Molecularly Targeted Agents in the Treatment of Recurrent or Metastatic Squamous Cell Carcinomas of the Head and Neck

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Despite decades of research, therapeutic options are limited for patients who have recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). Currently, the most active regimens combining either cisplatin or carboplatin with fluorouracil (FU) or a taxane have been associated with a 30% response rate, a 3- to 4-month median progression-free survival, and a median overall survival of 6 to 8 months.1 However, cytotoxic treatment is associated with frequent and severe toxicities and treatment-related mortality in this patient population. For patients who experience treatment failure with first-line therapy for recurrent or metastatic disease, retrospective analysis has demonstrated a median overall survival of 3 to 4 months even with treatment, underscoring the aggressiveness of this malignancy and the need for more effective therapies.

Interest has been substantial in developing novel agents that specifically modulate growth factor and signaling pathways that are dysregulated in tumor cells. Cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor (EGFR), was the first molecularly targeted agent to be approved for clinical use in combination with radiation therapy for patients who have locally advanced SCCHN, based on a phase III trial that demonstrated an overall survival benefit compared with radiation alone.2 It has also been approved as monotherapy for patients who have recurrent or metastatic...
SCCHN and have progressed on platinum-based therapy, based on an open-label, multicenter phase II trial.³

In this article, the authors summarize the current status of clinical evaluation of molecularly targeted agents, including anti-EGFR and antiangiogenic agents, in SCCHN, focusing on the recurrent or metastatic setting. They then discuss potential strategies to develop novel agents in this setting.

TARGETING THE EPIDERMAL GROWTH FACTOR RECEPTOR

The EGFR expression occurs in up to 90% of patients who have advanced SCCHN, and has been shown to be associated with poor prognosis and resistance to therapy.⁴ Activation of EGFR promotes processes responsible for tumor growth and progression, including proliferation and maturation, angiogenesis, invasion, metastasis, and evasion of apoptosis.⁵ Thus, anti-EGFR agents have been extensively evaluated in SCCHN, including monoclonal antibodies that target the extracellular domain of EGFR, such as cetuximab and panitumumab, and receptor tyrosine kinase inhibitors that target the intracellular domain, such as gefitinib and erlotinib. Agents that target both EGFR and human epidermal growth factor receptor 2 (HER-2), such as lapatinib, have also been studied in SCCHN because HER-2 is the preferred dimerization partner of EGFR and EGFR/HER-2 heterodimers may potentiate receptor signaling and resistance to EGFR inhibitors.

Epidermal Growth Factor Receptor Inhibitors as Single Agents

EGFR inhibitors as single agents are moderately active in recurrent or metastatic SCCHN (Table 1).³,⁶–¹² Most of these studies are uncontrolled, single-arm phase II trials. The inclusion criteria vary substantially among these studies, especially with respect to prior therapy allowed, hence precluding direct comparisons across studies. In general, monoclonal antibodies appear to have a slight advantage in terms of higher overall response rate (about 10%–13%) than small molecule tyrosine kinase inhibitors (about 2.0%–10.6%). In a large randomized trial (IMEX), 486 patients who had recurrent SCCHN were randomized to gefitinib 250 mg daily, gefitinib 500 mg daily, or weekly methotrexate. Neither gefitinib 250 mg/day nor gefitinib 500 mg/day demonstrated an improvement in overall survival over methotrexate (5.6 months, 6.0 months, and 6.7 months, respectively).¹⁰ The dual inhibition of EGFR and HER-2 with lapatinib does not appear to be more effective than the inhibition of EGFR alone.¹²

Epidermal Growth Factor Receptor Inhibitors in Combination with Chemotherapy

Data from preclinical models suggested at least additive effects of EGFR inhibitors when administered with cisplatin,¹³ thus providing the rationale for combination therapy, particularly for patients who have sufficient organ functions and performance status to receive aggressive palliative chemotherapy. Adding platinum to EGFR inhibitors appears to confer no additional benefit over platinum alone, either in response rate or overall survival (see Table 1).¹⁴–¹⁷ Cetuximab has also been evaluated in combination with paclitaxel or docetaxel (see Table 1).¹⁸,¹⁹ The results are difficult to interpret given the lack of a control arm but appear to be in line with those reported using cisplatin and EGFR inhibitors.

After it had been shown that the triple combination of cetuximab, cisplatin, and FU was feasible,²⁰ the EXTREME study randomized patients who had previously untreated recurrent or metastatic SCCHN to the classic platinum plus 5-fluorouracil (5FU) combination with or without cetuximab (see Table 1).²¹ The overall survival was significantly improved for patients receiving chemotherapy and cetuximab (10.1
months versus 7.4 months, \( P = .036 \). Panitumumab, a fully humanized monoclonal antibody against EGFR, is currently being evaluated in a phase III study with a similar design. EGFR inhibitors have also been evaluated in combination with a platinum and a taxane as a triplet combination (see Table 1).\(^{22-24}\) Results of these trials are encouraging; disease control rates as high as 90% have been reported. However, toxicities of triple combination are high, with rates of febrile neutropenia reaching 25%. Hence, such combinations remain investigational until randomized data are available.

**Biomarkers for Epidermal Growth Factor Receptor Inhibitors’ Efficacy**

When EGFR inhibitors first entered the clinic, their effectiveness was anticipated only in patients who had tumors that expressed EGFR, and tumor response was expected to be proportional to the level of EGFR expression. However, studies so far have failed to demonstrate a consistent relationship between pretreatment tumor EGFR expression, typically measured by immunohistochemistry from archival specimens, and response to EGFR inhibition.\(^{3,16}\) No validated markers of sensitivity or resistance to EGFR inhibitors currently exist in SCCHN, although potential markers of therapeutic benefit have been identified, including EGFR gene copy numbers on archival specimen and phosphorylated EGFR on paired tumor biopsies.\(^{25,26}\) However, these biomarkers have been identified from single-arm phase II studies and therefore await validation in randomized phase III studies.

In patients who have advanced colorectal cancer, multiple studies have shown that the benefits of EGFR inhibition with monoclonal antibodies are confined to patients who have wild-type Kirsten ras (KRAS). In fact, patients harboring KRAS mutations may suffer potential harm with anti-EGFR therapy.\(^{27}\) Even though KRAS mutations are rare in SCCHN, being less than 5%,\(^{28}\) an urgent need exists to determine whether such an observation holds true in advanced SCCHN as well.

**TARGETS BEYOND EPIDERMAL GROWTH FACTOR RECEPTOR**

New targets beyond EGFR have been identified in SCCHN as playing key roles in tumor proliferation and metastases.\(^{29}\) Among these targets, tumoral angiogenesis is the most active area of research because vascular endothelial growth factor (VEGF) expression has been demonstrated to be highly correlated with prognosis in patients who have SCCHN.\(^{30}\) Two classes of antiangiogenic agents, monoclonal antibodies that target the VEGF, such as bevacizumab, and multitargeted receptor tyrosine kinase inhibitors that target the VEGF receptor (VEGFR), such as sorafenib or sunitinib, have been evaluated in advanced SCCHN. Agents targeting other targets, such as Src, the insulin-like growth factor 1 receptor (IGF-1R), and the proteasome are also in clinical evaluation.

**Vascular Endothelial Growth Factor**

It has been demonstrated that EGFR activation can up-regulate VEGF, and this phenomenon correlated with resistance to anti-EGFR agents.\(^{31}\) Therefore, studies of bevacizumab in combination with cetuximab or erlotinib without any chemotherapeutic agent have been performed in patients who had recurrent or metastatic SCCHN (see Table 1).\(^{32,33}\) In these two studies, patients were allowed up to one prior regimen for their recurrent or metastatic disease. Among 51 patients treated with bevacizumab and erlotinib, three severe adverse events related to bleeding, one of which was fatal, were reported. No hemorrhagic events were reported among 18 patients treated with bevacizumab and cetuximab. Response rates of 27% and 14% were reported with the bevacizumab/cetuximab and bevacizumab/erlotinib doublets, respectively.
### Table 1
Clinical trials of molecularly targeted therapies in recurrent or metastatic squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase</th>
<th>Tumor Type and Treatment Setting</th>
<th>Treatment</th>
<th>n</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>TTP (m)</th>
<th>PFS (m)</th>
<th>OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-EGFR molecularly targeted therapies (single agent)</strong></td>
<td></td>
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<tr>
<td>Cetuximab (Erbitux)</td>
<td>II 2nd line R/M SCCHN³</td>
<td></td>
<td>Cetuximab 400 mg/m² followed by weekly 250 mg/m²</td>
<td>103</td>
<td>0</td>
<td>13</td>
<td>7</td>
<td>2.3</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>II 1st or 2nd line R/M SCCHN⁶</td>
<td></td>
<td>Gefitinib 500 mg/d</td>
<td>52</td>
<td>2.1</td>
<td>8.5</td>
<td>42.6</td>
<td>3.4</td>
<td>—</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>II 1st or 2nd line R/M SCCHN⁷</td>
<td></td>
<td>Gefitinib 500 mg/d</td>
<td>32</td>
<td>0</td>
<td>9</td>
<td>28</td>
<td>3</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>II 2nd or 3rd line R/M SCCHN⁸</td>
<td></td>
<td>Gefitinib 250 mg/d</td>
<td>70</td>
<td>0</td>
<td>1.4</td>
<td>31.6</td>
<td>—</td>
<td>1.8</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>II 2nd or 3rd line R/M SCCHN⁹</td>
<td></td>
<td>Gefitinib 500 mg/d</td>
<td>47</td>
<td>0</td>
<td>2</td>
<td>26</td>
<td>2.6</td>
<td>—</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>II 1st or 2nd line R/M SCCHN¹⁰</td>
<td></td>
<td>Gefitinib 250 mg/d</td>
<td>158</td>
<td>—</td>
<td>2.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.6</td>
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<tr>
<td></td>
<td>II 1st or 2nd line R/M SCCHN¹¹</td>
<td></td>
<td>Gefitinib 500 mg/d</td>
<td>167</td>
<td>—</td>
<td>7.6</td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>161</td>
<td>—</td>
<td>3.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.7</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>II 1st or 2nd line R/M SCCHN¹²</td>
<td></td>
<td>Erlotinib 150 mg/d</td>
<td>115</td>
<td>0</td>
<td>4.3</td>
<td>33.9</td>
<td>—</td>
<td>2.3</td>
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<tr>
<td>Lapatinib (Tykerb)</td>
<td>II R/M SCCHN with (A) or without (B) prior EGFR inhibitor¹³</td>
<td></td>
<td>Lapatinib 1500 mg/d (A)</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>37</td>
<td>1.6</td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>Lapatinib 1500 mg/d (B)</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>1.7</td>
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<td><strong>Anti-EGFR molecularly targeted therapies (doublet combination)</strong></td>
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<tr>
<td>Cetuximab (Erbitux)</td>
<td>II 2nd line R/M SCCHN¹⁴</td>
<td></td>
<td>Platinum + cetuximab</td>
<td>96</td>
<td>0</td>
<td>10</td>
<td>43</td>
<td>2.4</td>
<td>—</td>
<td>5</td>
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<tr>
<td></td>
<td>II 2nd line R/M SCCHN¹⁵</td>
<td></td>
<td>Cisplatin + cetuximab (SD)</td>
<td>51</td>
<td>4</td>
<td>14</td>
<td>59</td>
<td>—</td>
<td>4.9</td>
<td>11.7</td>
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<td></td>
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<td></td>
<td>Cisplatin + cetuximab (PD/1)</td>
<td>25</td>
<td>0</td>
<td>20</td>
<td>44</td>
<td>—</td>
<td>3</td>
<td>6.1</td>
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<td></td>
<td></td>
<td></td>
<td>Cisplatin + cetuximab (PD/2)</td>
<td>54</td>
<td>0</td>
<td>6</td>
<td>46</td>
<td>—</td>
<td>2</td>
<td>4.3</td>
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<tr>
<td></td>
<td>III 1st line R/M SCCHN¹⁶</td>
<td></td>
<td>Cisplatin + cetuximab</td>
<td>57</td>
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<td>26</td>
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<td>4.2</td>
<td>9.2</td>
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<td></td>
<td></td>
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<td>Cisplatin + placebo</td>
<td>60</td>
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<td>2.7</td>
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<tr>
<td></td>
<td>II 2nd line R/M SCCHN¹⁸</td>
<td></td>
<td>Docetaxel + cetuximab</td>
<td>47</td>
<td>0</td>
<td>20</td>
<td>27</td>
<td>—</td>
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<tr>
<td></td>
<td>II 1st line R/M SCCHN¹⁹</td>
<td></td>
<td>Paclitaxel + cetuximab</td>
<td>46</td>
<td>24</td>
<td>36</td>
<td>28</td>
<td>—</td>
<td>5</td>
<td>NR</td>
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<tr>
<td>Erlotinib (Tarceva)</td>
<td>II 1st line R/M SCCHN¹⁷</td>
<td></td>
<td>Cisplatin + erlotinib 100 mg/d</td>
<td>44</td>
<td>3</td>
<td>19</td>
<td>49</td>
<td>—</td>
<td>3.3</td>
<td>7.9</td>
</tr>
</tbody>
</table>

*Note: SD = Stable Disease, TTP = Time to Progression, PFS = Progression-Free Survival, OS = Overall Survival.*
<table>
<thead>
<tr>
<th>Cetuximab (Erbitux)</th>
<th>II 1st line R/M SCCHN</th>
<th>Platinum + 5FU + cetuximab</th>
<th>53</th>
<th>4</th>
<th>32</th>
<th>38</th>
<th>5.1</th>
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<th>9.8</th>
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<tr>
<td>III 1st line R/M SCCHN</td>
<td>Cisplatin + 5FU + cetuximab</td>
<td>220</td>
<td>—</td>
<td>36*</td>
<td>45</td>
<td>5.6*</td>
<td>—</td>
<td>10.1*</td>
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<tr>
<td></td>
<td>Cisplatin + 5FU</td>
<td>222</td>
<td>—</td>
<td>20</td>
<td>40</td>
<td>3.3</td>
<td>—</td>
<td>7.4</td>
<td></td>
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<tr>
<td>II 2nd line R/M SCCHN</td>
<td>Carboplatin + paclitaxel + cetuximab</td>
<td>23</td>
<td>4</td>
<td>30</td>
<td>22</td>
<td>5</td>
<td>—</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>II 1st line R/M SCCHN</td>
<td>Cisplatin + docetaxel + gefitinib 250 mg/d</td>
<td>17</td>
<td>37.5</td>
<td>25</td>
<td>12.5</td>
<td>—</td>
<td>5.1</td>
<td>NR</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>II 1st line R/M SCCHN</td>
<td>Cisplatin + docetaxel + erlotinib 150 mg/d</td>
<td>47</td>
<td>8</td>
<td>58</td>
<td>28</td>
<td>—</td>
<td>6</td>
<td>11</td>
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<tr>
<td><strong>Antiangiogenic molecularly targeted therapies</strong></td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>II 1st or 2nd line R/M SCCHN</td>
<td>Bevacizumab 15 mg/kg q3w + cetuximab</td>
<td>18</td>
<td>0</td>
<td>27</td>
<td>53</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>II 1st or 2nd line R/M SCCHN</td>
<td>Bevacizumab 15 mg/kg q3w + erlotinib 150 mg/d</td>
<td>51</td>
<td>4</td>
<td>10</td>
<td>56</td>
<td>—</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>II 1st line R/M SCCHN</td>
<td>Bevacizumab 15 mg/kg q3w + pemetrexed</td>
<td>25</td>
<td>14</td>
<td>23</td>
<td>59</td>
<td>—</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>II 1st line R/M SCCHN</td>
<td>Sorafenib 800 mg/d</td>
<td>44</td>
<td>0</td>
<td>3</td>
<td>45</td>
<td>4.2</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>II 2nd line R/M SCCHN or NPC</td>
<td>Sorafenib 800 mg/d</td>
<td>28</td>
<td>0</td>
<td>4</td>
<td>37</td>
<td>1.8</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>II 1st to 3rd line R/M SCCHN</td>
<td>Sunitinib 50 mg/d 4 wk on, 2 wk off</td>
<td>22</td>
<td>0</td>
<td>6</td>
<td>28</td>
<td>2.3</td>
<td>—</td>
<td>4.7</td>
</tr>
</tbody>
</table>

*Abbreviations: CR, complete response; NR, not reached; OS, overall survival; PD/1, patients who have progressive disease after platinum-based therapy; PD/2, patients who have progressive disease within 3 months after platinum-based therapy; PFS, progression-free survival; PR, partial response; R/M, recurrent or metastatic; SD, stable disease; TTP, time to progression; 5FU, 5-fluorouracil.

* Statistically significant.
Feinstein and colleagues performed a phase II trial of pemetrexed and bevacizumab in previously untreated recurrent or metastatic disease (see Table 1). Among 25 patients evaluable for toxicity, three hemorrhagic events were reported, one gastric and two at the tumor site. In addition, two toxic deaths were reported, one from febrile neutropenia and the other from tracheal bleeding. Among 22 patients evaluable for response, 3 (14%) had a complete response, 5 (23%) had a partial response, and 13 (59%) had stable disease. Median progression-free survival was 7 months.

**Vascular Endothelial Growth Factor Receptor**

Small molecule tyrosine kinase inhibitors so far included sorafenib and sunitinib. Williamson and colleagues performed a phase II trial of sorafenib 400 mg twice daily in 44 patients who were chemotherapy naïve for their recurrent or metastatic SCCHN (see Table 1). Median time to progression and overall survival were 4 months and 8 months, respectively. Sorafenib has also been studied by Elser and colleagues in 28 patients who had refractory recurrent or metastatic SCCHN or nasopharyngeal carcinoma (see Table 1). Results of this study were disappointing, with a time to progression of 1.8 months.

Similarly, a phase II trial was performed with sunitinib given at the dose of 50 mg daily for 4 weeks followed by a 2-week rest period in first- to third-line treatment of patients who had recurrent or metastatic SCCHN (see Table 1). Among 22 patients evaluable for toxicity, 5 experienced hemorrhagic events. Efficacy results were comparable to those observed with sorafenib given in pretreated patients. Based on these findings, sorafenib or sunitinib given as a single agent in pretreated patients who have recurrent or metastatic SCCHN does not demonstrate sufficient antitumor activity.

In summary, antiangiogenic therapies as single agents have shown limited antitumor activity in recurrent or metastatic SCCHN. In addition, potential vascular complications will further hinder development of this class of agents in this patient population.

**Src**

Because EGFR can be activated by multiple ligands and can, in turn, mediate several downstream signaling pathways, in vitro studies have evaluated the possibility of blocking ligands or downstream effectors of EGFR. Src kinase is a nonreceptor cytoplasmic tyrosine kinase that plays a key role in modulating multiple cellular functions including invasion, adhesion, motility, migration proliferation, and survival. Preclinical evaluations demonstrated a strong rationale for targeting Src in SCCHN. Src inhibition using dasatinib, an ATP-binding competitive tyrosine kinase inhibitor, in SCCHN cell lines in vitro has led to cell cycle arrest and apoptosis. Inhibitors of Src kinase, such as dasatinib and AZD0530, are currently undergoing phase II evaluations in recurrent or metastatic SCCHN.

**Insulin-Like Growth Factor 1 Receptor**

EGFR activation can also be achieved through cross-talk with other receptors, such as G-protein-coupled receptors, platelet-derived growth factor receptor, and IGF-1R. Barnes and colleagues demonstrated in a panel of SCCHN cell lines that IGF-1R expression is increased and that IGF-1R and EGFR functionally heterodimerize. Antiproliferative effects were observed with an IGF-1R inhibitor in these cell lines and tumor xenografts. In addition, combined treatment with anti–IGF-1R antibody and cetuximab yielded a more effective reduction in cellular proliferation than with either agent alone. IMC-A12, which is a monoclonal antibody targeting IGF-R1, is currently being
studied with or without cetuximab in a phase II trial in patients who have recurrent or metastatic SCCHN.42

**Proteasome**

The 26S proteasome is central for the ubiquitin-proteasome degradation pathway. Bortezomib is a selective inhibitor of the 26S proteasome that has been approved for the treatment of hematologic malignancies. Preclinical studies have shown that bortezomib has antitumor activity in SCCHN models.43 Bortezomib is currently being studied in phase II trials in combination with irinotecan or docetaxel in recurrent or metastatic SCCHN.44,45

**DEVELOPMENTAL STRATEGIES**

**Phase II Trial Designs**

The overall response rate has often been used as a primary end point in phase II trials in advanced SCCHN. Novel agents, such as those targeting the VEGF pathway, may be cystostatic, rather than cytotoxic, in nature. These agents may induce tumor necrosis without any tumor shrinkage. Thus, relying on the response rate as the sole indicator of antitumor activity may be misleading and could potentially result in abandoning agents prematurely. Possible solutions include incorporation of the rate of prolonged stable disease (eg, >4–6 months) or progression-based end points in future trials. These end points may provide more realistic assessments of antitumor activity than those based primarily on tumor shrinkage. In addition, innovative pharmacodynamic end points, such as intratumoral blood flow perfusion parameters based on dynamic contrast-enhanced CT/MRI, may be more relevant than conventional response criteria for these agents.

The most commonly used study design for phase II studies is the Simon two-stage design. The published literature indicates that significant tumor shrinkage is only observed in a small proportion of patients who have advanced SCCHN, such that response rates of 15% to 20% typically stated in the alternative hypothesis of a two-stage design are unlikely to be attainable even with the most active compounds. For instance, based on the published data with EGFR inhibitors, the objective response rate of these agents in advanced SCCHN is fairly consistent, at less than 10% for gefitinib and erlotinib, and at 13% for cetuximab. Therefore, the development of cetuximab in advanced SCCHN would have been terminated if it was tested in a phase II study with a two-stage design using an unattainably high response rate in the alternative hypothesis (eg, ≥20%). In designing future phase II studies in advanced SCCHN, the null hypothesis should be that the objective response rate is less than or equal to 5% versus the alternative hypothesis that the objective response rate is greater than or equal to 15%. Unfortunately, such a design would necessitate a large sample size. Therefore, more innovative study designs, such as an adaptive trial design that enables continual assessment, should be actively explored in future studies in advanced SCCHN.

Randomized phase II trials may be an alternative to assess the efficacy of a novel agent in advanced SCCHN. These trials should be designed as phase II/III studies so that they can transition into phase III studies if the primary end point of the phase II portion is met. This type of design has the advantages of providing a realistic estimation of treatment benefits and a shorter time interval between the phase II and phase III portions. However, the number of patients required for the phase II portion is larger than that for single-arm studies.
Phase III Trial Designs

If the activity of a novel agent (drug X) appears to be comparable to, or better than, that of cetuximab in phase II trials, two strategies can be applied for further development in SCCHN (Fig. 1). The first strategy is to test drug X in the only Food and Drug Administration (FDA)-approved indication for cetuximab in the recurrent or metastatic setting, namely as a single agent for the treatment of patients for whom prior platinum-based therapy has failed. A possible trial design could be drug X versus cetuximab alone in these patients. The primary end point should be overall survival, and secondary end points should include quality of life. In the situation in which no significant difference in overall survival can be detected, a difference in quality of life would prove that drug X compares favorably to cetuximab. This strategy to benchmark directly against cetuximab may enable drug X to obtain accelerated approval in the platinum-refractory SCCHN population, but the success of such a strategy would require impressive antitumor activity of such an agent given as monotherapy. The second strategy for testing drug X is outside of FDA-approved indications for cetuximab. In this scenario, a possible trial design could be drug X versus chemotherapy alone in patients for whom cetuximab-based treatment has failed. The primary end point for such a trial should be overall survival. Secondary end points should include quality of life. Assuming that cetuximab will get FDA approval in combination with platinum and 5FU in first-line treatment based on the EXTREME study, another trial design could be drug X in combination with platinum and 5FU versus cetuximab in combination with platinum and 5FU in a first-line recurrent or metastatic setting. The primary end point should also be overall survival and secondary end points should also include quality of life.

Within FDA-approved indications for cetuximab

Outside of FDA-approved indications for cetuximab

![Fig. 1. Phase III clinical trial designs to develop molecularly targeted agents in recurrent or metastatic SCCHN. FDA, Food and Drug Administration; OS, overall survival; QoL, quality of life; R/M, recurrent or metastatic.](image-url)
Stratification Based on Human Papilloma Virus

Recent data indicate that human papilloma virus (HPV)-related SCCHN is a distinct disease with a better prognosis. The prognostic impact of HPV-related SCCHN is less clear in the recurrent or metastatic setting; hence, it may not be relevant to distinguish HPV-related from non–HPV-related SCCHN for its prognostic difference. However, it seems that HPV-induced HNSCC displays distinct molecular features that may rationally lead to test-specific molecularly targeted agents. Preclinical studies recently presented show that repression of E6/E7 gene expression leads to activation of the Notch and nuclear factor–kappa B pathways only in HPV16-positive oropharyngeal cancer cell lines. On the contrary, PTEN seems to be inactivated independently of AKT. Future trial designs should consider distinguishing between HPV-related and non–HPV-related SCCHN as a patient selection or stratification strategy.

SUMMARY

Molecularly targeted agents already belong to the treatment strategy for patients who have SCCHN. Novel molecular targets and corresponding therapies continue to emerge. Identification of predictive biomarkers of resistance or sensitivity to these therapies remains one of the main challenges in the optimal selection of patients most likely to benefit from them. However, clinical trials with these novel agents need to be designed rationally to improve the overall outcome of patients. Given the emerging evidence that HPV-related SCCHN appears to represent a distinct entity, compared with non–HPV-related disease, these two subgroups should be evaluated prospectively in specific trials.

REFERENCES

21. Vermorken JB, Rivera F. Platinum-based chemotherapy plus cetuximab in head 
22. Buentzel J, de Vries A, Micke O. Experience with cetuximab plus paclitaxel/car-
boplatinum in primary platinum-resistant recurrent head and neck cancer [ab-
stract 6077]. In: Programs and abstracts of the American Society of Clinical 
evaluate gefitinib combined with docetaxel and cisplatin in patients with recurrent 
and/or metastatic squamous-cell carcinoma of the head and neck [abstract 5563]. In: Programs and abstracts of the American Society of Clinical Oncology 
24. Kim ES, Kies MS, Glisson BS, et al. Final results of a phase II study of erlotinib, 
docetaxel and cisplatin in patients with recurrent/metastatic head and neck can-
cer [abstract 6013]. In: Programs and abstracts of the American Society of Clinical 
namic biomarker studies in tumor and skin tissue samples of patients with recur-
rent or metastatic squamous cell carcinoma of the head and neck treated with 
27. Le Tourneau C, Vidal L, Siu LL. Progress and challenges in the identification of 
biomarkers for EGFR and VEGFR targeting anticancer agents. Drug Resist Updat 
tions in locally advanced head and neck squamous cell carcinoma and influence 
with regards to response to chemoradiation therapy [abstract 17005]. In: Pro-
grams and abstracts of the American Society of Clinical Oncology meeting. Chi-
29. Le Tourneau C, Faivre S, Siu LL. Molecular targeted therapy of head and neck 
cancer: review and clinical development challenges. Eur J Cancer 2007;43: 
2457–66.
30. Lothaire P, de Azambuja E, Dequanter D, et al. Molecular markers of head and 
neck squamous cell carcinoma: promising signs in need of prospective evalu-
factor family members are differentially regulated by c-erbB signaling in head 
32. Kies MS, Gibson MK, Kim SW, et al. Cetuximab (C) and bevacizumab (B) in pa-
tients with recurrent or metastatic head and neck squamous cell carcinoma 
33. Vokes EE, Cohen EE, Mauer AM, et al. A phase I study of erlotinib and bevacizu-
mab for recurrent or metastatic squamous cell carcinoma of the head and neck 
(HNC) [abstract 5504]. In: Programs and abstracts of the American Society of 
34. Feinstein TM, Raez LE, Rajasenan KK, et al. Pemetrexed (P) and bevacizumab 
(B) in patients (pts) with recurrent or metastatic head and neck squamous cell 
carcinoma (HNSSC): updated results of a phase II trial [abstract 6069]. In: Pro-
grams and abstracts of the American Society of Clinical Oncology meeting. Chi-


