

# Emerging Molecular Targeted Therapies in Squamous Cell Carcinoma of the Head and Neck

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**Abstract:** In recent years, several therapeutic advances have been made in squamous cell carcinoma of the head and neck (SCCHN). However, despite multimodality therapy, patients with locally advanced SCCHN continue to demonstrate suboptimal 5-year survival rates. The addition of novel, targeted agents to traditional therapies holds promise for clinical benefit. This review will focus on new agents that are promising and their potential role in the treatment of SCCHN.

Squamous cell carcinoma of the head and neck (SCCHN) remains a challenging disease and is associated with significant morbidity and mortality both in the United States and worldwide.<sup>1</sup> Approximately 40,000 new cases of SCCHN are diagnosed each year in the United States.<sup>2</sup> In recent years, new insights into the molecular events and alterations that characterize SCCHN have led to the development of novel therapeutic approaches. Historically, therapy for SCCHN has included surgery, radiotherapy, and traditional cytotoxic chemotherapeutic agents; however, despite multimodality therapy, patients with locally advanced SCCHN demonstrate 5-year survival rates of 50% or less.<sup>3-5</sup> Although recent trials have shown encouraging results using aggressive concomitant chemoradiotherapy with or without induction chemotherapy in patients with locally advanced disease,<sup>6</sup> further improvements in survival and locoregional control may be realized by combining traditional therapies with new, targeted agents. Moreover, treatment results for recurrent or metastatic SCCHN are generally poor; effective therapies are desperately needed. This review focuses on several of the promising new, targeted agents and their potential role in fighting this disease.

## Targeting Epidermal Growth Factor

Effective targeting of SCCHN and its precursor lesions requires an understanding of the molecular events that occur in the stepwise progression from normal-appearing mucosa to invasive carcinoma. One of the most important discoveries has been the role of the epidermal growth factor receptor (EGFR) in SCCHN. The EGFR

### Keywords

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(ErbB-1), a member of the ErbB subfamily of receptors, is overexpressed in multiple epithelial malignancies, including SCCHN.<sup>7,8</sup> The EGFR resides in the plasma membrane and is composed of three domains: the extracellular ligand-binding domain, the transmembrane segment, and the intracellular tyrosine kinase domain. Binding of the receptor's ligands—epidermal growth factor (EGF), amphiregulin, and transforming growth factor (TGF)- $\alpha$ —leads to homodimerization and heterodimerization of the EGFR with other members of the EGFR family (ErbB-2, ErbB-3, and ErbB-4), which results in activation of the EGFR tyrosine kinase and phosphorylation of multiple downstream targets. This intracellular signaling cascade promotes cellular processes including cell proliferation, motility, adhesion, invasion, and angiogenesis.<sup>7,8</sup> Increased expression of the EGFR has been described in normal mucosa of patients with SCCHN, as well as in preneoplastic lesions, pointing to an early potential role of this receptor in SCCHN carcinogenesis.<sup>9-11</sup> Importantly, EGFR overexpression has been noted in approximately 80–90% of SCCHN cases.<sup>12-14</sup>

#### ***Anti-EGFR Monoclonal Antibodies***

Cetuximab (Erbix, ImClone/Bristol-Myers Squibb), a recombinant human/mouse chimeric monoclonal antibody, is one of the first EGFR inhibitors to be studied in SCCHN. Cetuximab binds specifically to the extracellular domain of the EGFR and competitively inhibits the binding of ligands to the receptor.<sup>15-17</sup> Preclinically, cetuximab is synergistic with radiotherapy and chemotherapy. Human oral squamous cell carcinoma cell lines treated with cetuximab demonstrate cell accumulation in the radiosensitive G1 phase, which is associated with increased expression of the cell cycle inhibitors p27Kip1 and p15ink4b. Furthermore, cetuximab treatment results in a decrease of cells in the S phase of the cell cycle, the phase during which sublethal damage repair in response to radiotherapy occurs.<sup>18-20</sup> A synergistic or additive effect is also noted when cetuximab is combined with chemotherapy. The potential mechanisms for this phenomenon include non-cross-resistant mechanisms of action and enhanced sensitivity to chemotherapy secondary to altered activity of genes that control cell growth and proliferation.<sup>21-25</sup> Importantly, evidence suggests that the EGFR pathway plays a role in cellular sensitivity to cisplatin, thus providing an opportunity to overcome resistance through manipulation of the EGFR.<sup>26-28</sup>

Clinically, cetuximab has demonstrated encouraging results both as a single agent and when combined with radiotherapy or chemotherapy. Trigo and colleagues<sup>29</sup> showed that cetuximab monotherapy was active in 103 patients with platinum-refractory SCCHN. In this study, the objective response rate was 13%, the median

time to progression 2.3 months, and the median survival 5.9 months. Currently, it is uncertain whether the readministration of platinum contributes to the efficacy of cetuximab in platinum-refractory SCCHN.

Cetuximab has also demonstrated promising results in combination with radiotherapy. Bonner and coauthors<sup>30</sup> reported the results of a phase III multicenter randomized trial that evaluated radiotherapy (with stratification for once-a-day, twice-a-day, or concomitant boost) with or without concurrent cetuximab in patients with locoregionally advanced SCCHN. Importantly, statistically significant improved locoregional control and overall survival were noted for the cetuximab arm, with a median duration of locoregional control and overall survival of 24.4 months and 49 months, respectively, versus 14.9 months and 29.3 months, respectively, for the radiation-only arm. The magnitude of the survival benefit (about 10% at 3 years) attained with the addition of cetuximab to radiation is comparable to the survival benefit with the addition of chemotherapy to radiation for the treatment of locally advanced SCCHN. On the basis of this positive phase III trial, cetuximab obtained regulatory approval for the treatment of SCCHN in the United States.

With respect to chemotherapy, the addition of cetuximab to cisplatin has proven especially interesting. In a small phase Ib trial of previously treated patients with recurrent SCCHN whose tumors demonstrated high levels of EGFR expression, cetuximab in combination with cisplatin resulted in a response rate of 67% in 9 evaluable patients, including 3 patients who had progressive disease during cisplatin-based therapy prior to study entry.<sup>31</sup> Two phase II trials of cetuximab in combination with cisplatin or carboplatin in patients with platinum-refractory metastatic and/or recurrent SCCHN were recently reported. Baselga and coworkers<sup>32</sup> demonstrated that cetuximab in combination with cisplatin or carboplatin resulted in an objective response rate of 10% and a disease control rate of 53% (objective response rate plus stable disease rate) with a median time to progression and overall survival of 2.8 and 6.1 months respectively. Herbst and colleagues<sup>33</sup> treated 131 patients with recurrent or metastatic platinum-refractory SCCHN with the combination of cetuximab and cisplatin and demonstrated an overall response rate of 13%.

Given these encouraging results in a historically poor-prognosis group of patients, Burtness and coworkers<sup>34</sup> conducted a phase III randomized trial that compared cisplatin plus placebo versus cisplatin plus cetuximab in the first-line treatment of patients with recurrent or metastatic SCCHN. The combination demonstrated a significantly improved response rate (23% vs 10%) over cisplatin alone. Although there was a trend toward

improved median progression-free survival with cisplatin/cetuximab versus cisplatin alone (4.2 vs 2.7 months;  $P=.09$ ), the difference did not reach statistical significance. Surprisingly, the cisplatin/cetuximab combination was less active in tumors with the highest EGFR expression (as evaluated by immunohistochemistry) than in tumors with intermediate EGFR expression. This counterintuitive result may be explained by ligand-independent signaling in tumors particularly rich in EGFR, failure of cetuximab to saturate the EGFR receptors at the doses given, or activation of targets downstream of EGFR that contribute to cetuximab resistance.<sup>34</sup>

A number of new anti-EGFR monoclonal antibodies are also being studied in various malignancies, including SCCHN. Panitumumab (Amgen), a human IgG2 anti-EGFR monoclonal antibody that can be administered less frequently than cetuximab and has a lower incidence of infusional reactions, will be studied in SCCHN.<sup>35,36</sup> Matuzumab (Merck/Takeda), a humanized IgG1 anti-EGFR monoclonal antibody, is also of interest for the treatment of SCCHN. In a phase I trial in advanced EGFR-positive malignancies, 2 of 4 patients with SCCHN achieved an objective response with matuzumab.<sup>37</sup> Further studies of matuzumab in SCCHN are warranted.

#### **Small Molecule EGFR Tyrosine Kinase Inhibitors**

Two oral EGFR tyrosine kinase inhibitors, gefitinib (Iressa, AstraZeneca) and erlotinib (Tarceva, OSI Pharmaceuticals), have been extensively studied in SCCHN. Unlike cetuximab, these agents target the intracellular portion of the EGFR through inhibition of the receptor's tyrosine kinase activity. Gefitinib, a quinazoline, is an oral selective inhibitor of the EGFR tyrosine kinase. Gefitinib arrests cells in the G0–G1 phase of the cell cycle, promotes apoptosis, and inhibits angiogenesis. In SCCHN cell lines, gefitinib has also been shown to inhibit phosphorylation of three downstream signal transducers including AKT, STAT3, and MAPK, and upregulates p27Kip1 and p21 in association with G0–G1 growth arrest.<sup>38,39</sup> Like with cetuximab, preclinical studies have demonstrated additive or synergistic effects with radiotherapy or chemotherapy. In SCCHN cell lines and tumor xenografts, the combination of gefitinib and cisplatin additively increased the cytotoxic effect of cisplatin.<sup>39-43</sup>

Three phase II trials of gefitinib in recurrent or metastatic SCCHN have been reported.<sup>44-46</sup> Taken together, these studies showed objective response rates between 1% and 11%. In the first phase II study the median time to tumor progression was 3.4 months and the median survival time was 8 months. At present, it is uncertain whether a dose-response effect exists for gefitinib activity in SCCHN. In one of the trials, gefitinib demonstrated greater activity in the subset of previously untreated

patients ( $n=20$ ) with an objective response rate of 20% and a disease control rate of 45%, compared to 0% and 25%, respectively, in the previously treated cohort ( $n=12$ ).

Erlotinib, a potent oral reversible selective small molecule inhibitor of EGFR tyrosine kinase has also shown modest single-agent activity in recurrent or metastatic SCCHN. A phase II multicenter study of erlotinib in patients with recurrent or metastatic SCCHN demonstrated an objective response rate of 4.3% with disease stabilization in 38.3% of patients and a median progression-free and overall survival of 9.6 weeks and 6 months, respectively.<sup>47</sup>

Clinical studies are presently evaluating the combination of the tyrosine kinase inhibitors with radiotherapy and/or chemotherapy. In fact, promising preliminary results with induction chemotherapy followed by the addition of gefitinib to hyperfractionated radiation, 5-fluorouracil, and hydroxyurea followed by gefitinib maintenance therapy in previously untreated patients with advanced SCCHN were reported by Cohen and colleagues.<sup>48</sup> At a median follow-up of 20 months, a complete response rate of 88% and a progression-free survival rate of 95% were reported. In the first-line treatment of recurrent or metastatic SCCHN, the addition of an EGFR tyrosine kinase inhibitor to cisplatin and docetaxel has produced promising preliminary results.<sup>49,50</sup> Kim and colleagues<sup>50</sup> reported an objective response rate of 77% in the first 22 patients treated with cisplatin/docetaxel/erlotinib. Belon and coworkers<sup>49</sup> reported an objective response rate of 50% in 24 patients treated with cisplatin/docetaxel plus gefitinib.<sup>49</sup> An ongoing phase III randomized, placebo-controlled trial, conducted by the Eastern Cooperative Oncology Group, is evaluating the combination of docetaxel versus docetaxel plus gefitinib in patients with performance status 2 or previously treated recurrent/metastatic SCCHN. Studies employing the various agents that target EGFR in SCCHN are ongoing (Table 1). Lapatinib (GlaxoSmithKline), an oral reversible small molecule inhibitor of ErbB1/ErbB2 tyrosine kinases, represents an additional novel agent currently under investigation for treatment of locally advanced metastatic SCCHN.<sup>51,52</sup>

#### **Targeting Cyclooxygenase-2**

Cyclooxygenase (COX)-2, a rate-limiting enzyme in the synthesis of prostaglandin (PG)  $E_2$  from arachidonic acid, is overexpressed in multiple epithelial malignancies, including SCCHN. While COX-1 is expressed constitutively in many cells, COX-2 expression is induced by mitogens, cytokines, oncogenes, carcinogens, and tumor-promoting phorbol esters.<sup>53-55</sup> Similar to EGFR, abnormal COX-2 expression is noted in several steps in

**Table 1.** Selected Ongoing Clinical Trials Using EGFR Inhibitors in SCCHN

Drug	Phase of Trial	Therapy	Sponsor	Population
Cetuximab	III	Concurrent accelerated fractionated RT and cisplatin ± cetuximab	RTOG	First-line stage III or IV oropharynx, hypopharynx, larynx
Cetuximab	II	Induction docetaxel, cetuximab, and cisplatin followed by RT, cetuximab, and cisplatin	Industry/University of Pittsburgh	Stage III–IVb head and neck cancer, all sites
Cetuximab	II	Adjuvant cetuximab and chemoradiotherapy	RTOG	Resected stage III or IV SCCHN at high risk for recurrence
Cetuximab	II	cetuximab, cisplatin, and definitive RT	ECOG	Unresectable, locally advanced or regional stage IV SCCHN
Erlotinib	I/II	Erlotinib and docetaxel	Ohio State University/Arthur G. James Cancer Hospital	Locally advanced, metastatic or recurrent SCCHN
Erlotinib	II	Single-agent erlotinib	Johns Hopkins Oncology Center/Sidney Kimmel Comprehensive Cancer Center	Metastatic and/or locally recurrent SCCHN
Gefitinib	III	Gefitinib (250 mg vs 500 mg) vs methotrexate	Industry	Previously treated recurrent SCCHN
Gefitinib	I/II	Gefitinib/cisplatin/RT	New York Weill Cornell Cancer Center	First-line locally advanced SCCHN

EGFR = epidermal growth factor receptor; ECOG = Eastern Cooperative Oncology Group; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SCCHN = squamous cell carcinoma of the head and neck.

the phenotypic transformation from normal-appearing mucosa to invasive SCCHN. In addition to a 50-fold increase in COX-2 mRNA expression in the adjacent normal-appearing mucosa of head and neck cancer patients, a 150-fold increase in COX-2 expression is noted in invasive SCCHN as compared to normal controls.<sup>54</sup> Gallo and colleagues<sup>56</sup> demonstrated that 86% of SCCHN tumors examined were positive for COX-2 protein expression by immunohistochemistry, with the majority demonstrating moderate or diffuse staining for COX-2. Expression of COX-2 also increased with advanced tumor stage and loss of differentiation.

The purported role of COX-2 in carcinogenesis is varied and presents an attractive target for both therapy and chemoprevention of SCCHN. The COX-2 enzyme has peroxidase activity, which can promote the conversion of procarcinogens to carcinogens at exposed COX-2-expressing mucosa. An approximately fourfold increase in COX-2 expression is noted in oral mucosa of active smokers versus those who never smoked.<sup>57</sup> Importantly, a link with the EGFR pathway in both premalignant and malig-

nant tissue has been noted. Activation of the EGFR leads to increased levels of COX-2 mRNA, COX-2 protein, and synthesis of PGs in oral epithelial cells and in cancer cell lines.<sup>11,54,58,59</sup> Treatment of nonmalignant oral epithelial cell lines with a saline extract of tobacco smoke resulted in increased expression of both COX-2 and EGFR tyrosine kinase (related to increased release of EGFR ligands, TGF- $\alpha$  and amphiregulin). Neutralizing antibody to the EGFR blocked the tobacco smoke-mediated induction of COX-2.<sup>57,60</sup> Other potential links between COX-2 and the EGFR pathway include increased EGFR signaling through PGE<sub>2</sub>-activated matrix metalloproteinase activity, PGE<sub>2</sub>-induced expression of amphiregulin (an EGFR ligand), and PGE<sub>2</sub>-induced transactivation of EGFR.<sup>61-64</sup>

A role for COX-2 in angiogenesis has also been noted. COX-2-derived prostaglandins PGE<sub>2</sub> and PGI<sub>1</sub> are associated with increased expression of vascular endothelial growth factor (VEGF) through PG-induced production of hypoxia-inducible factor 1 (HIF-1)- $\alpha$ . In SCCHN cell lines, EGF-induced synthesis of PGE<sub>2</sub> resulted in increased VEGF mRNA expression and was

blocked by COX-2 inhibition, thus providing further evidence of a multilayered relationship between COX-2 and the EGFR as well as VEGF. In human metastatic lymph nodes, significant correlations have been noted between COX-2 expression, tumor vascularization, and VEGF expression and between COX-2 expression, microvessel density, and VEGF expression.<sup>65-67</sup> Taken together, these findings underscore the need for a multitargeted approach to the successful treatment of SCCHN. Although a comprehensive discussion of the role of COX-2 inhibitors in cancer prevention is not within the scope of this article, the COX-2-mediated effects described above underscore the interest in this class of agents for chemoprevention.

### ***COX-2 Inhibitors in Combination Therapy***

COX-2 inhibitors have demonstrated encouraging preclinical results in combination with targeted agents or cytotoxic chemotherapy.<sup>68,69</sup> As noted earlier, data demonstrate a direct interaction between COX-2 and EGFR, presenting dual targets for signaling inhibition.<sup>61,70</sup> In a study of SCCHN cell lines, the combination of an EGFR inhibitor and a COX-2 inhibitor (celecoxib [Celebrex, Pfizer]) either additively or synergistically inhibited the growth of all five SCCHN cell lines examined, as characterized by G1 cell cycle arrest and apoptosis and suppressed capillary formation of endothelium. Additionally, the combination of agents demonstrated significantly reduced expression of EGFR, ERK 1/2 and AKT protein compared with either agent alone.<sup>61</sup> In a murine model of SCCHN, the combination of gefitinib and celecoxib demonstrated a significant delay in tumor progression over either agent alone and resulted in a significant decrease in PGE<sub>2</sub> production and downregulation of EGFR, ERK, VEGF, and Ki-67 expression.<sup>71</sup> A phase I trial of gefitinib and celecoxib in recurrent or metastatic SCCHN demonstrated a 22% response rate with no dose-limiting toxicities.<sup>72</sup> These results are promising and suggest a potential enhancement of gefitinib activity in recurrent/metastatic SCCHN.

The addition of COX-2 inhibitors to radiation in the treatment of SCCHN is also of interest. Prostaglandin production can have radioprotective effects through such mechanisms as enhanced DNA damage repair, decreased apoptosis in response to radiotherapy and promotion of cellular proliferation after radiotherapy. In preclinical investigation, this effect has been abrogated by the addition of nonsteroidal anti-inflammatory drugs.<sup>22,73-76</sup> Moreover, the addition of celecoxib to radiotherapy or chemoradiotherapy results in inhibition of sublethal damage repair and decreased expression of nuclear factor-kappa B, a negative regulator of apoptosis whose expression can be induced by radiation.<sup>22</sup>

### **Targeting VEGF or Its Receptor**

VEGF and its receptor play a key role in the angiogenesis associated with cancer and cancer progression. Importantly, VEGF levels are elevated in invasive SCCHN tumors and VEGF subtype A correlates with microvessel density and poor prognosis in SCCHN.<sup>77-80</sup> Traditional cytotoxic agents including cisplatin and carboplatin increase VEGF expression in SCCHN tumors.<sup>81</sup> Thus, investigating ways to block VEGF is warranted. While specific VEGF inhibitors exist, VEGF remains linked to activation of the COX-2 and EGFR pathways, providing potential adjunct means of blocking the effect of VEGF on carcinogenesis and tumor progression.

Angiogenesis represents a complex balance between proangiogenic and antiangiogenic factors. HIF- $\alpha$  is a transcription factor that is upregulated under hypoxic conditions and stimulates neovascularization. SCCHN tumors demonstrate increased HIF-1- $\alpha$  protein and a significant association between HIF-1- $\alpha$  expression and VEGF expression.<sup>82</sup> In renal cell carcinoma, TGF- $\alpha$ , a ligand for the EGFR, is induced by HIF-1- $\alpha$ , providing a link between a proangiogenic pathway and the EGFR.<sup>83</sup> Moreover, EGFR blockade can significantly decrease VEGF expression.<sup>84,85</sup> Thus, EGFR inhibition alone may result in decreased angiogenesis. In fact, gefitinib and cetuximab demonstrate a dose-dependent inhibition of microvessel density and VEGF expression in preclinical models.<sup>86-89</sup> However, maximal antiangiogenic properties may be realized from the combined blockade of VEGF/VEGFR and EGFR.

### ***Combined Targeting of EGFR and VEGF/VEGFR***

The three VEGFR tyrosine kinase subtypes vary in their target cells and effects. Though VEGFR-1 and VEGFR-3 are involved in endothelial and monocyte motility and lymphoangiogenesis, respectively, VEGFR-2 plays a major role in angiogenesis and cell proliferation.<sup>90-93</sup> Bevacizumab (Avastin, Genentech) is a recombinant humanized anti-VEGF monoclonal antibody that has been introduced in cancer therapy and is currently approved by the US Food and Drug Administration for use with chemotherapy in metastatic colorectal cancer.<sup>94</sup> Bevacizumab prevents the interaction of VEGF with VEGFR-1 and VEGFR-2. Multiple randomized trials<sup>95,96</sup> have shown promising results with the use of bevacizumab in combination with chemotherapy regimens in various solid tumor malignancies. Studies in SCCHN are ongoing.

Combined targeting of important signaling pathways may enhance therapeutic efficacy.<sup>97</sup> There is a strong rationale for combined EGFR and VEGF blockade for the treatment of head and neck cancer. EGFR inhibition has

**Table 2.** Selected Ongoing Trials of Novel Agents in SCCHN

Drug	Phase of Trial	Therapy	Sponsor	Population
Bevacizumab	I/II	Erlotinib and cetuximab ± bevacizumab	Institute for Drug Development	Metastatic or unresectable renal cell, colorectal, SCCHN, pancreatic or non-small cell lung cancer
Bevacizumab	II	Pemetrexed and bevacizumab	University of Pittsburgh/Hillman Cancer Center	Metastatic or locally recurrent SCCHN
Bevacizumab	II	Bevacizumab in combination with docetaxel and radiotherapy	Case Comprehensive Cancer Center	First-line stage III or IV SCCHN
Lapatinib	II	Single-agent lapatinib	University of Chicago Cancer Research Center	Recurrent and/or metastatic SCCHN
Lapatinib	II	Single-agent lapatinib	University of Virginia Cancer Center	Recurrent and/or metastatic SCCHN

SCCHN = squamous cell carcinoma of the head and neck.

an effect on angiogenesis and results in downregulation of VEGF.<sup>98</sup> Preclinical data suggest that resistance to EGFR inhibitors is associated with increased VEGF levels.<sup>99</sup> This has also been demonstrated in a clinical study in which intratumoral mRNA levels of VEGF were inversely associated with cetuximab response in patients with advanced colorectal cancer.<sup>100</sup> Preclinical studies have reported enhanced inhibition of tumor growth with combined anti-EGFR and antiangiogenesis blockade in various tumor models, including head and neck cancer.<sup>84,101,102</sup> To that end, Vokes and coworkers<sup>103</sup> conducted a phase I/II trial to evaluate the safety and potential activity of bevacizumab in combination with erlotinib in patients with recurrent or metastatic SCCHN. In the phase I component of the study, erlotinib and bevacizumab could be safely given at full single-agent doses of 150 mg daily and 15 mg/kg every 3 weeks, respectively.<sup>104</sup> Results from the phase II study component showed a response rate of 14%, stable disease in 54% of patients, median progression-free survival of 3.8 months, and median overall survival of 6.8 months.<sup>103</sup> Antitumor activity with erlotinib/bevacizumab appears to be superior to that of single-agent erlotinib as reported in a previous phase II trial.<sup>47</sup>

AZD2171 (AstraZeneca), an oral, highly potent VEGFR tyrosine kinase inhibitor, has also demonstrated promise in preliminary studies. Treatment of human tumor xenografts with AZD2171 demonstrated dose-dependent growth inhibition and a reduction in microvessel den-

sity.<sup>105</sup> A phase I trial of the combination of AZD2171 and gefitinib is now recruiting patients with several tumor types, including refractory metastatic SCCHN.

#### **Dual Inhibitors**

Molecules that are dual inhibitors have also emerged. ZD6474 (Zactima, AstraZeneca), a dual VEGFR-2 and EGFR tyrosine kinase inhibitor, has demonstrated activity in cancer cells that have an acquired resistance to anti-EGFR therapy after continued dosing. Phase II trials of ZD6474 in SCCHN are planned.

#### **Targeting Raf Kinase**

Although not a specific EGFR or VEGF inhibitor, one other agent is important in this setting. Sorafenib (Nexavar, Bayer), a Raf kinase inhibitor, is now being evaluated in clinical trials of refractory SCCHN. The Ras/Raf/MEK/ERK pathway represents a common downstream pathway for several key growth factor tyrosine kinases, including VEGFR-2 and the EGFR. Ras activates the Raf/MEK/ERK pathway by activation of Raf kinase, which then phosphorylates and activates MEK followed by ERK. Of note, activated MEK has transforming ability as well as antiapoptotic effects. Activated ERK modulates genes involved in cell proliferation, differentiation, angiogenesis, and apoptosis. Although SCCHN does not demonstrate a high frequency of Ras mutations,

the tumors overexpress growth factor receptors involved in the Ras/Raf/MEK pathway, such as EGFR.<sup>106</sup> Trials in SCCHN are planned.

## Summary

Although the treatment of SCCHN has realized recent advances in terms of local regional control and progression-free survival using traditional modalities, the emergence of novel agents provides an exciting opportunity to improve on these achievements through the incorporation of these agents into the curative therapy of locally advanced SCCHN. Multiple ongoing and planned trials of novel agents should provide exciting new data on how to successfully fight this disease (Table 2). Strategies include the addition of these novel agents to induction chemotherapy, concurrent chemoradiotherapy, and/or adjuvant therapy. Incorporating tissue biomarkers into these studies will add to the understanding of SCCHN biology and mechanism of action of novel agents as well as to the most appropriate use of these agents.

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