

# Novel therapies in metastatic head and neck squamous cell carcinoma

Anne S. Tsao, MD

Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

The diagnosis of recurrent or metastatic head and neck squamous cell cancer (HNSCC) confers an overall survival time of 6–9 months. Traditionally, frontline chemotherapy regimens consisted of platinum-based doublet regimen with either 5-fluorouracil or a taxane. However, in recent years, the addition of novel biologic agents has provided new options for the management of HNSCC. The following review will highlight the major studies that are reshaping the therapeutic landscape of HNSCC.

**R**ecurrent or metastatic head and neck squamous cell carcinoma (HNSCC) is difficult to treat, with a median overall survival time of 6–9 months and a median progression-free survival time of 2–4 months.<sup>1,2</sup> In the past few years, the standard approach to first-line treatment of metastatic HNSCC in patients having a good performance status was to use a platinum-based doublet regimen with either 5-fluorouracil (5-FU) or a taxane.<sup>1–4</sup> These combination regimens demonstrate higher response rates, although randomized phase III trials comparing the combination of cisplatin and 5-FU with single-agent cisplatin, 5-FU, or methotrexate do not confirm an overall survival benefit.<sup>1,2</sup> It is therefore acceptable to use single-agent chemotherapy or doublet regimens in the first-line treatment of metastatic HNSCC. However, in recent years, the advent of novel biologic agents has provided new options for the management of this cancer.

Several novel therapeutics are under investigation in metastatic HNSCC. To date, the ones that have had the greatest impact on therapy include the monoclonal antibodies and tyrosine kinase inhibitors that target the epidermal growth factor receptor (EGFR). Inhibitors of vascular endothelial growth factor (VEGF) and its receptor are under investigation as well, since other solid tumor types, such as lung and colorectal cancers, have had significant improvement in survival with the addition of antiangiogenic therapy. The main EGFR inhibitors include cetuximab (Erbix), erlotinib (Tarceva), and gefitinib (Iressa). The main VEGF inhibitor is the monoclonal antibody bevacizumab

(Avastin), although new multitargeted oral antiangiogenic agents, such as sunitinib (Sutent) and cediranib (Recentin, AZD2171), are also being investigated. This review summarizes and discusses the latest clinical trials using these agents in the setting of metastatic HNSCC.

## EGFR inhibitors

It is well established that EGFR is an important target in HNSCC treatment. It is reasonable to assert that all patients with HNSCC should receive EGFR inhibitor therapy at some point in their treatment. However, the optimal time and sequence, as well as whether these agents should be combined with chemotherapy, remain unclear in the metastatic or recurrent setting.

Today, inhibition of EGFR can be achieved with both monoclonal antibodies and tyrosine kinase inhibitors. Cetuximab, an immunoglobulin G (IgG) monoclonal antibody, has been developed the most and is farthest along in HNSCC. It is already approved for use in HNSCC in the locally advanced setting to be given concurrently with radiotherapy.<sup>5</sup> Erlotinib, an oral small molecule tyrosine kinase inhibitor, is also under active investigation, with promising early results. Table 1 summarizes the main findings from trials of these agents in HNSCC populations.

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Correspondence to: Anne S. Tsao, MD, Director, Mesothelioma Program, Assistant Professor, Department of Thoracic/Head & Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; telephone: 713-792-6363; fax: 713-792-1220; e-mail: astsao@mdanderson.org.

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TABLE 1

## Selected trials of EGFR inhibitors in metastatic HNSCC

Trial	EGFR inhibitor	Additional chemotherapy	Patient population	Number of patients	Response rate	Median PFS (months)	Median OS (months)
Phase III							
Vermorken et al <sup>8</sup> (EXTREME)	Cetuximab	Platinum + 5-FU	Chemotherapy naive	222	36%	5.6	10.1 ( <i>P</i> = 0.04)
	Placebo	Platinum + 5-FU		220	20%	3.3	
Burtneß et al <sup>6</sup>	Cetuximab	Cisplatin	Chemotherapy naive	57	26%	4.2	9.2 ( <i>P</i> = 0.21)
	Placebo	Cisplatin		60	10%	2.7	
Phase II							
Herbst et al <sup>12</sup>	Cetuximab	Cisplatin <sup>a</sup>	Platinum failure	51 (SD)	18%	7.4	11.7
				25 (PD1)	20%	4.2	6.1
				54 (PD2)	6%	4.1	4.3
Baselga et al <sup>13</sup>	Cetuximab	Platinum	Platinum failure	96	10%	85 days	183 days
Kim et al <sup>9</sup>	Erlotinib	Cisplatin + docetaxel	Chemotherapy naive	50	68%	6	11
Siu et al <sup>7</sup>	Erlotinib	Cisplatin	Chemotherapy naive	51	21%	3.3	7.9
Soulieres et al <sup>11</sup>	Erlotinib	—	≤ One prior regimen <sup>b</sup>	115	4.3%	9.6 weeks	6
Cohen et al <sup>15</sup>	Gefitinib (500 mg)	—	≤ One prior regimen	52	10.6%	3.4	8.1
Cohen et al <sup>16</sup>	Gefitinib (250 mg)	—	Unlimited prior therapy	70	1.4%	1.8	5.5

EGFR = epidermal growth factor receptor; HNSCC = head and neck squamous cell carcinoma; PFS = progression-free survival; OS = overall survival; 5-FU = 5-fluorouracil

<sup>a</sup> Patients received two cycles of either cisplatin + paclitaxel or cisplatin + 5-FU. Patients with a complete or partial response continued on chemotherapy, whereas those with stable disease (SD) or whose disease progressed (PD1, PD2) went onto cisplatin + cetuximab.

<sup>b</sup> Patients were eligible to enroll if they had prior chemotherapy for definitive treatment within the past 6 months and had up to one prior palliative treatment.

### EGFR inhibitors as first-line therapy

Doublet regimens consisting of platinum agents combined with the EGFR inhibitors have been investigated in patients who are chemotherapy naive.<sup>6,7</sup> ECOG 5397, a phase III trial, compared single-agent cisplatin with the combination of cisplatin and cetuximab and reported higher response rates with the doublet regimen (26% vs 10%; *P* = 0.03).<sup>6</sup> However, there was no statistically significant improvement in median progression-free (4.2 months vs 2.7 months; *P* = 0.09) and overall survival (9.2 months vs 8.0 months; *P* = 0.21), although the trial was not appropriately powered to detect these survival differences. The combination of erlotinib with cisplatin has been evaluated in a phase I/II trial, which showed a median progression-free survival duration of 3.3 months and an overall survival duration of 7.9 months.<sup>7</sup> In this study, Siu et al reported a low toxicity rate, with only 3% of patients having grade 3 or

higher fatigue and lymphopenia.<sup>7</sup> Additional, grade 1/2 toxicities reported included rash, hypomagnesemia, anemia, fatigue, lymphopenia, and dry skin. As the EGFR-platinum combinations have not definitively demonstrated a significant survival benefit, they have not been intensively explored as a standard first-line treatment for metastatic disease.

Recently, triplet regimens in which EGFR inhibitors are added to doublet chemotherapy have shown promising efficacy in the first-line setting. At the 2007 meeting of the American Society of Clinical Oncology (ASCO), Vermorken et al<sup>8</sup> presented results of a multicenter European phase III trial called the EXTREME trial. This trial randomized 442 patients with recurrent or metastatic HNSCC to receive either platinum-5-FU with placebo (PF) or platinum-5-FU with cetuximab (PF-C). Patients enrolled on this trial were required to be chemotherapy-naïve unless chemotherapy

was used for definitive treatment and given more than 6 months previously. The platinum agent administered was either cisplatin (100 mg/m<sup>2</sup>) or carboplatin area under the concentration-versus-time curve (AUC 5) on day 1 every 3 weeks. The 5-FU was administered at a dosage of 1,000 mg/m<sup>2</sup> per day for 4 days, and the cetuximab was given as a loading dose of 400 mg/m<sup>2</sup>, then by weekly infusions at 250 mg/m<sup>2</sup>. A maximum of 6 cycles of chemotherapy were allowed, and the cetuximab was continued after the 6 cycles of chemotherapy as a maintenance regimen until disease progression or unacceptable toxicity occurred. No crossover was allowed on this trial.

In all, 222 patients were randomized to receive PF-C and 220 patients were randomized to receive PF. There were no significant differences between the two arms in terms of the median number of chemotherapy cycles, removal from study because

of adverse events, and death during therapy or within 30 days of the last therapy. The only difference in grade 3/4 toxicities was a higher incidence in the cetuximab arm of sepsis ( $P = 0.02$ ), hypomagnesemia ( $P = 0.05$ ), and skin rash ( $P < 0.001$ ), as well as four cases of infusion-related reactions. The median duration of cetuximab treatment was 18 weeks, with 100 patients proceeding from the concurrent chemotherapy phase to the cetuximab maintenance phase; the median duration of maintenance therapy was 11 weeks. All three efficacy parameters favored the cetuximab-containing therapy; specifically, patients receiving that therapy had a higher response rate (36% vs 20%;  $P < 0.001$ ), better progression-free survival (hazard ratio, 0.54;  $P < 0.001$ ), and better overall survival (hazard ratio, 0.8;  $P = 0.04$ ). Moreover, both the progression-free and overall survival benefit was seen across most of the subgroups analyzed. The EXTREME trial is therefore the first phase III study in metastatic or recurrent HNSCC to show a survival benefit over platinum doublet combination regimens.

A separate phase II study<sup>9</sup> analyzed the benefit of a triplet regimen using chemotherapy combined with erlotinib. This single-institution trial conducted at The University of Texas M. D. Anderson Cancer Center enrolled patients with metastatic or recurrent HNSCC who had not received any prior EGFR-targeted therapy nor any prior chemotherapy unless it was used as definitive therapy more than 6 months before the time of enrollment. All patients on this trial received cisplatin and docetaxel (Taxotere) every 3 weeks for 6 cycles maximum and also received erlotinib daily throughout the chemotherapy and then continued erlotinib as maintenance therapy until disease progression or unacceptable toxicity occurred. The first six patients received lower doses of docetaxel (60

mg/m<sup>2</sup>) and erlotinib (100 mg orally daily), but when no toxicity was seen, the remaining patients received 75 mg/m<sup>2</sup> of cisplatin, 75 mg/m<sup>2</sup> of docetaxel, and 150 mg of erlotinib orally per day. Growth factor support was recommended with this regimen.

Fifty patients were enrolled, and the most noteworthy toxicities were grade 3/4 neutropenia (64%) and febrile neutropenia (10%). There was a 14% rate each of grade 3/4 anemia, diarrhea, nausea, and dehydration. In addition, 8% of patients experienced grade 3/4 skin toxicity. The efficacy data ( $n = 47$ ) revealed an 8% complete response rate, a 60% partial response rate, and a 28% rate of stable disease, for an overall response rate of 68%. Of the 25 patients with recurrent disease in a previously radiated field, 3 had a complete response, 11 had a partial response, and 8 had stabilization of their disease. The progression-free survival duration was 6 months, the overall survival duration was 11 months, and the 1-year survival rate was 48%. A randomized phase II trial is being planned to further evaluate this regimen's safety and efficacy.

#### *EGFR inhibitors in pretreated HNSCC*

Studies using single-agent EGFR inhibitors in patients with HNSCC who have been previously treated typically show response rates of 4%–13%.<sup>10,11</sup> Three phase II trials have demonstrated that cetuximab has activity as a single agent<sup>10</sup> or in combination with platinum agents.<sup>12,13</sup> Vermorken et al<sup>14</sup> conducted an analysis of 278 patients who had experienced progression on platinum-based therapy from these three separate prospective trials<sup>10,12,13</sup> to clarify the role of cetuximab in the platinum-refractory population. In this analysis, cetuximab-treated patients were compared with a retrospective cohort of patients who received best supportive care or other chemotherapy (single-agent or doublet therapy).

Cetuximab monotherapy yielded a response rate of 13%, a disease control rate of 46%, a median time to progression of 2.3 months, and a median overall survival duration of 5.9 months. It is important to note that in this cohort of patients, 53 patients who progressed on cetuximab monotherapy went on to receive platinum-cetuximab therapy.<sup>10,14</sup> Cetuximab with platinum therapy (cisplatin or carboplatin) yielded similar results: a response rate of 10%, a disease control rate of 53%, a median time to progression of 2.8 months, and a median overall survival duration of 6.1 months. In contrast, patients who received chemotherapy alone had a response rate of 0%, a disease control rate of 9%, and a median overall survival duration of 3.6 months. All three trials reported grade 3/4 toxicities with the EGFR inhibitor-containing therapy, but the rates were  $< 8\%$  for each, with the exception of the 4%–17% incidence of fatigue or malaise. There was a 3% incidence of grade 3/4 skin rash. Taken together, these findings suggest that patients with HNSCC who have progression on platinum therapy may have a clinical benefit with cetuximab (as monotherapy or combined with platinum) in the salvage setting.

Both erlotinib and gefitinib have been studied in the salvage setting of HNSCC. Soulieres et al<sup>11</sup> reported that in a phase II monotherapy trial, erlotinib (150 mg daily) yielded a 4.3% response rate, a median progression-free survival duration of 9.6 weeks (2.2 months), and an overall survival duration of 6 months.

Cohen et al<sup>15,16</sup> reported two phase II trials that used different doses of gefitinib as monotherapy. In the first trial, which used 500 mg of gefitinib daily, patients with metastatic or recurrent HNSCC were eligible if they had received no more than one prior systemic treatment (for definitive or palliative purposes).<sup>15</sup> Eighty-five percent of the patients enrolled had been exposed to che-

TABLE 2

## Early results from antiangiogenic agent–based regimens in metastatic HNSCC

Trial	Regimen	Patient population	Arm	Number of patients	Response rate	Grade 3/4 toxicities
Kies et al <sup>19</sup>	Cetuximab + bevacizumab	≤ One prior regimen <sup>a</sup>		18	27%	Proteinuria, dysphagia, stomatitis, hypertension, rash, fatigue, airway obstruction
Feinstein et al <sup>20</sup>	Pemetrexed + bevacizumab	Chemotherapy naïve <sup>a</sup>		25	36%	Bleeding, <sup>b</sup> dysphagia, fatigue, neutropenia, hypokalemia, hyponatremia, infection
Choong et al <sup>21</sup>	Sunitinib	≤ Two prior regimens	A B	15 7	8% 0%	Lymphopenia, mucositis, epistaxis, pulmonary hemorrhage, fatigue, nausea/vomiting, gastrointestinal bleeding, superficial tumor bleed
Machiels et al <sup>22</sup>	Sunitinib	Platinum failure		38	3%	16% grade 3–5 bleeds, four grade 5 head and neck tumor bleeds, 15 tumor skin ulcerations and/or tumor fistula, fatigue, anorexia, thrombocytopenia, anemia, stomatitis, vomiting, diarrhea
Saura et al <sup>23</sup>	Cediranib	< Two prior therapies		15	20%	Proteinuria, fatigue/asthenia, diarrhea, hypertension, one tumor hemorrhage, one tracheoesophageal fistula

HNSCC = head and neck squamous cell carcinoma

<sup>a</sup> Patients were allowed prior chemotherapy if it was utilized for definitive treatment and was administered over 6 months prior to enrollment on the study.

<sup>b</sup> One fatal bleed (grade 5) occurred in a patient with tracheal invasion. In two additional cases, the patient had tumor-related bleeding. The fourth case was a gastric bleed due to a percutaneous fluoroscopic gastrostomy-related ulcer.

therapy either concurrent with radiotherapy (43%) or as initially part of radiotherapy and then again for recurrent disease (33%) or for recurrent or metastatic disease alone (25%). The response rate was 10.6%, the progression-free survival duration was 3.4 months, and the overall survival duration was 8.1 months.

In the second trial, which used 250 mg of gefitinib daily, patients who had received an unlimited number of prior therapies were allowed to enroll.<sup>16</sup> The benefit was markedly less, with a response rate of 1.4%, a progression-free survival duration of 1.8 months, and an overall survival duration of 5.5 months. In the subgroup analysis, the number of prior therapies did not affect the efficacy results. Based on the findings from these two trials, it is suggestive that the EGFR tyrosine kinase inhibitors may have a dose–response effect.

Other EGFR inhibitors in early trials include two irreversible tyrosine kinase inhibitors: EKB-569 and CI-1033. In addition, the reversible pan-HER tyrosine kinase inhibi-

tor GW2016 is being evaluated.

### Angiogenesis inhibitors

Antiangiogenic treatment is becoming a fundamental strategy in solid tumor oncology. Inhibitors of VEGF and its receptor, VEGFR, have proven efficacy in non-small cell lung cancer (NSCLC) and in colorectal cancer, breast cancer, and renal cell carcinoma. However, early trials in NSCLC demonstrated that antiangiogenic agents had the potential to cause fatal pulmonary hemoptysis in patients with squamous cell carcinoma.<sup>17</sup> Bevacizumab was studied in a large randomized front-line NSCLC trial called ECOG 4599 that excluded squamous cell carcinoma and demonstrated an improvement in response rate, progression-free survival, and overall survival when combined with carboplatin–paclitaxel over the chemotherapy alone.<sup>18</sup> This triplet regimen was subsequently approved for use in chemotherapy-naïve NSCLC patients who do not have squamous cell carcinoma histology.<sup>18</sup>

Given the concerns about potential

life-threatening bleeding, antiangiogenic agents have not been extensively studied in HNSCC. Nonetheless, preliminary results of five clinical trials using VEGF and VEGFR inhibitors were presented at the 2008 and 2009 meetings of ASCO.<sup>19–23</sup> These early results with small numbers of patients, summarized in Table 2, show an elevated rate of bleeding toxicity,<sup>20–23</sup> although one trial of 18 patients did not report any bleeding complications.<sup>19</sup>

The first trial, by Kies et al,<sup>19</sup> tested dual inhibition of VEGF and EGFR with the combination of bevacizumab and cetuximab in patients with HNSCC who had been previously treated (n = 15 evaluable). This trial found a 27% partial response rate and a 53% rate of stable disease. Although these patient numbers are small, the initial response rate was higher than that seen with cetuximab monotherapy in patients with HNSCC treated on a salvage basis.<sup>10,14</sup> In a separate, ongoing trial, bevacizumab combined with erlotinib for metastatic HNSCC is under investigation. It remains to

be seen whether this trial will show a benefit in HNSCC, because in the pretreated NSCLC population, a large phase III trial of bevacizumab-erlotinib (BETA Lung) found that the combination improved progression-free survival but not overall survival.<sup>24</sup>

In the second trial presented at ASCO 2008, bevacizumab was combined with pemetrexed (Alimta) in chemotherapy-naïve patients with HNSCC.<sup>20</sup> Pemetrexed targets the enzymes thymidylate synthase, glycylamide ribonucleotide formyltransferase (GARFT), and dihydrofolate reductase (DHFR). This study reported a 16% rate of bleeding complications, including one fatality, in the initial 25 patients. The preliminary efficacy results reported were a 36% response rate, a 59% rate of stable disease, and a median time to disease progression of 7 months. Although the patients studied had not received any chemotherapy, these results are surprisingly good, as in the NSCLC arena, pemetrexed has recently been shown in large clinical trials not to be as efficacious in the subset of patients having squamous cell carcinoma.<sup>25,26</sup> The proposed explanation is that squamous cell cancers produce such high levels of thymidylate synthase that it counteracts the effect of pemetrexed and is an intrinsic mechanism of resistance.<sup>27</sup> It is possible that bevacizumab may confer substantial benefit when added to chemotherapy in patients with HNSCC.

In the past two ASCO meetings, two salvage clinical trials evaluated sunitinib, an inhibitor of VEGFR-1, -2, and -3; the platelet-derived growth factor receptor (PDGFR)  $\alpha/\beta$ ; RET; Kit; and Flt-3 have been presented.<sup>21,22</sup> In the ASCO 2008 trial<sup>21</sup>, sunitinib was given orally at 50 mg daily for 4 weeks followed by a 2-week break, for a total cycle length of 6 weeks. All patients had been pretreated with two or fewer prior therapies. They were divided into two cohorts: cohort A, for

patients with an ECOG performance status score of 0 or 1, and cohort B, for patients with an ECOG performance status score of 2. There were 8 total cases of bleeding among the first 22 patients (3 cases of epistaxis, 2 of pulmonary hemorrhage, 2 of gastrointestinal bleeding, and 1 of superficial tumor bleeding). In cohort A, the response rate was 8% and the rate of stable disease was 25%; in cohort B, there were no responses, although 29% of patients had stable disease. The median overall survival duration was 19 weeks, and the time to disease progression was 10 weeks. As cohort A did not meet its primary endpoint, the trial was closed to accrual.

At ASCO 2009, sunitinib was administered at 37.5 mg/d every 6 weeks in a phase II trial called GORTEC 2006-01.<sup>22</sup> All patients had failed to respond to prior platinum therapy. Thirty-eight patients were evaluable for efficacy and only one patient had a confirmed partial response. The median progression-free survival was 60 days, and median overall survival was 102 days. There was a significant amount of grade 3/4 toxicity (32% fatigue; 16% anorexia; 13% thrombocytopenia; 11% anemia; and 8% each of stomatitis, vomiting, and diarrhea). There was a reported 16% grade 3–5 bleeding toxicity. Four patients had grade 5 bleeding, three of whom had tumor within < 5 mm of the carotid artery. Fifteen patients had reported complications with worsened tumor skin ulceration and/or development of tumor fistula.<sup>22</sup>

The last study administered single agent cediranib at 30 mg daily every 3 weeks to patients with metastatic/recurrent HNSCC and NSCLC who had fewer than two prior therapies.<sup>23</sup> Cediranib targets VEGFR and PDGFR. In this trial, there were 15 HNSCC patients evaluable for efficacy and 3 patients with a partial response. The most common toxicities reported were proteinuria, fatigue, asthenia, diarrhea, and hypertension.

Forty-two percent of the patients experienced grade 3 or higher toxicity, with one patient each developing tumor hemorrhage and a tracheoesophageal fistula. There were no reported deaths at the time of presentation.

As these studies had small sample sizes,<sup>19–23</sup> conclusions cannot be drawn on the benefit of antiangiogenic treatment in HNSCC. However, these early trials suggest that there may be an increased risk of bleeding toxicity. Further evaluation and vigilance regarding the toxicities are required to ascertain whether the benefit is worth the risk.

### Other agents

Other agents that have been investigated in early-phase clinical trials in head and neck cancers include farnesyl transferase inhibitors (lonafarnib, tipifarnib),<sup>28,29</sup> cyclin kinase inhibitors (flavopiridol),<sup>30,31</sup> intratumorally injected adenoviral vectors (Onyx-015, Ad-p53),<sup>32–34</sup> cyclooxygenase-2 inhibitors (celecoxib [Celebrex]),<sup>35–37</sup> mammalian target of rapamycin (mTOR) inhibitors,<sup>38</sup> insulin-like growth factor receptor (IGFR) inhibitors, histone deacetylase inhibitors, Src kinase inhibitors,<sup>39</sup> and heat shock protein 90 inhibitors. Of these agents, the IGFR inhibitors appear to be the most promising.<sup>40,41</sup> Initial evidence from phase II trials suggests that patients with squamous cell carcinoma of the lungs have high response rates to inhibitors of this target.<sup>42</sup> Trials of IGFR inhibitors in the aerodigestive tumors are ongoing.

### Conclusion

Although the EXTREME trial showed that first-line triplet regimens containing cetuximab have a clinical benefit in patients with recurrent or metastatic HNSCC, it is unclear whether sequencing chemotherapy with EGFR, targeted therapy would achieve a similar survival benefit while preserving quality of life. Therefore, for patients with metastatic

HNSCC undergoing palliative therapy, the standard treatment practice for patients with metastatic HNSCC includes single-agent therapy, platinum doublets, and now triplet regimens. Decisions on therapy currently should be based on a patient's performance status and comorbidities, as unfortunately there are no current validated biomarkers that have predictive ability for targeted EGFR therapy in HNSCC. At ASCO 2009, an analysis of EGFR fluorescent in situ hybridization (FISH) was performed on tumor samples from the EXTREME trial and showed that there was no predictive value for cetuximab.<sup>43</sup> Unlike colorectal cancer and NSCLC, HNSCC tumors do not typically have EGFR mutations and less than 3% of HNSCC tumors have K-RAS mutations. As there are no current molecular biomarkers to aid in treatment decisions, the optimal timing for use of an EGFR inhibitor is unknown at this time, but it is safe to say that all patients with metastatic HNSCC should receive one of these agents at some point in their therapy.

Antiangiogenic therapy has proven clinical efficacy in other types of epithelial tumors. However, bleeding complications often arise in the squamous cell carcinoma population, and it remains unclear how to prevent these adverse events. At this time, antiangiogenic treatments should be given to patients with HNSCC only in the setting of a clinical trial and with appropriate education of the patients about the potential risks.

The addition of targeted therapies will likely be crucial to improving HNSCC treatment. The optimal first-line regimen, exact sequencing of agents in first-line or second-line therapy, and whether biologics should be used in combination with chemotherapy remain unclear at this time. However, with the recent progress made with the EGFR inhibitors and the appearance of promising agents

such as the IGFR inhibitors, the future appears brighter for patients with metastatic or recurrent HNSCC.

#### References

- Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992;10:1245-1251.
- Jacobs C, Lyman G, Velez-Garcia E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992;10:257-263.
- Glisson BS, Murphy BA, Frenette G, et al. Phase II trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. *J Clin Oncol* 2002;20:1593-1599.
- Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group phase II study. *Cancer Invest* 2007;25:182-188.
- Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567-578.
- Burtness B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005;23:8646-8654.
- Siu LL, Soulieres D, Chen EX, et al. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital phase II consortium and National Cancer Institute of Canada Clinical Trials Group study. *J Clin Oncol* 2007;25:2178-2183.
- Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116-1127.
- Kim E, Tsao A, William W, et al. A phase II study of erlotinib in combination with cisplatin and docetaxel in metastatic or recurrent head and neck squamous cell carcinoma. *J Clin Oncol* 2007;25(18S):6013.
- Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol*

2007;25:2171-2177.

- Soulieres D, Senzer NN, Vokes EE, et al. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004;22:77-85.
- Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005;23:5578-5587.
- Baselga J, Trigo JM, Bourhis J, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005;23:5568-5577.
- Vermorken JB, Herbst RS, Leon X, et al. Overview of the efficacy of cetuximab in recurrent and/or metastatic squamous cell carcinoma of the head and neck in patients who previously failed platinum-based therapies. *Cancer* 2008;112:2710-2719.
- Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2003;21:1980-1987.
- Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res* 2005;11:8418-8424.
- Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184-2191.
- Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542-2550.
- Kies M, Gibson M, Kim S, et al. Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma (SCCHN): an interim analysis. *J Clin Oncol* 2008;26(15S):6072.
- Feinstein T, Raez L, Rajaseenan K, et al. Pemetrexed (P) and bevacizumab (B) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC): updated results of a phase II trial. *J Clin Oncol* 2008;26(15S):6069.
- Choong N, Cohen E, Kozloff M, et al. Phase II trial of sunitinib in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol* 2008;26(15S):6064.
- Machiels J, Henry S, Zanetta S, et al. A phase II study of sunitinib in patients with recurrent and/or metastatic squamous head and neck carcinoma GORTEC 2006-01. *J Clin*

Oncol 2009;27(15S):6024.

23. Saura C, Baselga J, Herbst RS, et al. Antitumor activity of cediranib in patients with metastatic or recurrent head and neck cancer or recurrent NSCLC: an open label exploratory study. *J Clin Oncol* 2009;27(15S): 6023.

24. Hainsworth J, Herbst RS. A phase III, multicenter, placebo-controlled, double-blind randomized clinical trial to evaluate the efficacy of bevacizumab (Avastin) in combination with erlotinib (Tarceva) compared with erlotinib alone for treatment of advanced NSCLC after failure of standard frontline chemotherapy (BETA). *J Thorac Oncol* 2008;3(suppl 4):S302.

25. Ciuleanu T, Brodowicz T, Belani C, et al. Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: a phase III study. *J Clin Oncol* 2008;26(15S):8011.

26. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.

27. Ceppi P, Volante M, Saviozzi S, et al. Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. *Cancer* 2006;107:1589–1596.

28. Kim ES, Kies M, Herbst RS. Novel therapeutics for head and neck cancer. *Curr Opin Oncol* 2002;14:334–342.

29. Yang C, Kies M, Glisson B, et al. A phase II study of lonafarnib (SCH66336) in patients with chemo-refractory advanced head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol* 2005;23(16S):5565.

30. Patel V, Senderowicz AM, Pinto D Jr, et al. Flavopiridol, a novel cyclin-dependent ki-

nase inhibitor, suppresses the growth of head and neck squamous cell carcinomas by inducing apoptosis. *J Clin Invest* 1998;102:1674–1681.

31. Kelland LR. Flavopiridol, the first cyclin-dependent kinase inhibitor to enter the clinic: current status. *Expert Opin Investig Drugs* 2000;9:2903–2911.

32. Ganly I, Kirn D, Eckhardt G, et al. A phase I study of Onyx-015, an E1B attenuated adenovirus, administered intratumorally to patients with recurrent head and neck cancer. *Clin Cancer Res* 2000;6:798–806.

33. Nemunaitis J, Khuri F, Ganly I, et al. Phase II trial of intratumoral administration of ONYX-015, a replication-selective adenovirus, in patients with refractory head and neck cancer. *J Clin Oncol* 2001;19:289–298.

34. Vatteemi E, Claudio PP. Adenoviral gene therapy in head and neck cancer. *Drug News Perspect* 2006;19:329–337.

35. Chen Z, Zhang X, Li M, et al. Simultaneously targeting epidermal growth factor receptor tyrosine kinase and cyclooxygenase-2, an efficient approach to inhibition of squamous cell carcinoma of the head and neck. *Clin Cancer Res* 2004;10:5930–5939.

36. Lippman SM, Gibson N, Subbaramaiah K, et al. Combined targeting of the epidermal growth factor receptor and cyclooxygenase-2 pathways. *Clin Cancer Res* 2005;11:6097–6099.

37. Wirth LJ, Haddad RI, Lindeman NI, et al. Phase I study of gefitinib plus celecoxib in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005;23:6976–6981.

38. Jimeno A, Kulesza P, Wheelhouse J, et al. Dual EGFR and mTOR targeting in squamous cell carcinoma models, and develop-

ment of early markers of efficacy. *Br J Cancer* 2007;96:952–959.

39. Johnson FM, Saigal B, Talpaz M, et al. Dasatinib (BMS-354825) tyrosine kinase inhibitor suppresses invasion and induces cell cycle arrest and apoptosis of head and neck squamous cell carcinoma and non-small cell lung cancer cells. *Clin Cancer Res* 2005;11:6924–6932.

40. Le Tourneau C, Siu LL. Molecular-targeted therapies in the treatment of squamous cell carcinomas of the head and neck. *Curr Opin Oncol* 2008;20:256–263.

41. Barnes CJ, Ohshiro K, Rayala SK, et al. Insulin-like growth factor receptor as a therapeutic target in head and neck cancer. *Clin Cancer Res* 2007;13:4291–4299.

42. Karp D, Paz-Ares L, Novello S, et al. High activity of the anti-IGF-IR antibody CP-751,871 in combination with paclitaxel and carboplatin in squamous NSCLC. *J Clin Oncol* 2008;26(15S):8015.

43. Licitra L, Rolland F, Bokemeyer C, et al. Biomarker potential of EGFR gene copy number by FISH in the phase III EXTREME study: platinum-based CT plus cetuximab in first-line recurrent/metastatic SCCHN. *J Clin Oncol* 2009;27(15S):6005.

#### ABOUT THE AUTHOR

*Affiliation:* Dr. Tsao is an Assistant Professor and Director of the Mesothelioma Program in the Department of Thoracic/Head & Neck Medical Oncology, the University of Texas M. D. Anderson Cancer Center, Houston, TX.

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