all treatment and adverse event–related expenses despite no survival difference. More recently, 2 groups of investigators have attempted to evaluate the cost per life year gained and quality-adjusted life year (QALY) gained from the addition of cetuximab to the backbone of cisplatin and 5-FU based on the results of the EXTREME study.\textsuperscript{40,41} They found that the incremental cost-effectiveness was 92,226 GBP ($154,919) for each life year gained and 121,367 GBP ($203,879) per QALY. They concluded that the use of cetuximab in this setting was not cost-effective and not recommended because the costs were substantially higher than those normally acceptable to the British National Health Service.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Regimen</th>
<th>Dosing</th>
<th>Total Monthly Dose (mg)</th>
<th>Cost per mg (USD)</th>
<th>Total Drug Price for Example Patient (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin IV</td>
<td>Cisplatin and 5-FU q28d</td>
<td>100 mg/m\textsuperscript{2}</td>
<td>200</td>
<td>$0.43</td>
<td>$87</td>
</tr>
<tr>
<td>Carboplatin IV</td>
<td>Carboplatin and 5-FU q28d</td>
<td>AUC of 6 mg/mL/min</td>
<td>619</td>
<td>$0.20</td>
<td>$123</td>
</tr>
<tr>
<td>Docetaxel IV</td>
<td>Docetaxel q21d</td>
<td>75 mg/m\textsuperscript{2}</td>
<td>200</td>
<td>$18.26</td>
<td>$3,652</td>
</tr>
<tr>
<td>Paclitaxel IV</td>
<td>Cisplatin and paclitaxel q21d</td>
<td>175 mg/m\textsuperscript{2}</td>
<td>467</td>
<td>$0.67</td>
<td>$314</td>
</tr>
<tr>
<td>5-FU IV</td>
<td>Cisplatin and 5-FU q28d</td>
<td>1000 mg/m\textsuperscript{2}/d x 4 d</td>
<td>8000</td>
<td>$0.01</td>
<td>$74</td>
</tr>
<tr>
<td>Capecitabine PO</td>
<td>Capecitabine bid x 14 d then off x 7 d</td>
<td>1000 mg/m\textsuperscript{2} bid (4 tablets, 500 mg each)</td>
<td>150 tablets</td>
<td>$39.88\textsuperscript{b}</td>
<td>$5,982</td>
</tr>
<tr>
<td>Methotrexate IV</td>
<td>Methotrexate q7d IV</td>
<td>40 mg/m\textsuperscript{2}</td>
<td>240</td>
<td>$0.05</td>
<td>$11</td>
</tr>
<tr>
<td>Cetuximab IV</td>
<td>Cisplatin, 5-FU with weekly cetuximab</td>
<td>250 mg/m\textsuperscript{2}</td>
<td>2000</td>
<td>$6.11</td>
<td>$12,227</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Cost per 500-mg tablet.

Biomarkers as Predictors of Clinical Benefit

The past decade has seen major advances in the treatment of several cancers through the use of predictive biomarkers, such as HER2/neu overexpression as a predictor of response to trastuzumab in breast cancer, and EGFR mutation as a predictor of response to erlotinib in non-small cell lung cancer. Although there are markers and panels of markers that, when evaluated over the treatment and follow-up interval, can predict therapeutic responses in patients with SCCHN,\textsuperscript{42-45} no markers yet exist that have robustly demonstrated utility in terms of chemotherapy selection. Examples of candidates for these biomarkers include ERCC1 protein or mRNA levels as predictors of resistance to platinum compounds, but the data are inconsistent and antibody reagents for ERCC1 have been problematic.\textsuperscript{46,47} Thymidine synthase (TS) and thymidine phosphorylase (TP) have been investigated as potential markers of 5-FU benefit without conclusive or consistent results.\textsuperscript{48}

More recently, a shift has occurred from biochemical-based to genetics-based assays, and
even whole-genome sequencing is advocated by
some as a rational and often “actionable” approach
to drug benefit prediction. As discussed, although a
few examples exist in which genetic alterations have
proved useful in other cancers, no validated markers
exist for selecting among treatment choices for
recurrent and/or metastatic SCCHN. Most genetic
alterations in SCCHN are loss of function of tumor
suppressor genes in the TP53, CDKN2A, and PTEN
pathways. These alterations are not presently easily
targetable by drugs, because restoring function as
an anticancer strategy has not yet been possible.49
Similarly, for the recently discovered NOTCH1
inactivating mutations in SCCHN (≈12%–19%),
no specific therapy exists to restore function.49–51
Claims that up to 80% of oral cavity squamous
cell carcinoma have targetable genetic alterations,
for example, are based on biological plausibility
concerning agents against these targets, rather than
clinical demonstration of efficacy.52,53
Emerging
targets of interest include FGFR, HER2, MET,
PI3K, and mTOR, but the promise of benefit from
inhibiting these targets has yet to be realized.54,55
Despite the large amount of advertising for the
use of these genomic and genetic screening assays,
reported improvements in outcome are limited to a
small minority of highly selected patients. Therefore,
use of these assays to determine treatment should be
limited to the context of experimental treatment.
Widespread ad hoc use should be discouraged.

Over the past decade it has become clear
that HPV-related oropharyngeal squamous cell
carcinomas are a clinically unique subset of SCCHN,
with a much better prognosis. Results of the
SPECTRUM trial, using p16 immunohistochemistry
as a surrogate for HPV, suggest that for panitumumab,
benefit may be limited to the p16-negative patients,
but a retrospective evaluation of a subset of patients
in the EXTREME trial demonstrated no association
between p16 or HPV and OS or PFS benefit for
cetuximab.36,56 Therefore, although p16/HPV seems
to be prognostic in recurrent and/or metastatic
SCCHN, data do not yet support a benefit prediction
role for p16/HPV in this population with respect
to systemic therapy treatment, and the data are
conflicting for anti-EGFR1 monoclonal antibodies.

### Practical Treatment Advice

#### Single Agents

Methotrexate and paclitaxel are appropriate initial
single-agent choices for patients with recurrent
and/or metastatic SCCHN. These agents have the
advantage of good patient tolerability, have
well-established track records of relevant anticancer
activity, and are not overly burdensome in terms of
administration. 5-FU is also an appropriate agent,
but the need for continuous infusion is a significant
burden for many patients. Capecitabine, cetuximab,
and docetaxel also have reasonable anticancer
activity; however, their high cost precludes their
recommendation over much less expensive choices.
This approach is favored especially after early relapse
from cisplatin-based chemoradiation treatment,
when rechallenge with a platinum is unlikely to
be beneficial. The taxanes can be dosed either on
a weekly or every-21-day schedule, but the weekly
schedule has the advantage of better tolerability and
less irrevocable toxicity per dose, so the clinician has
the option to modify dosing more frequently based on
patient tolerability issues. Table 5 lists recommended
doses and schedules of administration. It is common,
especially in pretreated patients, to hold taxane
dosing every few weeks on an as-needed basis because
of cumulative bone marrow toxicity. Cisplatin and
carboplatin are generally not used as single agents.
Cisplatin especially has a worse adverse event
profile than the agents listed earlier and therefore,
without convincing evidence of superiority versus
methotrexate or the taxanes, should not be used
alone.

#### Multiagent Treatment

For patients with good performance status and appro-
priate organ function (ie, renal, hepatic) with rapidly
progressive or symptomatic disease, triple-agent treat-
ment with PFC or PT plus cetuximab (PTC) (Table
5) may be appropriate, but one must balance the
markedly increased adverse event profile and cost of
these multidrug combinations against the promise of
modest median OS extension. Many favor PTC over
PFC because of its better tolerability and the infusion
pump requirement with 5-FU, despite the fact that
a taxane triplet has not been evaluated in a phase II
study and therefore is not supported by level 1 evi-
dence per the NCCN Clinical Practice Guidelines in
Oncology for Head and Neck Cancers.57
Finally, although many patients benefit from these standard treatments, knowledge remains limited because so few definitive adequately powered studies have been performed. Patients and clinicians should be encouraged to participate both in trials of new promising experimental agents and in trials whose purpose is to better define the role of currently available treatments.

### References


### Table 5 Commonly Used Systemic Treatment Options for Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>40–60 mg/m² IV</td>
<td>Weekly indefinitely</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>80–90 mg/m² IV</td>
<td>Weekly indefinitely</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>25–30 mg/m² IV</td>
<td>Weekly indefinitely</td>
</tr>
<tr>
<td>PTC</td>
<td>Cisplatin or carboplatin; Cisplatin, 100 mg/m² IV; carboplatin, AUC of 5 mg/mL/min IV day 1; 5-FU, 1000 mg/m² x 6 d IVCI days 1–4</td>
<td>q21d x 6</td>
</tr>
<tr>
<td></td>
<td>5-FU</td>
<td>q21d x 6</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>Cetuximab, 400 mg/m² IV day 1, then 250 mg/m² IV</td>
</tr>
<tr>
<td>PTC</td>
<td>Cisplatin</td>
<td>Cisplatin, 75 mg/m² IV day 1</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>Paclitaxel, 75 mg/m² IV day 1</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>Cetuximab, 400 mg/m² IV day 1, then 250 mg/m² IV</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; IV, intravenous; IVCI, intravenous continuous infusion; PTC, cisplatin/carboplatin, 5-FU, cetuximab; PTC, cisplatin, paclitaxel, cetuximab.
Treatment of Metastatic Head and Neck Cancer


