CLINICAL INVESTIGATION

Emerging therapies for head and neck cancer: review of the Phase II and III trials

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The purpose of this article is to summarize recent clinical trials with therapeutic intent of new systemic agents for head and neck squamous cell carcinoma (HNSCC), including molecularly targeted agents and novel cytotoxins. Recent therapeutic gains have been obtained by combining cetuximab, a monoclonal antibody targeting the EGF receptor (EGFR) with cytotoxins for incurable recurrent HNSCC and in curative-intent treatment with radiation for locoregionally advanced HNSCC. Building on this experience, further development of cetuximab in combination with other targeted therapies and in other settings with cytotoxins and radiation are highlighted. Beyond EGFR-targeted therapy, ongoing and or completed trials to investigate molecularly-targeted agents, including inhibitors of angiogenesis, the IGF-1 receptor and mammalian target of rapamycin are discussed alone, and combined with EGFR inhibitors, cytotoxins and/or radiation. The experience with recently studied cytotoxic agents is reviewed and their potential addition to the therapeutic armamentarium is discussed.

Keywords: EGF receptor • head and neck cancer • IGF receptor • molecular-targeted therapies • novel cytotoxins • VEGF

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The majority of patients diagnosed with head and neck squamous cell carcinoma (HNSCC) will present with locoregionally advanced disease for which aggressive multimodality therapy, including various combinations of surgery, radiation and chemotherapy generally offers less than 50% chance of long-term disease control and results in significant acute and chronic morbidity for patients. The addition of chemotherapy to the primary management of HNSCC does confer benefits in both locoregional and distant disease control and organ preservation rates, all of which can contribute to improved quality and quantity of survival. However, the effect is modest in degree, toxicity can be problematic and for patients in whom cure is not achieved, drug resistance in the recurrent tumor resulting in short survival is generally observed. Hence, clinical research in HNSCC has recently focused on the development of molecularly targeted agents and novel cytotoxics that may improve the therapeutic index. In this article, we will summarize the results of recent clinical trials with these emerging therapies.

Molecularly targeted agents

EGF receptor inhibitors

Based on preclinical data demonstrating the role of EGF receptor (EGFR) signaling in promotion of HNSCC growth and progression, and clinical data demonstrating that high levels of EGFR expression are associated with poor prognosis, the receptor is a rational therapeutic target [1,2]. Indeed, cetuximab, a monoclonal antibody to the extracellular ligand-binding domain of EGFR, is the only targeted agent approved by the US FDA for treatment of HNSCC. Other monoclonal antibodies to EGFR

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under investigation in HNSCC include panitumumab, zalutumumab and nimotuzumab. Small molecule oral tyrosine kinase inhibitors (TKIs) that target the intracellular catalytic domain of EGFR (e.g., gefitinib and erlotinib; Figure 1) have also been studied. Given that HER-2 is the preferred dimerization partner of EGFR and EGFR/HER-2 heterodimers may potentiate resistance to EGFR inhibitors [3], dual TKIs of both EGFR and HER-2, such as lapatinib (reversible inhibitor) and BIBW-2992 (Afatinib; irreversible inhibitor), have also been evaluated in HNSCC. Newer irreversible pan-HER TKIs, such as PF299804, bind to EGFR, HER-2 and HER-4, and are currently under investigation. The irreversible EGFR inhibitors, Afatinib and PF299804, have both also demonstrated preclinical activity against tumor cells bearing a truncated EGFR protein, lacking the extracellular ligand binding domain (EGFR variant III); this is present in approximately 40% of HNSCC [4,5].

EGFR inhibitors as monotherapy & in combination with radiation/chemoradiation

Cetuximab (C225, Erbitux®; ImClone systems), a chimeric monoclonal IgG1 antibody directed against the EGFR, was the first molecularly-targeted agent approved by a regulatory agency for use in combination with radiation for patients with locally advanced oropharynx, hypopharynx and larynx squamous cell carcinoma. The approval was based on a 10% increase in 3 year survival compared with radiation alone (55 vs 45%) in a landmark Phase III trial (median survival 49 vs 29.3 months; hazard ratio [HR]: 0.74 [95% CI: 0.57–0.97], p = 0.03; Table 1) [6]. This survival impact appears directly related to improved locoregional control with a 3 year rate of 47% with cetuximab compared with 34% with radiation alone. In a recent update of this trial, the survival impact persisted (46 vs 36%) at 5 years [7]. Furthermore, an exploratory subgroup

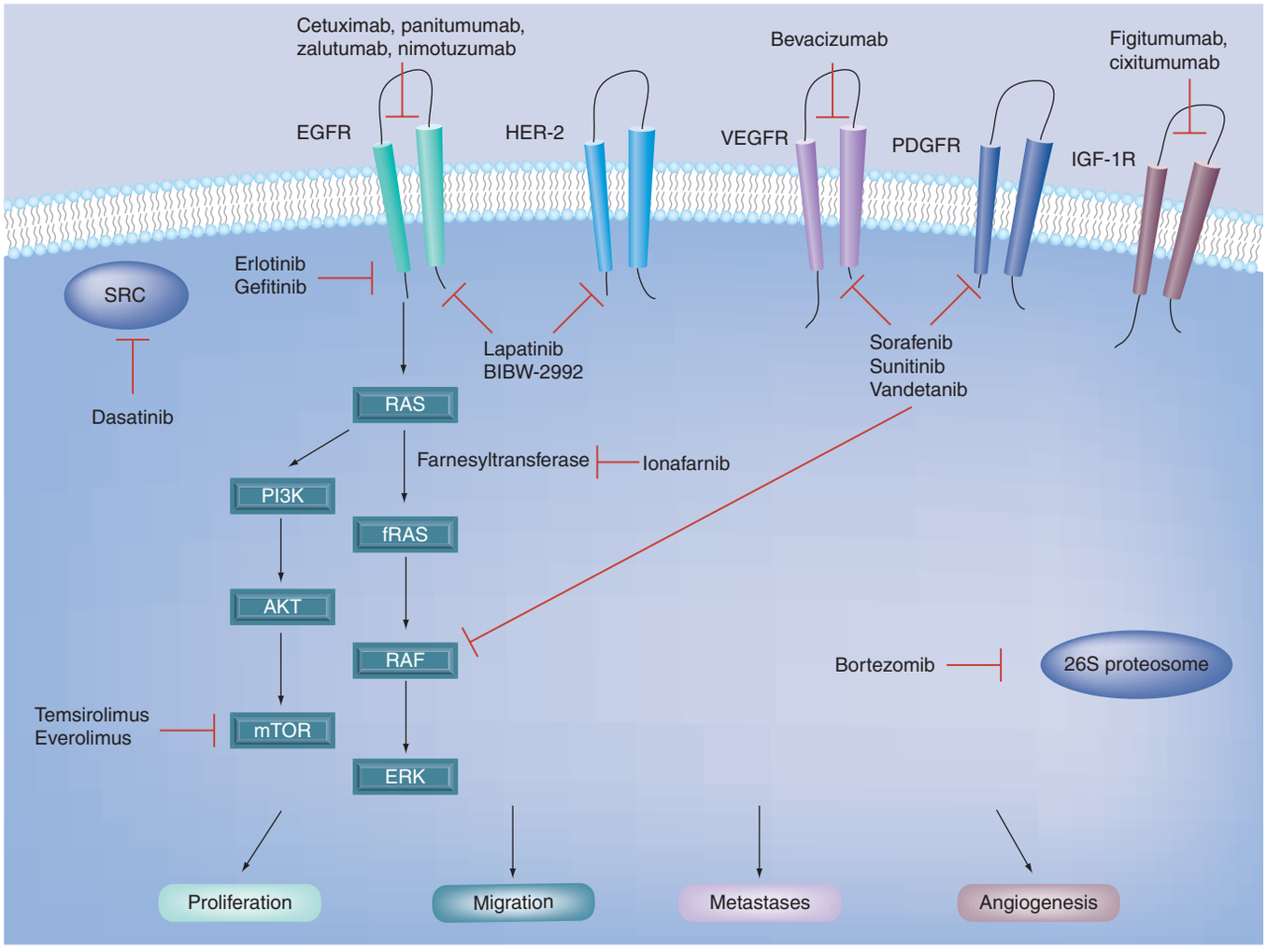

Figure 1. Selected signaling pathways dysregulated in head and neck squamous cell carcinoma and corresponding molecularly targeted agents.

Table 1. EGF receptor inhibitors tested in Phase II/III trials as monotherapy and in combination with radiation/chemoradiation in head and neck squamous cell carcinoma.

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
EGFR inhibitors combined with radiation/chemoradiation											
Cetuximab	III	First-line III/IV LA HNSCC	Cetuximab + RT	211	–	–	–	24.4	17.1	49	[6]
			RT alone	213	–	–	–	14.9	12.4	29.3	
	III	First-line III/IV LA HNSCC† (NCT00265941)	Cetuximab + cisplatin + accelerated RT	–	–	–	–	–	–	–	
			Cisplatin 100 mg/m^2 + accelerated RT	–	–	–	–	–	–	–	
Panitumumab	III	First-line LA HNSCC† (NCT00820248; NCIC HN.6)	Panitumumab 9 mg/kg every 3 weeks iv. + accelerated RT	–	–	–	–	–	–	–	
			Cisplatin 100 mg/m^2 every 3 weeks + RT	–	–	–	–	–	–	–	
	II	First-line LA HNSCC† (NCT00500760; CONCERT-1)	Panitumumab 9 mg/kg every 3 weeks + cisplatin 75 mg/m^2 every 3 weeks + RT	153	–	–	–	–	–	–	
			Cisplatin 100 mg/m^2 every 3 weeks + RT	–	–	–	–	–	–	–	
	II	First-line LA HNSCC† (NCT00547157; CONCERT-2)	Panitumumab + RT	–	–	–	–	–	–	–	
			Cisplatin + RT	–	–	–	–	–	–	–	
Nimotuzumab	II	First-line III/IVa LA HNSCC	CCRT (nimotuzumab 200 mg every week + concurrent RT + cisplatin 50 mg every week)	–	–	–	–	–	–	NR (47% at 2 years)	[10]
			CCRT (cisplatin 50 mg every week + RT)	–	–	–	–	–	–	21.9 (21% at 2 years)	
			CCRT (nimotuzumab 200 mg every week + RT)	–	–	–	–	–	–	14.3 (34% at 2 years)	
			RT	–	–	–	–	–	–	12.7 (13% at 2 years)	
Lapatinib	II	III/IV LA HNSCC	CCRT (lapatinib 1500 mg daily + cisplatin 100 mg/m^2 [days 1, 22, 43]) → maintenance lapatinib	34	53 post-CCRT	12	0	–	20.4	30.9	[18]
			CCRT (placebo daily + cisplatin 100 mg/m^2 [days 1, 22, 43]) → maintenance placebo	33	36 post-CCRT	12	0	–	12.1	23	

†Ongoing trial.

BSC: Best supportive care; CCRT: Concurrent chemoradiation; CR: Complete response; EGFR: EGF receptor; HNSCC: Head and neck squamous cell carcinoma; iv.: Intravenously; LA: Locally advanced; max.: Maximum; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; R/M: Recurrent and/or metastatic; RT: Radiation; SD: Stable disease; TTP: Time to progression.

Table 1. EGF receptor inhibitors tested in Phase II/III trials as monotherapy and in combination with radiation/chemoradiation in head and neck squamous cell carcinoma (cont.).

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
EGFR inhibitor as monotherapy											
Cetuximab	II	Second-line R/M HNSCC	Cetuximab	103	0	13	33	2.3	–	6	[8]
Zalutumumab	III	Second-line R/M HNSCC, open-label 2:1 BSC	Zalutumumab (max. 16 mg/kg) + BSC	191	1	5.2	35	–	2.5	6.7	[9]
			BSC (+ optional methotrexate)	95	0	1.1	25.3	–	2.1	5.2	
Gefitinib	II	Second- or third-line R/M HNSCC	Gefitinib 250 mg/day	70	0	1.4	31.6	–	1.8	5.5	[11]
	II	First- or second-line R/M HNSCC	Gefitinib 500 mg/day	52	2.1	8.5	42.6	3.4	–	8.1	[12]
	II	Second- or third-line R/M HNSCC	Gefitinib 500 mg/day	47	0	2	26	2.6	–	4.3	[13]
	II	First- or second-line R/M HNSCC	Gefitinib 500 mg/day	32	0	9	28	3	–	6	[15]
	III	Second- or third-line R/M HNSCC	Gefitinib 250 mg/day	158	–	2.7	–	–	–	5.6	[16]
			Gefitinib 500 mg/day	167	–	7.6	–	–	–	6	
			Methotrexate 40 mg/m^2 iv. every week	161	–	3.9	–	–	–	6.7	
Erlotinib	II	First- or second-line R/M HNSCC	Erlotinib 150 mg/day	115	0	4.3	33.9	–	2.3	6	[14]
Lapatinib	II	R/M HNSCC with (A) or without (B) prior EGFR inhibitor	Lapatinib 1500 mg/day (A)	27	0	0	37	1.6	–	–	[17]
			Lapatinib 1500 mg/day (B)	15	0	0	20	1.7	–	–	
BIBW-2992	II	First- or second-line platinum-resistant R/M HNSCC†	BIBW-2992 50 mg/day	60	–	21.7	35	–	4	NR	[19]
			Cetuximab	60	–	13.3	48.3	–	2.5	NR	
PF-00299804	II	First-line R/M HNSCC†	PF-299804 45 mg/day	35	0	10.5	63.2	–	3.4	7.5	[20]

†Ongoing trial.

BSC: Best supportive care; CCRT: Concurrent chemoradiation; CR: Complete response; EGFR: EGF receptor; HNSCC: Head and neck squamous cell carcinoma; iv.: Intravenously; LA: Locally advanced; max.: Maximum; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; R/M: Recurrent and/or metastatic; RT: Radiation; SD: Stable disease; TTP: Time to progression.

analysis of pretreatment factors indicated that oropharynx subsite, early T stage (T1–3 vs T4), treatment in the USA, male sex, high Karnofsky Performance Scale (90–100) and age <65 years all predicted benefit from cetuximab with radiation compared with radiation alone [7]. Since many of these predictive factors are more commonly observed in human papilloma virus (HPV)-associated oropharynx cancer, this has led to speculation that HPV association may be the major predictive factor for benefit from cetuximab. However, since this is an exploratory retrospective analysis, no firm conclusions can be made. Further elucidation of this may be possible when the results of a large randomized Phase III trial (RTOG 0522) of 720 patients comparing chemoradiation with cisplatin with or without cetuximab are available. This study has completed accrual and results are awaited (NCT00265941) in 2011.

In the recurrent and/or metastatic (R/M) setting, single-agent cetuximab was approved as monotherapy by the FDA based on a multicenter Phase II trial enrolling 103 patients with R/M HNSCC who had progressed on either cis- or carboplatin. This single-arm trial demonstrated an objective response rate (ORR) of 13% and stable disease rate of 33% with cetuximab alone (Table 1) [8]. The median time to progression (TTP) was 2.3 months and the median overall survival (OS) was 6 months.

More recently, zalutumumab (HuMax-EGFr; GenMab), a fully humanized IgG1 monoclonal antibody targeting the EGFR, and best supportive care (BSC) versus BSC with optional methotrexate, were tested in a Phase III trial of patients with platin-refractory R/M SCCHN (Table 1) [9]. The dose of zalutumumab was titrated to grade 2 rash. A total of 78% of patients in the BSC ± methotrexate arm received methotrexate. ORR was 6% in the zalutumumab arm and 1% in the control arm. There was a nonsignificant difference in the primary end point of median survival for benefit from zalatumumab (6.7 vs 5.2 months, HR: 0.77 [95% CI: 0.57–1.05], p = 0.065). Although there was a significant improvement in median progression-free survival (PFS; 9.9 vs 8.4 weeks; HR: 0.62 [95% CI: 0.47–0.83], p = 0.001) it can be argued that this is not a clinically relevant improvement [9]. Quality of life data have not been reported in this palliative trial. Zalatumumab added to chemoradiation is being compared with chemoradiation alone in an ongoing randomized trial (DAHANCA 19, NCT00496652).

Panitumumab (Vectibix®; Amgen), also a fully humanized monoclonal antibody against the EGFR, is being evaluated in a randomized Phase III trial in locally advanced (LA) HNSCC comparing panitumumab and accelerated radiation with conventionally fractionated radiation and cisplatin (NCIC HN.6, NCT00820248). Panitumumab combined with radiation or added to chemoradiation is under investigation in two Phase II trials (CONCERT-1, NCT00500760 and CONCERT-2, NCT00547157) with the primary end point of local regional control rate at 2 years. Two trials with panitumumab and chemoradiation in the postoperative high-risk setting are ongoing: a single-arm study (NCT00798655) and a large randomized Phase III study with target accrual of 800 patients (NCT01142414).

Nimotuzumab (BIOMAb EGFR; Biocon), an IgG1 humanized monoclonal antibody, has a lower receptor affinity for EGFR than cetuximab and can achieve therapeutic levels without eliciting skin toxicity, the most problematic and common toxicity of other anti-EGFR antibodies. A Phase IIB trial of 113 Indian patients with LA HNSCC randomized patients into two groups; group A received nimotuzumab plus radiation (N + RT) versus radiation (RT), and group B received nimotuzumab plus concurrent chemoradiation with cisplatin (N + CRT) versus chemoradiation with cisplatin (CRT) as definitive first-line therapy (Table 1) [10]. The locoregional response was 100% in the N + CRT arm versus 70% in the CRT arm, and 76% in the N + RT arm versus 37% in the RT arm. Patients in the N + CRT arm had a higher OS compared with those in the CRT arm (HR: 0.35, p = 0.01). Important caveats include a lower RT dose of 60–66 Gy in this study, and an imbalance in the percentage of oropharyngeal cancers (78% in N + RT vs 48% in RT study arms), which may affect outcomes in a positive direction related to HPV-associated cancer. A Phase II trial of nimotuzumab as part of induction therapy (NCT00910117) and a Phase III study of postoperative adjuvant nimotuzumab combined with chemoradiation are underway (NCT00957086).

Gefitinib (Iressa®; AstraZeneca) and erlotinib (Tarceva®; OSI Pharmaceuticals) were tested as monotherapy in R/M HNSCC in Phase II studies, which demonstrated an ORR generally below 10% and a similar OS to cetuximab monotherapy (Table 1) [11–15]. The variable restrictions on prior therapy in these Phase II studies has limited the interpretation of these results according to treatment line. The only Phase III trial of an EGFR TKI, compared single-agent gefitinib with methotrexate in patients with at least one prior line of treatment for R/M HNSCC or those who were not able to tolerate platinum (IMEX) (Table 1) [16]. Gefitinib (at 250 or 500 mg/day) was not superior to methotrexate for the primary end point, median survival. Lapatinib (Tykerb®; GlaxoSmithKline), a dual inhibitor of EGFR and HER-2, was tested as monotherapy in a Phase II trial of 42 patients with R/M HNSCC with or without prior exposure to an EGFR inhibitor [17]. There were

no objective responses and median TTP was 7 weeks in both groups (Table 1) [17]. However, preliminary data from a small randomized Phase II trial of chemoradiation with and without lapatinib demonstrated positive trends in complete response rate and survival ($p > 0.05$) that have spurred plans to further study the drug in that setting (Table 1) [18]. Ongoing trials include a randomized trial in the postoperative setting for high-risk patients of chemoradiation with and without lapatinib followed by maintenance lapatinib (NCT00424255). In addition, lapatinib is being studied with radiation alone in patients who cannot tolerate concurrent chemotherapy (NCT00490061).

Currently, new irreversible EGFR TKIs are being tested in Phase II studies as single agents in R/M HNSCC. Afatinib is the first TKI to demonstrate antitumor activity that appears to be at least comparable to cetuximab in HNSCC in an ongoing Phase II randomized trial of afatinib versus cetuximab in platinum-resistant R/M HNSCC (Table 1) [19]. The ORR of afatinib was 22% compared with 13% for cetuximab in 120 evaluable patients to date (Table 1). PF-00299804, as first-line treatment of R/M HNSCC in an ongoing single-arm Phase II study, has demonstrated an ORR of 10% in 38 evaluable patients to date (Table 1) [20].

EGFR inhibitors & single-agent chemotherapy combinations

Preclinical data have demonstrated EGFR inhibition can be synergistic with cisplatin in inhibiting tumor growth and can lead to increased radiosensitization [21], thus providing rationale to test combination therapies. In patients with previously untreated R/M HNSCC, cetuximab combined with cisplatin conferred an additive benefit in ORR when compared with cisplatin and placebo in a Phase III trial (ORR 26 vs 10%, $p = 0.03$) (Table 2) [22]. No significant benefit in PFS or OS was seen, although the trial was underpowered to demonstrate these effects. By contrast, in platinum-refractory R/M HNSCC, cetuximab combined with cisplatin chemotherapy had low response rates (~10%) as evidenced in two Phase II trials (Table 2) [23,24]. These response rates are similar to those achieved with cetuximab alone in this setting and, thus, there appears to be no advantage to the reintroduction or continuation of cisplatin when using cetuximab in platinum-refractory R/M HNSCC.

Cetuximab has also been combined with weekly paclitaxel as first-line treatment for patients with R/M HNSCC. This combination demonstrated a 60% ORR and median PFS of 5 months in 42 evaluable patients [25]. These outcomes are generally favorable to those with paclitaxel alone and suggest at least additive effects. Survival results from this trial are not yet reported [25].

Erlotinib combined with cisplatin demonstrated modest efficacy in a Phase II trial in patients with previously untreated R/M HNSCC (Table 2) that appears to be similar to results with cetuximab and cisplatin [26]. Gefitinib combined with docetaxel demonstrated an improvement in TTP when compared with docetaxel alone (3.5 vs 2.0 months, HR: 0.69 [95% CI: 0.48–0.99], $p = 0.05$), in heavily pretreated patients with R/M HNSCC in a Phase III trial (Eastern Cooperative Oncology Group [ECOG] 1302); however, there was no difference in the primary end point of OS [27].

EGFR inhibitors & doublet chemotherapy combinations

The triplet combination of cetuximab added to full-dose platinum (cisplatin/carboplatin) and fluorouracil (PF), was shown to be safe and achieved an ORR of 36% as first-line therapy in patients with R/M HNSCC in a Phase I/II trial (Table 3) [28]. The subsequent EXTREME study, which documented the enhanced efficacy of cetuximab added to PF compared with PF alone (median OS 10.1 vs 7.4 months, HR: 0.80 [95% CI: 0.64–0.99], $p = 0.04$) (Table 3) was the first randomized trial to show a survival benefit for any agent in the frontline R/M setting since methotrexate was compared with supportive care in the 1960s [29]. This milestone Phase III trial randomized 442 patients to six cycles of PF or weekly cetuximab added to PF. Patients with stable disease who received chemotherapy plus cetuximab continued to receive cetuximab until progression or unacceptable toxic effects. In addition to survival benefit, cetuximab–PF was also associated with significantly increased ORR (36 vs 20%), disease control rate (81 vs 60%) and PFS (5.6 vs 3.3 months, HR: 0.54, $p < 0.001$) when compared with PF alone. It is notable, however, that the increments in response rate and both median PFS and OS rates on the cetuximab arm are reminiscent of its single-agent effects in platin-refractory HNSCC [8]. Furthermore, there was very little crossover to cetuximab in the control arm patients after progression as the drug was not approved at that time by the EU. These data suggest that sequential therapy with cetuximab following chemotherapy progression may result in the same benefits as combined therapy. While data from this trial remain under review at the FDA, it is likely that an indication for cetuximab use in this setting will be obtained.

Mirroring the design of the EXTREME trial, panitumumab, combined with cisplatin and 5-fluorouracil (5-FU) was compared with cisplatin and 5-FU alone, in a Phase III trial of patients with R/M HNSCC (SPECTRUM). This trial did not demonstrate a benefit for panitumumab in its primary end point, OS (median OS 11.1 vs 9.0 months; HR: 0.87 [95% CI: 0.73–1.05],

p = 0.14) (Table 3) [30]. However there was a difference in ORR (36 vs 25%) and PFS (5.8 vs 4.6 months; HR: 0.78, [95% CI: 0.66–0.92], p = 0.004). Survival may have been affected by differences in treatment after progression with a small imbalance in subsequent targeted systemic agents (6% in the panitumumab arm vs 12% in the chemotherapy arm). Furthermore, in this global trial involving 26 countries, regional differences in benefit were observed (HR: 0.69 in the Americas vs HR: 1.11 in Eastern Europe). A randomized Phase II trial of docetaxel and cisplatin with or without panitumumab in the first-line treatment of R/M HNSCC, with cross over to second-line panitumumab monotherapy for those who fail the chemotherapy arm only is ongoing (NCT00454779).

Triplet combinations of EGFR inhibitors with platinum and taxane chemotherapy have also been evaluated. In the second-line R/M setting, a Phase II trial of 23 patients with platinum-resistant R/M HNSCC treated with cetuximab, carboplatin and paclitaxel showed a CR of 4%, PR of 30% and OS of 8 months. The contribution of carboplatin to response and survival outcomes is unclear; benefit may simply be related to the taxane and cetuximab combination (Table 3) [31]. Previous data from two much larger trials, which studied cetuximab and platins in platin-refractory patients, do not support the notion that cetuximab acts to reverse resistance to cisplatin [23,24]. Erlotinib and gefitinib have also been tested with platinum and taxane chemotherapy in small single-arm Phase II trials in the first-line setting for R/M HNSCC and demonstrated ORR of greater than 60% (Table 3) [32,33]. In the Phase II experience with erlotinib/docetaxel/cisplatin, routine growth factor support was utilized after neutropenic fever was observed in the first cohort of 18 patients. Promising median PFS and OS rates of 6 and 11 months, respectively, have led to an ongoing randomized trial comparing docetaxel and cisplatin, with and without erlotinib in R/M HNSCC (NCT1064479).

EGFR inhibitors as part of neoadjuvant (induction) therapy combinations

In the neoadjuvant setting, the quadruplet combination of cetuximab, docetaxel, cisplatinum and fluorouracil (TPF-C) was investigated in a Phase I trial of patients with locally advanced HNSCC by Haddad *et al.* [34]. Patients received three cycles of neoadjuvant chemotherapy with prophylactic antibiotics followed by chemoradiation [34]. At the 5-FU dose used in this TPF regimen (1000 mg/m^2 days 1–4) excessive enteral and myelosuppressive toxicity was encountered. Although the next lower dose level (850 mg/m^2) was the recommended Phase II dose in the publication, in practice, dose reduction to 700 mg/m^2 results in much greater

Table 2. EGF receptor inhibitors tested in Phase II/III trials in combination with single-agent chemotherapy in head and neck squamous cell carcinoma.

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
Cetuximab	III	First-line R/M HNSCC	Cisplatin + cetuximab	57	–	26	–	–	4.2	9.2	[22]
			Cisplatin + placebo	60	–	10	–	–	2.7	8	
	II	Second-line R/M HNSCC	Platinum + cetuximab	96	0	10	43	2.4	–	5	[23]
	II	Second-line R/M HNSCC	Cisplatin + cetuximab (SD)	51	4	14	59	–	4.9	11.7	[24]
			Cisplatin + cetuximab (PD/1)	25	0	20	44	–	3	6.1	
			Cisplatin + cetuximab (PD/2)	54	0	6	46	–	2	4.3	
	II	First-line R/M HNSCC	Paclitaxel + cetuximab	46	24	36	28	6.2	5	NR	[25]
Erlotinib	II	First-line R/M HNSCC	Erlotinib 100 mg daily + cisplatin	44	3	19	49	–	3.3	7.9	[26]
Gefitinib	III	Any line R/M HNSCC	Gefitinib 250 mg daily + docetaxel 35 mg/m^2 day 1, 8, 15	134	1	11	41	3.5	3.3	6.8	[27]
			Docetaxel 35 mg/m^2 day 1, 8, 15	136	2	3	32	2	2.2	6.2	

CR: Complete response; HNSCC: Head and neck squamous cell carcinoma; NR: Not reached; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; R/M: Recurrent and/or metastatic; SD: Stable disease; TTP: Time to progression.

Table 3. EGF receptor inhibitors tested in Phase II/III trials in combination with doublet chemotherapy or as part of neoadjuvant (induction) therapy combinations in head and neck squamous cell carcinoma.

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
EGF receptor inhibitor combined with doublet chemotherapy											
Cetuximab	II	First-line R/M HNSCC	Platinum + 5-FU + cetuximab	53	4	32	38	5.1	–	9.8	[28]
	III	First-line R/M HNSCC (EXTREME)	Platinum + 5-FU + cetuximab	220	–	36	–	4.8	5.6	10.1	[29]
			Platinum + 5-FU	222	–	20	–	3	3.3	7.4	
	II	Second- or third-line R/M HNSCC	Carboplatin + paclitaxel + cetuximab	23	4	30	22	5	–	8	[31]
Panitumumab	III	First-line R/M HNSCC (SPECTRUM)	Cisplatin + 5-FU + panitumumab	327	–	–	–	–	5.8	11.1	[30]
			Cisplatin + 5-FU	330	–	–	–	–	4.6	9.0	
Erlotinib	II	First-line R/M HNSCC	Cisplatin + docetaxel + erlotinib 150 mg/day	47	8	58	28	–	6	11	[33]
Gefitinib	II	First-line R/M HNSCC	Cisplatin + docetaxel + gefitinib 250 mg/day	17	37.5	25	12.5	–	5.1	NR	[32]
EGF receptor inhibitor as part of neoadjuvant combinations											
Cetuximab	II	IV HNSCC	Induction (cetuximab + docetaxel + cisplatin + 5-FU) → RT + cetuximab	50	20	50	8	–	–	–	[35]
	II	First-line III/IVb LA HNSCC	Induction (cetuximab + docetaxel + cisplatin) → CCRT (cetuximab + cisplatin) → cetuximab for 6 months	39	5% after IC, 24% after CCRT	81% after IC, 76% after CCRT	14% after IC, 0% after CCRT	–	70% at 3 years	74% at 3 years	[37]
	II	First-line LA HNSCC	Induction (cetuximab + paclitaxel + carboplatin) → CCRT (cisplatin) or RT or surgery	47	19	77	4	–	87% at 3 years	91% at 3 years	[38]
Gefitinib	II	First-line III/IV LA HNSCC	Induction (carboplatin + paclitaxel) → split course CCRT (gefitinib 250 mg/day + 5-FU + hydroxyurea) → gefitinib 250 mg/day for 2 years total	69	10 after IC, 75% after CCRT	67 after IC, 7% after CCRT	9 after IC, 1% after CCRT	–	NR (72% at 4 years)	NR (74% at 4 years)	[39]
	II	First-line III/IV LA HNSCC	Induction (gefitinib 250 mg/day + docetaxel + carboplatin + 5-FU) → CCRT (gefitinib + docetaxel) → gefitinib for 2 years	62	36 after CCRT	44 after CCRT	14 after CCRT	–	32	NR (54% at 3 years)	[40]

5-FU: 5-fluorouracil; CCRT: Concurrent chemoradiation; CR: Complete response; HNSCC: Head and neck squamous cell carcinoma; IC: Induction chemotherapy; LA: Locally advanced; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; R/M: Recurrent and/or metastatic; RT: Radiation; SD: Stable disease; TTP: Time to progression.

feasibility to deliver TPF-C. The ORR rate was 100% in the 28 patients treated in this Phase I trial; by radiographic criteria these were all partial responses. Of the patients who had a biopsy of the primary site prior to chemoradiation, the pathologic complete response rate was 80% (16 out of 20). Another group has investigated TPF-C, also in the neoadjuvant setting, in a Phase II study of 50 patients with unresectable HNSCC [35]. Patients received 4 cycles of TPF-C, utilizing a lower dose of cisplatin (75 vs 100 mg/m^2) and higher dose of 5-FU (750 mg/m^2 days 1–5) than recommended by Haddad *et al.* [34]. Neoadjuvant therapy was followed by cetuximab with concomitant boost radiation (Table 3) [35]. The ORR after four cycles of induction was 70%, compared with a 68% ORR with TPF alone in a Phase III trial [36]. All patients received granulocyte colony-stimulating factor and antibiotic prophylaxis. Despite this, a concerning febrile neutropenia rate of 26% and two treatment-related deaths were observed [35]. These two trials underscore the toxicity of adding cetuximab to an aggressive chemotherapy regimen. Whether there is an increase in efficacy to balance this excess toxicity awaits further investigation.

Cetuximab has also been studied in combination with doublet chemotherapy in the neoadjuvant setting. This includes a Phase II trial of cetuximab, docetaxel and cisplatin for three cycles followed by radiation with concurrent cisplatin and cetuximab weekly and then maintenance cetuximab for 6 months (Table 3) [37]. The ORR after induction was 86% (32 out of 37); after concurrent chemoradiation with cetuximab ORR was 100% in 33 evaluable patients. The febrile neutropenia rate during induction was 10%. Cetuximab added to cisplatin and radiation resulted in grade 3–4 mucositis and hypomagnesemia in 54 and 39% of patients, respectively. Estimated median PFS and OS at 3 years are 70 and 74%, respectively, which are promising; however, these results may be confounded by the prognostic impact of HPV-associated cancer in a proportion of patients (64% of 28 tumors evaluable were HPV and /or p16 positive). Comparison of outcomes in this subset of patients did not demonstrate improved survival in the 18 patients with HPV-associated cancer, albeit, firm conclusions cannot be made due to the small number in both groups.

Cetuximab has been added to a novel weekly regimen of paclitaxel and carboplatin (PCC) and investigated in a Phase II trial of 47 patients with previously untreated HNSCC with advanced nodal stage (≥N2b) (Table 3) [38]. This regimen was associated with a 96% ORR and no episodes of febrile neutropenia, although growth factor support was required in 64% of patients and treatment delays for neutropenia were needed in 60% of patients. The incidence of grade 3–4 rash was unexpectedly high at 45%. This approach was also associated with a promising median OS and PFS of 91 and 87% at 3 years, respectively and, interestingly, no relapses in 12 patients with HPV-positive oropharyngeal tumors. Again, the contribution of improved prognosis due to HPV-associated cancer may contribute to the promising outcome. An ongoing Phase II randomized trial is comparing PCC to TPF-cetuximab in the neoadjuvant setting for patients with ≥N2b HNSCC (NCT01154920).

In LA HNSCC, a Phase II trial of induction paclitaxel/carboplatin followed by gefitinib with concurrent chemoradiation (hydroxyurea and fluorouracil) followed by 2 years of maintenance gefitinib showed a CR rate of 90% in 69 patients after concurrent chemoradiation [39]. Estimated PFS and OS at 4 years are 72 and 74%, respectively. The incidence of HPV-associated cancer has not been reported for this trial. The addition of gefitinib to the triplet of docetaxel, carboplatin and fluorouracil followed by radiation concurrent with docetaxel and gefitinib, and maintenance gefitnib for 2 years, was associated with estimated PFS and OS at 3 years of 41 and 54%, respectively, in 50 out of 62 patients who were able to complete therapy [40]. These rates are similar to those obtained with chemoradiation alone.

Lapatinib added to induction chemotherapy (docetaxel/cisplatin/5-FU) followed by CRT with or without lapatinib was tested in LA HNSCC by the EORTC in a Phase I/II trial (NCT00498953) and stopped due to prohibitive toxicity in the induction phase at the first dose level of lapatinib, hence Phase II was never reached [41].

Overall, the experience with the addition of EGFR TKIs to chemotherapy and chemoradiation has proven less feasible than combinations with cetuximab and other antibodies. Justification for routine use of these regimens will require further evidence from ongoing and planned clinical trials.

Angiogenesis inhibitors

VEGF expression is inversely correlated with prognosis in patients with HNSCC, providing rationale to target VEGF and its receptors [42,43]. Antiangiogenic agents, such as monoloclonal antibodies that target VEGF (bevacizumab) and TKIs of VEGF receptor (VEGFR) in addition to other receptor kinases (sorafenib, sunitinib, vandetanib and cediranib) have been studied in HNSCC.

Bevacizumab (Avastin®; Genentech) is the best-studied angiogenesis inhibitor in HNSCC, having been evaluated in combination with other targeted agents, chemotherapy and radiation. EGFR activation resulting in VEGF upregulation, has been implicated as a mechanism of resistance to anti-EGFR agents and,

thus, co-targeting of EGFR and VEGF is an attractive therapeutic strategy [44,45]. Thus, a Phase I/II study of bevacizumab combined with erlotinib was performed in 51 patients with R/M HNSCC as first- or second-line therapy (Table 4) [46]. The ORR was 15% (four patients had CR and three patients had PR out of 48 evaluable patients) and the median PFS and OS were 4.1 and 7.1 months, respectively. Treatment-naive patients had better outcomes in this study. Three patients had serious bleeding events of grade 3 or higher. Of interest, phosphorylated VEGFR-2 on tumor cells and phosphorylated EGFR on endothelial cells in pretreatment biopsies were associated with complete response and tumor shrinkage in a small subset of 11 patients with available tissue. Using this same theme, bevacizumab combined with cetuximab is being investigated in a Phase II trial in R/M HNSCC that has recently completed accrual and final data are awaited (Table 4) [47]. This trial restricted entry to patients at low-risk of tumor-related hemorrhage. Interim analysis in 31 patients demonstrated an ORR of 17% and one patient with grade 3 bleeding. Although this is slightly higher than response rate to cetuximab alone (13%), the patient population is also highly selected.

The addition of bevacizumab to chemotherapy has been studied in a Phase II trial in combination with pemetrexed in 40 patients with previously untreated R/M HNSCC. The combination demonstrated an ORR of 30% and median TTP and OS of 4.9 and 11.5 months, respectively (Table 4) [48]. There were four grade 3 and two fatal bleeding events (grade 3–5 bleeding 15%) and one patient died from sepsis, suggesting excess toxicity with this regimen. An ongoing Phase III ECOG study will randomize 400 patients to cisplatin, docetaxel and fluorouracil combination chemotherapy with or without bevacizumab until progression in R/M HNSCC (NCT00588770). The primary end point is OS; however, the tolerability and toxicity particularly with respect to vascular complications, will be of equal importance.

The evaluation of bevacizumab in LA HNSCC is supported by *in vitro* studies demonstrating that bevacizumab may potentiate the efficacy of radiation. A single-arm Phase II study of bevacizumab added to induction chemotherapy (carboplatin/paclitaxel/5-FU) followed by bevacizumab and erlotinib added to concurrent chemoradiation with paclitaxel in 55 patients with LA HNSCC, demonstrated a 56% ORR after induction and a 77% ORR after completion of therapy,;however, the toxicity included two treatment-related deaths (intestinal perforation and stroke) (Table 4) [49]. Furthermore, severe grade mucositis was observed in 76% of patients during the radiation phase. PFS and OS at 18 months are promising at 85 and 87%; more mature survival data are awaited, especially with regards the incidence and impact of HPV-associated oropharynx cancer on outcome. A randomized Phase II trial of radiotherapy concurrent with cetuximab and pemetrexed with or without bevacizumab in LA HNSCC is ongoing [50].

The multitargeted receptor TKIs exert anti-tumor effects by affecting pathways associated with tumor angiogenesis, cell growth and proliferation through inhibition of VEGFR, PDGF receptor (PDGFR) and other kinases. Sorafenib (Nexavar; Onyx Pharmaceuticals) is an oral kinase inhibitor of VEGFR, PDGFR and Raf. A Phase II trial of sorafenib in 44 chemotherapy-naive patients with R/M HNSCC, yielded only one PR (2%) and the PFS and OS was 4 and 9 months, respectively (Table 4) [51]. Despite the low response rate, sorafenib was well tolerated and the PFS and OS are comparable to what is obtained with chemotherapy in the frontline R/M setting. In the first- or second-line treatment of R/M HNSCC, a Phase II trial of sorafenib at the same dosage in 28 patients with R/M HNSCC or nasopharyngeal carcinoma, demonstrated one PR (4%) [52]. Median TTP and OS were 1.8 and 4.2 months respectively, likely reflecting the prior chemotherapy exposure of 70% of patients in the study, and supporting a lack of anti-tumor activity in chemotherapy-treated patients. Sorafenib added to paclitaxel and carboplatin chemotherapy is being studied in an ongoing single-arm Phase II trial in the frontline setting for R/M HNSCC [53]. Interim analysis of the first 28 evaluable patients revealed one CR with an ORR of 72% with the primary end point of median PFS not yet reported. Grade 3 hand–foot syndrome has been observed in 15% of patients reflecting toxicity from sorafenib. Cotargeting VEGFR and EGFR is being studied in an ongoing randomized trial of cetuximab with and without sorafenib in the first- or second-line treatment of R/M HNSCC (NCT00939627).

Sunitinib (Sutent®; Pfizer Inc) is another TKI of VEGFR, PDGFR and Raf, also approved for renal cell carcinoma. Although the activity of single-agent sunitinib in Phase II trials in R/M HNSCC is similar to that of sorafenib, survival in these studies has been short compared with predicted outcomes based on patient selection. A Phase II trial of 22 patients treated in the frontline setting for R/M HNSCC, demonstrated only one patient with partial response, median TTP of approximately 2 months, and median OS of approximately 5 months (Table 4) [54]. Another Phase II trial of 38 patients with platinum-refractory R/M HNSCC also yielded low response rates (one patient had PR) and short median PFS and OS of 2 months and 3.4 months respectively (Table 4) [55]. Concerns

Table 4. Angiogenesis inhibitors tested in Phase II/III trials in head and neck squamous cell carcinoma.

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
Bevacizumab	II	First- or second-line R/M HNSCC	Bevacizumab 15 mg/kg every 3 weeks + erlotinib 150 mg/day	51	8	6	31	–	4.1	7.1	[46]
	II	First-line R/M HNSCC	Bevacizumab 15 mg/kg every 3 weeks + pemetrexed 500 mg/kg every 3 weeks	40	5	30	57	4.9	–	11.5	[48]
	II	First- or second-line R/M HNSCC† (NCT00409565)	Bevacizumab 15 mg/kg every 3 weeks + cetuximab	32	0	17	60	–	2.7	8.1	[47]
	II	First-line III/IV LA HNSCC	Induction (bevacizumab 15 mg/kg every 3 weeks + paclitaxel + carboplatin + 5-FU) → CCRT (bevacizumab 15 mg/kg weeks 1 and 4 + erlotinib 150 mg/day + paclitaxel)	55	–	–	–	–	90% at 2 years	88% at 2 years	[49]
Sorafenib	II	First-line R/M HNSCC	Sorafenib 400 mg twice daily	44	0	2	45	4.2	4	9	[51]
	II	Second-line R/M HNSCC or NPC	Sorafenib 400 mg twice daily	27	0	4	37	1.8	–	4.2	[52]
	II	First-line R/M HNSCC†	Sorafenib + paclitaxel + carboplatin	28	4	68	21	–	NR	NR	[53]
	II	First- or second-line R/M HNSCC† (NCT00939627)	Sorafenib + cetuximab	–	–	–	–	–	–	–	
			Placebo + ceutximab	–	–	–	–	–	–	–	
Sunitinib	II	First-line R/M HNSCC in patients with:									[54]
		PS 0–1 or	Sunitinib 50 mg/day 4/6 weeks	15	0	8.3	25	2.1	–	5.3	
		PS 2	Sunitinib 50 mg/day 4/6 weeks	7	0	0	29	2.6	–	4.8	
	II	First- or second-line R/M SCCHN	Sunitinib 37.5 mg daily	38	0	2.6	47.4	–	2	3.4	[55]
Vandetanib	II	First-line III/IV LA HNSCC adjuvant‡ (NCT00720083)	Concurrent RT + cisplatin + vandetanib	–	–	–	–	–	–	–	
			Concurrent RT + cisplatin	–	–	–	–	–	–	–	

†Ongoing trial.

‡Closed prematurely.

5-FU: 5-fluorouracil; CCRT: Concurrent chemoradiation; CR: Complete response; HNSCC: Head and neck squamous cell carcinoma; LA: Locally advanced; NPC: Nasopharynx carcinoma; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; PS: Performance status; R/M: Recurrent and/or metastatic; RT: Radiation; SD: Stable disease; TTP: Time to progression.

of toxicity were raised by the high rate of grade 5 head and neck bleeds (four patients or 16%) in addition to 15 patients with worsening tumor skin ulceration and/or fistula, possibly related to angiogenesis inhibition in a prior radiation field.

Vandetanib (Zactima™; ZD6474; Astra Zeneca) is a selective oral multitargeted TKI of EGFR, VEGFR and RET. At the 300 mg/day dose, both EGFR and VEGFR are inhibited; at 100 mg/day, the drug mainly inhibits VEGFR. In LA HNSCC, a Phase II trial of 170 patients was planned, randomizing patients with high-risk pathologic features to postoperative radiation concurrent with cisplatin with or without vandetanib (NCT00720083). This study has been closed prematurely at the industry sponsor's request. A Phase I trial assessing tolerance for vandetanib with radiation alone and with cisplatin/radiation in patients with stage III–IV HNSCC has completed accrual (NCT00450138). Interim results indicate the MTD of vandetanib with radiation was 200 mg/day; with radiation and cisplatin the tolerated dose was 100 mg [56]. Full results of this trial are awaited; notably, experience with expansion cohorts in both settings will help judge efficacy of vandetanib added to radiation and chemoradiation.

IGF-1 receptor inhibitors

The IGF-1 receptor (IGF-1R) plays a critical role in epithelial cancer development, proliferation and survival. IGF-1R is overexpressed in HNSCC and its ligand IGF, can cause activating phosphorylation of IGF-1R and EGFR [57]. IGF-1R and EGFR heterodizmerization may promote erlotinib resistance through activation of IGF-1R and its downstream mediators including antiapoptotic surviving proteins and mTOR-mediated *de novo* EGFR synthesis, whereas inactivation of IGF-1R increases sensitivity to erlotinib [58].

IGF-1 receptor inhibitors in clinical testing in HNSCC include monoclonal antibodies against IGF-1R, such as figitumumab (CP-751871; Pfizer), cixitumumab (IMC-A12; ImClone Systems) and IGF-1R TKI, such as BMS-754807. Monotherapy activity with IGF-1R inhibitors in epithelial malignancies is not predicted based, at least in part, on the absence of evidence that it functions as a classic oncogene; no identifying activating mutations have been identified and gene amplification is rare.

Despite pessimism regarding monotherapy effects, single-agent figitumumab was tested in a Phase II study of 17 patients with R/M HNSCC who were resistant to platinum or unfit for chemotherapy (GORTEC 2008–02; Table 5) [59]. The study population included only males and 50% had prior treatment with cetuximab. The most common grade 3–4 toxicities were hyperglycemia (41%) and asthenia (24%). The trial was stopped after 12 weeks due to futility (stable disease rate two out of 17 or 7%) and the median PFS and OS was 52 and 63 days, respectively. Despite the lack of clinical benefit, correlative analyses showed downregulation of IGF-1R and upregulation of AKT, EGFR and pEGFR by IHC in eight patients with paired tumor biopsies. Plasma IGF, insulin, insulin-like growth factor-binding protein-3 and TGF-α were increased in 11 patients with paired plasma samples. The disappointing results reflect the lack of activity of IGF-1R blockade alone and the need to address resistance mechanisms, such as IGF-1R and EGFR crosstalk.

Co-targeting of IGF-1R and EGFR in preclinical models has demonstrated increased complete tumor regression, compared with IGF-1R monoclonal antibody blockade or EGFR monoclonal antibody alone, thus providing rationale for clinical testing of this approach. A Phase II randomized study of cixitumumab with or without cetuximab in patients with platinum-resistant R/M HNSCC has completed accrual and results are awaited (NCT00617734). A planned preoperative, randomized, three arm, Phase II trial of cixitumumab versus cetuximab versus cixitumumab and cetuximab, will hopefully provide further insight into the pharmacodynamic effects of IGF-1R and EGFR co-targeting (NCT00957853).

mTOR inhibitors

The mTOR is a serine-theronine kinase and member of the PI3K-related kinase family responsible for regulation of cell growth, proliferation and apopotosis. Preclinical models in HNSCC have demonstrated that the mTOR inhibitor, rapamycin, inhibits DNA synthesis and induces apoptosis of HNSCC cells [60]. In HNSCC, the mTOR inhibitors that are furthest in clinical testing are temsirolimus (CCI-779) and everolimus (RAD-001). Temsirolimus is being studied in small, ongoing, single-arm Phase II trials in R/M HNSCC as monotherapy (NCT01172769) and in combination with weekly paclitaxel and carboplatin (NCT01016769). A single-arm, Phase I/II study of temsirolimus added to cetuximab and cisplatin in previously untreated R/M HNSCC is also underway (NCT01015664). The combination of rapamycin and erlotinib produced synergistic effects on growth inhibition in *in vivo* models, suggesting that co-targeting with mTOR and EGFR inhibition may be a useful strategy [61]. Two single-arm, Phase II trials in treatment refractory R/M HNSCC, will evaluate this approach of combining:

- Everolimus with erlotinib (NCT00942734)
- Everolimus with cetuximab and platinum chemotherapy (NCT01009346)

A randomized Phase II trial of adjuvant everolimus versus placebo is underway (NCT001111058).

Everolimus is also under investigation in Phase I trials in LA HNSCC as part of induction therapy with docetaxel and cisplatin (NCT01133678), or combined with concurrent radiation with cisplatin (NCT00858663).

Proteasome inhibitors

The 26S proteasome is central to the ubiquitin-proteasome degradation pathway, which is responsible for intracellular degradation of proteins involved in regulation of cell growth. Bortezomib (Velcade; Millennium Pharmaceuticals), a selective inhibitor of the 26S proteasome, has demonstrated antitumor activity and radiosensitizing properties in preclinical HNSCC models (Table 5) [62]. An ECOG Phase II trial of 102 patients with R/M HNSCC randomized to bortezomib (arm A) versus bortezomib plus irinotecan upon progression (arm B) reported single-agent bortezomib was well tolerated but its activity was disappointing with an ORR of 13% and median PFS of 1.6 months [63]. The activity of bortezomib plus irinotecan was not greater than prior studies of irinotecan alone, and the toxicity included two treatment-related deaths. Bortezomib is being evaluated in R/M HNSCC in combination with docetaxel in a single-arm Phase II study (NCT00425750).

Src family kinases

Src kinases are nonreceptor cytoplasmic tyrosine kinases that play a key role in normal cellular signal transduction pathways. Src activity leads to upregulation of signaling cascades associated with cellular invasion, migration, proliferation and survival. Src inhibition with dasatinib (Sprycel; BMS-354825; Bristol-Myers Squibb) led to cell cycle arrest and apoptosis in HNSCC cell lines and cell lines resistant to erlotinib (Table 5) [64]. Dasatinib is a potent multitargeted inhibitor of Src, BCR-ABL, cKIT and PDGFR. A Phase II trial of 15 patients with R/M HNSCC, dasatinib dosed at 100 mg twice daily produced no objective responses [65]. Toxicity was high leading to hospitalization in four patients and drug discontinuation in five patients. Despite the lack of single-agent activity in R/M HNSCC, a Phase I/II trial of dasatinib, cetuximab and radiation with or without cisplatin in LA HNSCC is underway (NCT00882538). Dasatinib, erlotinib, the combination and placebo are being studied in the preoperative setting in both HNSCC and non-small-cell lung cancer in a four-arm ongoing randomized trial with the main goal of studying biomarker modulation in resected tumor (NCT00779389). Saracatinib (AZD 0530) is another inhibitor of Src, BCR-ABL, currently in Phase II testing in R/M HNSCC (NCT00513435).

Table 5. Other molecularly targeted agents tested in Phase II/III trials in head and neck squamous cell carcinoma.

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
Figitumumab	II	First- or second-line HNSCC	Figitumumab 20 mg/kg iv. every 3 weeks	17	0	0	7	–	1.7	2.1	[59]
Bortezomib	II	First- or second-line R/M HNSCC	Bortezomib	23	0	13	17.4	–	1.6	9.1	[63]
			Bortezomib + irinotecan upon progression	38	0	2.6	26.3	–	1.5	7.3	
Dasatinib	II	First- or second-line R/M HNSCC	Dasatinib 100 mg twice daily	15	0	0	1	–	–	–	[65]
	II	First-line LA HNSCC* (NCT00882583)	Dasatinib + cetuximab + RT	–	–	–	–	–	–	–	
			Dasatinib + cetuximab + cisplatin + RT	–	–	–	–	–	–	–	
Lonafarnib (SCH66336)	II	First-line R/M HNSCC	Lonafarnib 200 mg twice daily	15	0	0	47	2.0	–	9.2	[66]

*Ongoing trial.
CR: Complete response; HNSCC: Head and neck squamous cell carcinoma; LA: Locally advanced; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; R/M: Recurrent and/or metastatic; RT: Radiation; SD: Stable disease; TTP: Time to progression.

Farnesyl transferase inhibitors

Farnesyl transferase inhibitors block farnesylation of several key proteins, including Ras, ultimately leading to cell growth arrest. Lonafarnib (SCH66336), an oral tricyclic peptidomimetic compound that inhibits farnesyl protein transferase, was tested in a monotherapy Phase II trial in 15 patients with platinum refractory R/M HNSCC (Table 5) [66]. The most common adverse events were diarrhea, nausea and fatigue. There were no objective responses and no further evaluation of single-agent lonafarnib is planned.

Novel cytotoxic agents

Cytotoxic agents with single-agent activity and common use in HNSCC include the platinating agents, cisplatin and carboplatin, the taxanes, paclitaxel and docetaxel and fluorouracil. Methotrexate had been used very commonly historically. Due to its relatively low single-agent activity in comparison with platins and taxanes, it is now most commonly used in second- and third-line therapy for patients with recurrent/metastatic disease. Three cytotoxic agents have been recently evaluated in HNSCC, including pemetrexed, ixabepilone (BMS-2457550) and S-1.

Pemetrexed (Alimta®; Eli Lilly) is a folate antimetabolite that inhibits three enzymes used in purine and pyrimidine synthesis; thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. It is approved for the treatment of mesothelioma in combination with cisplatin, and for the treatment of non-small-cell lung cancer with nonsquamous histology. In previously untreated patients with R/M HNSCC, single-agent pemetrexed demonstrated a response rate of 27% in a single-arm Phase II trial [67]. However, in patients with previously treated R/M HNSCC, a Phase I trial of single agent pemetrexed in patients who had received one or two prior regimens for R/M HNSCC reported partial response in just one of 23 patients. The drug, however, was well-tolerated in heavily pretreated patients [68]. Pemetrexed in combination with cisplatin was not more effective than cisplatin alone in a Phase III trial of 795 patients with R/M HNSCC (Table 6) [69]. However, a retrospective subset analysis did demonstrate superior OS and PFS for the combination in patients with good-performance status (ECOG 0 or 1) and patients with oropharyngeal primary cancers. Pemetrexed in combination with gemcitabine in a Phase II trial demonstrated a response rate of 16% in previously treated R/M HNSCC and 24% of patients developed neutropenia (grade ≥3) (Table 6) [70]. Currently, pemetrexed is being studied in Phase II trials in a variety of settings. In the R/M HNSCC, ongoing Phase II trials include pemetrexed in combination with carboplatin or cisplatin and cetuximab (NCT01087970), pemetrexed in combination with erlotinib (NCT00573989) and pemetrexed alone (NCT00293579). In LA HNSCC, current Phase II trials include pemetrexed combined with oxaliplatin as induction (NCT00503997), and radiotherapy concurrent with cetuximab and pemetrexed with or without bevacizumab [50].

Overall, pemetrexed has activity as a single agent in front-line therapy of R/M HNSCC. It does not appear to have substantial single-agent activity in previously treated patients [68]. Somewhat surprisingly, data from a Phase III trial demonstrated no significant increase in response rate with pemetrexed/cisplatin compared with cisplatin alone [69]. Furthermore there are no data comparing pemetrexed to 5-FU or methotrexate. Moreover, the survival for the patients with good performance status (ECOG 0–1) with cisplatin/pemetrexed combination therapy [69] was essentially the same survival seen with cisplatin/5-FU or cisplatin/paclitaxel in the Phase III ECOG trial (E1395) [71] restricted to performance status 0–1 patients, suggesting this survival may be what is observed with any effective doublet in this subset of patients with recurrent disease. The specific benefit for the oropharyngeal cancer patients in the Phase III trial by Urba *et al.*, may speak to pemetrexed's efficacy specifically in p16-expressing cancers (and in HNSCC, thus, the HPV-associated tumors) [69]. However, we note that the PFS benefit for this subset in the combination arm, was less than the survival difference, suggesting it is possible that the oropharynx patients on the doublet arm had better outcomes due to treatment post-progression such as with second-line cetuximab.

The epothilones are a new class of microtubule-stabilizing agents that bind β-tubulin and result in cell cycle arrest. Preclinical studies have shown antitumor activity in taxane-resistant cell lines [72]. Ixabepilone, is a semisynthetic derivative of epothilone B and has been studied in a Phase II trial in patients with previously-treated R/M HNSCC (Table 6) [73]. A total of 85 patients were stratified according to prior taxane exposure and randomized to ixabepilone every 3 weeks versus every week (3 weeks on and 1 week off). Only one patient out of 32 on the every 3-week schedule had an objective response. Taxane-naive patients randomized to the weekly ixabepilone arm had a response rate of 14%, whereas no responses were seen in taxane-exposed patients on this arm. The weekly taxane arm was unfortunately also associated with higher incidence of motor and sensory grade 3 neuropathy (31% of patients), occurring in both taxane-naive and -exposed patients. This trial confirmed that ixabepilone should not be tested further in patients with previously treated R/M HNSCC; the problematic neurotoxicity may limit further development of the weekly regimen, which was the most effective schedule in this trial.

S-1 is a novel oral chemotherapy composed of tegafur, gimestat and otostat potassium. Tegafur is a prodrug of 5-FU that is bioactivated via 5′-hydroxylation mediated by cytochrome p450. Gimestat inhibits dihydropyrimidine dehydrogenase, an enzyme that degrades 5-FU, to maintain prolonged 5-FU concentrations in plasma and in the tumor. Otostat potassium is distributed in the gastrointestinal tract and may alleviate the gastrointestinal toxicity due to 5-FU. S-1 has been commercially available in Japan since 1999 and used primarily to treat gastrointestinal cancers. Recently, a Phase II trial using S-1 and cisplatin in 34 patients with previously treated R/M HNSCC demonstrated an ORR of 44% and median survival of 16.7 months (Table 6) [74]. The main grade 3–4 toxicities were anorexia (27%), nausea (15%) and neutropenia or thrombocytopenia (12%). In LA HNSCC, S-1 combined with docetaxel as part of two cycles of induction therapy, followed by radiotherapy concurrent with daily cisplatin was tested in 25 patients (Table 6) [75]. A total of 20% of patients had grade 3–4 neutropenia. Induction with S-1 and docetaxel was associated with a PR of 84%, and following chemoradiation a CR in 80% of patients was achieved. A Phase I trial of induction with S-1, docetaxel and cisplatin (TPS) demonstrated an ORR of 70% (six CR and 22 PR out of 40 patients) to induction in patients with previously untreated, unresectable LA or R/M HNSCC [76]. There is as of yet no single-agent data for S-1, nor has there been comparison with 5-FU. Further study will be required to clarify its value in HNSCC.

Future perspective

It has been approximately 5 years since the approval of cetuximab by a regulatory agency for the treatment of HNSCC. It remains the first and only molecularly targeted agent with proven efficacy in this disease. The success of cetuximab in HNSCC has spurred enthusiasm to develop and test new molecularly targeted agents in HNSCC, in the hope of offering an improved therapeutic index compared with conventional chemotherapy and chemoradiation. Since the approval of cetuximab, progress has been slow. The role of cetuximab has extended to include use in combination with chemotherapy in incurable patients and we await the results of a large randomized trial with regards its efficacy in combination with standard chemoradiation. However, as we have reviewed herein, although many trials have been completed and are ongoing or planned, we do not yet have firm evidence of any additional effective molecularly targeted agents beyond cetuximab.

At the root of this slow progress is the absence, thus far, of predictive biomarkers for cetuximab, or for that matter, any of our therapies. To be certain, there are

Table 6. Novel cytotoxic agents tested in Phase II/III trials in head and neck squamous cell carcinoma.

Compound	Phase	Tumor type and treatment setting	Treatment	n	CR (%)	PR (%)	SD (%)	TTP (months)	PFS (months)	OS (months)	Ref.
Pemetrexed	III	Previously treated R/M HNSCC	Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 every 3 weeks	398	0.5	11.6	38.4	–	3.6	7.3	[69]
			Cisplatin 75 mg/m^2 + placebo every 3 weeks	397	1	7	34	–	2.8	6.3	
	II	First- or second-line R/M HNSCC	Pemetrexed 500 mg/m^2 + gemcitabine 1250 mg/m^2 every 2 weeks	25	0	16	28	–	–	8.8	[70]
	II	First-line R/M HNSCC	Pemetrexed 500 mg/m^2 every 3 weeks	35	0	27	44	3.9	–	7.3	[67]
Ixabepilone	II	First- or second-line R/M HNSCC	Ixabepilone 6 mg/m^2/day × 5 days every 3 weeks (taxane naive)	16	0	0	0	–	1.4	7.1	[73]
			Ixabepilone 6 mg/m^2/day × 5 days every 3 weeks (taxane exposed)	14	0	7	0	–	2	8	
			Ixabepilone 20 mg/m^2/day on day 1, 8 and 15 every 4 weeks (taxane naive)	32	0	16	0	–	1.8	6.9	
			Ixabepilone 20 mg/m^2/day on day 1, 8 and 15 every 4 weeks (taxane exposed)	18	0	0	0	–	1.6	6.8	
S-1	II	First- or second-line R/M HNSCC	S-1 40 mg/m^2 twice daily + cisplatin 70 mg/m^2	34	6	38	44	3.3	–	16.7	[74]
	II	First-line LA HNSCC	Induction (S-1 40 mg/m^2 twice daily for 2 weeks + docetaxel 40 mg/m^2 day 1) followed by concurrent daily cisplatin 6 mg/m^2 + RT	25	80	–	–	–	NR (76% at 2 years)	NR (70% at 2 years)	[75]

CR: Complete response; HNSCC: Head and neck squamous cell carcinoma; LA: Locally advanced; NR: Not reached; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; R/M: Recurrent and/or metastatic; SD: Stable disease; TTP: Time to progression.

interesting leads now suggesting HPV association in oropharynx cancer may predict for benefit from cetuximab [7] and conversely, that the absence of HPV association may predict for benefit from hypoxic cell sensitizers added to radiation or chemoradiation [77,78]. However, these findings from retrospective exploratory analyses can only be used to generate hypotheses to be studied in future prospective trials. Overall the identification of predictive biomarkers remains one of the major challenges in furthering the goal of personalized therapy in HNSCC.

Strategies to promote translational research in HNSCC are a major priority in clinical trial development [79]. There is no disagreement that the incorporation of biomarker evaluation and validation in clinical trial design will ultimately improve therapeutic decision-making and patient outcomes in the future. But there are obstacles to this transition in the clinical research paradigm; we must all work to increase acceptance of the need for obtaining mandatory tumor biopsies in the comprehensive evaluation of new treatments. We believe this is a critical step in accelerating progress. Issues in design are also paramount; strong clinical prognostic markers such as HPV status and smoking history should be included as stratification factors in randomized trials in order to delineate biomarkers as prognostic or predictive or both [80]. Designs that allow testing of novel agents in patients for whom resection is planned increases the chance that there will be adequate tissue in which to evaluate biomarker modulation, perhaps identifying a subset of patients for whom the therapy is most likely to be beneficial, and focusing further drug development. A natural outgrowth of increasingly personalized treatment approaches should lead to therapy that is more effective; for example it seems reasonable to hope that a 3 month improvement in median survival for patients with recurrent HNSCC will no longer represent an acceptable 'efficacy bar' in a more informed future.

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Executive summary

- The success of cetuximab in head and neck squamous cell carcinoma (HNSCC) has established molecularly targeted therapy as part of standard of care for curative- and palliative-intent therapy, in combination with radiation and chemotherapy.
- Although there have been no major advances in molecularly targeted therapy beyond EGF receptor-targeting with cetuximab, many trials are ongoing or planned as reviewed herein.
- New leads from retrospective analyses of previous trials suggest that predictive biomarkers for therapy of locally advanced HNSCC will be identified in the next decade. These leads would not have been identified without the retrospective analysis of tumor tissue.
- Future progress, therefore, in large part, depends upon the ability to correlate benefits from specific therapies with molecular genotype and phenotype in tumor tissue. Thus, routine acquisition of tumor for biomarker analysis should be incorporated into clinical trials with targeted agents. This should provide, at minimum, opportunities to capitalize on success, shed light on causes for failure and increasingly personalize approaches for our patients. We should be prepared to thoroughly interrogate tissue from patients who have had dramatic tumor regression with targeted agents; in this way pathways of oncogene addiction may be identified.
- The challenges of biomarker analysis are immense, especially in tumors such as HNSCC, which are predominantly related to tobacco-induced carcinogenesis. Hopefully, the paradigm of assessing DNA alterations (mutations, loss/gain, methylation), RNA expression profiling (micro- and messenger), and proteomics first in cell lines with confirmation in human tumor tissue, should inform as to the critical driving alterations in this cancer and, thus, the highest priority targets in future clinical trials. Biomarker analysis within the trial can then be directed, in part, to prove a specific hypothesis(es), in addition to broaden more exploratory initiatives.

Bibliography

1 Chung CH, Ely K, McGavran L *et al.* Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J. Clin. Oncol.* 24(25), 4170–4176 (2006).

2 Temam S, Kawaguchi H, El-Naggar AK *et al.* Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. *J. Clin. Oncol.* 25(16), 2164–2170 (2007).

3 Wheeler DL, Huang S, Kruser TJ *et al.* Mechanisms of acquired resistance to cetuximab: role of HER (ErbB) family members. *Oncogene* 27(28), 3944–3956 (2008).

4 Sok JC, Coppelli FM, Thomas SM *et al.* Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. *Clin. Cancer Res.* 12(17), 5064–5073 (2006).

5 Chau NG, Perez-Ordonez B, Zhang K *et al.* The association between EGFR variant III, HPV, p16, c-MET, EGFR gene copy number and response to EGFR inhibitors in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *Head Neck Oncol.* 3(11) (2011).

6 Bonner JA, Harari PM, Giralt J *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N. Engl. J. Med.* 354(6), 567–578 (2006).

7 Bonner JA, Harari PM, Giralt J *et al.* Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a Phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* 11(1), 21–28 (2010).

8 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.* 25(16), 2171–2177 (2007).

9 Machiels JH, Subramanian S, Ruzsa A *et al.* An open-label, randomized, Phase III trial of zalutumumab, a human monoclonal EGF receptor (EGFr) antibody, versus best supportive care, in patients with noncurable squamous cell carcinoma (SCCHN) of the head and neck who have failed standard platinum-based chemotherapy (ZALUTE). *J. Clin. Oncol.* 28(Suppl. 18), LBA5506 (2010).

10 Babu KG, Viswanath L, Reddy BK *et al.* An open-label, randomized, study of h-R3mAb (nimotuzumab) in patients with advanced (stage III or IVa) squamous cell carcinoma of head and neck (SCCHN): four-year survival results from a Phase IIb study. *J. Clin. Oncol.* 28(Suppl. 15), 5530 (2010).

11 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.* 11(23), 8418–8424 (2005).

12 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.* 21(10), 1980–1987 (2003).

13 Kirby AM, A'Hern RP, D'Ambrosio C *et al.* Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. *Br. J. Cancer* 94(5), 631–636 (2006).

14 Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. 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.* 22(1), 77–85 (2004).

15 Wheeler RH, Sharma P, Davis RK *et al.* Clinical and molecular Phase II study of gefitinib in patients (pts) with recurrent squamous cell cancer of the head and neck (H&N Ca). *J. Clin. Oncol.* 23 (16S), 5531 (2005).

16 Stewart JS, Cohen EE, Licitra L *et al.* Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J. Clin. Oncol.* 27(11), 1864–1871 (2009).

17 Abidoye OO, Cohen EE, Wong SJ *et al.* A Phase II study of lapatinib (GW572016) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *J. Clin. Oncol.* 24(Suppl. 18), 5568 (2006).

18 Harrington KJ, Berrier A, Robinson M *et al.* Phase II study of oral lapatinib, a dual-tyrosine kinase inhibitor, combined with chemoradiotherapy (CRT) in patients (pts) with locally advanced, unresected squamous cell carcinoma of the head and neck (SCCHN). *J. Clin. Oncol.* 28(Suppl. 15), 5505 (2010).

19 Seiwert TY, Clement PM, Cupissol D *et al.* BIBW-2992 versus cetuximab in patients with metastatic or recurrent head and neck cancer (SCCHN) after failure of platinum-containing therapy with a cross-over period for progressing patients: Preliminary results of a randomized, open-label Phase II study. *J. Clin. Oncol.* 28(Suppl. 15), 5501 (2010).

20 Le Tourneau C, Winquist E, Hotte SJ *et al.* Phase II trial of the irreversible oral pan-HER inhibitor PF-00299804 (PF) as first-line treatment in recurrent and/or metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN). *J. Clin. Oncol.* 28(Suppl. 15), 5531 (2010).

21 Cerniglia GJ, Pore N, Tsai JH *et al.* Epidermal growth factor receptor inhibition modulates the microenvironment by vascular normalization to improve chemotherapy and radiotherapy efficacy. *PLoS One* 4(8), e6539 (2009).

22 Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. 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.* 23(34), 8646–8654 (2005).

23 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.*, 23(24), 5568–5577 (2005).

24 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.* 23(24), 5578–5587 (2005).

25 Hitt R, Irigoyen A, Nunez J *et al.* Phase II study of combination cetuximab and weekly paclitaxel in patients with metastatic/recurrent squamous cell carcinoma of head and neck (SCCHN): Spanish Head and Neck Cancer Group (TTCC). *J. Clin. Oncol.* 25(Suppl. 18), 6012 (2007).

26 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.* 25(16), 2178–2183 (2007).

27 Argiris A, Ghebremichael M, Gilbert J, Burtness B, Forastiere A. A Phase III randomized, placebo-controlled trial of docetaxel (D) with or without gefitinib (G) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): a trial of the Eastern Cooperative Oncology Group (ECOG). *J. Clin. Oncol.* 27(Suppl. 15), 6011 (2009).

28 Bourhis J, Rivera F, Mesia R *et al.* Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J. Clin. Oncol.* 24(18), 2866–2872 (2006).

29 Vermorken JB, Mesia R, Rivera F *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N. Engl. J. Med.* 359(11), 1116–1127 (2008).

30 Vermorken JB, Stohlmacher J, Davidenko I *et al.* Primary efficacy and safety results of SPECTRUM, a Phase 3 trial in patients with recurrent and/or metastatic squamous cell carcinoma of the had and neck receiving chemotherapy with or without panitumumab. *Ann. Oncology* 21(Suppl. 8), LBA 26 (2010).

31 Buentzel J, de Vries A, Micke O. Experience with cetuximab plus paclitaxel/carboplatinum in primary platinum-resistant recurrent head and neck cancer. *J. Clin. Oncol.* 25(Suppl. 18), 6077 (2007).

32 Belon J, Irigoyen A, Rodriguez I *et al.* Preliminary results of a Phase II study to evaluate gefitinib combined with docetaxel and cisplatin in patients with recurrent and/or metastatic squamous-cell carcinoma of the head and neck. *J. Clin. Oncol.* 23(Suppl. 16), 5563 (2005).

33 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 cancer. *J. Clin. Oncol.* 25(Suppl. 18), 6013 (2007).

34 Haddad RI, Tishler RB, Norris C *et al.* Phase I study of C-TPF in patients with locally advanced squamous cell carcinoma of the head and neck. *J. Clin. Oncol.* 27(27), 4448–4453 (2009).

35 Mesia R, Vazquez S, Grau JJ *et al.* A single-arm Phase II trial to evaluate the combination of cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (TPF) as induction chemotherapy (IC) in patients (pts) with unresectable SCCHN. *J. Clin. Oncol.* 27(Suppl. 15), 6015 (2009).

36 Vermorken JB, Remenar E, van HC *et al.* Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N. Engl. J. Med.* 357(17), 1695–1704 (2007).

37 Argiris A, Heron DE, Smith RP *et al.* Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. *J. Clin. Oncol.* 28(36), 5294–5300 (2010).

38 Kies MS, Holsinger FC, Lee JJ *et al.* Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a Phase II prospective trial. *J. Clin. Oncol.* 28(1), 8–14 (2010).

39 Cohen EE, Haraf DJ, Kunnavakkam R *et al.* Epidermal growth factor receptor inhibitor gefitinib added to chemoradiotherapy in locally advanced head and neck cancer. *J. Clin. Oncol.* 28(20), 3336–3343 (2010).

40 Hainsworth JD, Spigel DR, Burris HA 3rd *et al.* Neoadjuvant chemotherapy/gefitinib followed by concurrent chemotherapy/radiation therapy/gefitinib for patients with locally advanced squamous carcinoma of the head and neck. *Cancer* 115(10), 2138–2146 (2009).

41 Specenier PM, Lalami Y, Vermorken J *et al.* EORTC 24051: unexpected side effects of a Phase I study of TPF induction chemotherapy (IC) followed by chemoradiation (CRT) with lapatinib (LAP), a dual EGFR/ErbB2 inhibitor, in patients with locally advanced larynx and hypopharynx squamous cell carcinoma (LA-LxHxSCC). *J. Clin. Oncol.* 27(Suppl. 15), 6017 (2009).

42 Sullu Y, Gun S, Atmaca S, Karagoz F, Kandemir B. Poor prognostic clinicopathologic features correlate with VEGF expression but not with PTEN expression in squamous cell carcinoma of the larynx. *Diagn. Pathol.* 5(35) (2010).

43 Hong DY, Lee BJ, Lee JC, Choi JS, Wang SG, Ro JH. Expression of VEGF, HGF, IL-6, IL-8, MMP-9, telomerase in peripheral blood of patients with head and neck squamous cell carcinoma. *Clin. Exp. Otorhinolaryngol.* 2(4), 186–192 (2009).

44 Ciardiello F, Troiani T, Bianco R *et al.* Interaction between the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) pathways: a rational approach for multi-target anticancer therapy. *Ann. Oncol.* 17(Suppl. 7), vii109–vii114 (2006).

45 O-Charoenrat P, Rhys-Evans P, Modjtahedi H, Eccles SA. Vascular endothelial growth factor family members are differentially regulated by c-erbB signaling in head and neck squamous carcinoma cells. *Clin. Exp. Metastasis* 18(2), 155–161 (2000).

46 Cohen EE, Davis DW, Karrison TG *et al.* Erlotinib and bevacizumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck: a Phase I/II study. *Lancet Oncol.* 10(3), 247–257 (2009).

47 Gibson MK, Kies M, Kim S *et al.* Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma: an updated report. *J. Clin. Oncol.* 27(Suppl. 15), 6049 (2009).

48 Argiris A, Karamouzis M, Gooding WE *et al.* Pemetrexed (P) and bevacizumab (B) in patients (pts) with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): final results and correlation with TS, MTHFR, and VEGF gene polymorphisms. *J. Clin. Oncol.* 28(Suppl. 15), 5533 (2010).

49 Meluch AA, Spigel D, Burris HA *et al.* Combined modality therapy with radiation therapy (RT), chemotherapy, bevacizumab, and erlotinib in the treatment of patients (pts) with locally advanced squamous carcinoma of the head and neck. *J. Clin. Oncol.* 27(Suppl. 15), 6012 (2009).

50 Kotsakis AP, Heron DE, Kubicek GJ *et al.* Phase II randomized trial of radiotherapy (RT), cetuximab (E), and pemetrexed (Pem) with or without bevacizumab (B) in locally advanced squamous cell carcinoma of the head and neck (SCCHN). *J. Clin. Oncol.* 28(Suppl. 15), TPS264 (2010).

51 Williamson SK, Moon J, Huang CH *et al.* Phase II evaluation of sorafenib in advanced and metastatic squamous cell carcinoma of the head and neck: Southwest Oncology Group Study S0420. *J. Clin. Oncol.* 28(20), 3330–3335 (2010).

52 Elser C, Siu LL, Winquist E *et al.* Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. *J. Clin. Oncol.* 25(24), 3766–3773 (2007).

53 Sabichi AL, Kies MS, Glisson BS *et al.* A Phase II study of sorafenib in combination with carboplatin and paclitaxel in patients with metastatic or recurrent squamous cell cancer of the head and neck (SCCHN). *J. Clin. Oncol.* 28(Suppl. 15), 5532 (2010).

54 Choong NW, Kozloff M, Taber D *et al.* Phase II study of sunitinib malate in head and neck squamous cell carcinoma. *Invest. New Drugs* 28(5), 677–683 (2010).

55 Machiels J-PH, Henry SP, Zanetta S *et al.* Phase II study of sunitinib in recurrent or metastatic squamous cell carcinoma of the head and neck: GORTEC 2006–2001. *J. Clin. Oncol.* 28(1), 21–28 (2010).

56 Papadimitrakopoulou V, Frank SJ, Blumenschein GR *et al.* Phase I evaluation of vandetanib with radiation therapy (RT) ± cisplatin in previously untreated advanced head and neck squamous cell carcinoma (HNSCC). *J. Clin. Oncol.* 27(Suppl. 15), 6016 (2009).

57 Barnes CJ, Ohshiro K, Rayala SK, El-Naggar AK, Kumar R. Insulin-like growth factor receptor as a therapeutic target in head and neck cancer. *Clin. Cancer Res.* 13(14), 4291–4299 (2007).

58 Morgillo F, Woo JK, Kim ES, Hong WK, Lee HY. Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. *Cancer Res.* 66(20), 10100–10111 (2006).

59 Schmitz S, Kaminsky-Forrett M, Henry S *et al.* Phase II study of figitumumab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: GORTEC 2008–2002. *J. Clin. Oncol.* 28(Suppl. 15), 5500 (2010).

60 Amornphimoltham P, Patel V, Sodhi A *et al.* Mammalian target of rapamycin, a molecular target in squamous cell carcinomas of the head and neck. *Cancer Res.* 65(21), 9953–9961 (2005).

61 Buck E, Eyzaguirre A, Brown E *et al.* Rapamycin synergizes with the epidermal growth factor receptor inhibitor erlotinib in non-small-cell lung, pancreatic, colon and breast tumors. *Mol. Cancer Ther.* 5(11), 2676–2684 (2006).

62 Sunwoo JB, Chen Z, Dong G *et al.* Novel proteasome inhibitor PS-341 inhibits activation of nuclear factor-κB, cell survival, tumor growth, and angiogenesis in squamous cell carcinoma. *Clin. Cancer Res.* 7(5), 1419–1428 (2001).

63 Gilbert J, Lee J, Argiris A *et al.* Phase II randomized trial of bortezomib (B) plus irinotecan (I) or B with addition of I at progression in recurrent (R) or metastatic (M) squamous cell carcinoma of the head and neck (SCCHN) (E1304): a trial of the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 27(Suppl. 15), 6020 (2009).

64 Johnson FM, Saigal B, Talpaz M, Donato NJ. 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.* 11(19), 6924–6932 (2005).

65 Brooks HD, Glisson B, Lu C *et al.* Phase II study of dasatinib in the treatment of head and neck squamous cell carcinoma (HNSCC). *J. Clin. Oncol.* 27(Suppl. 15), 6022 (2009).

66 Hanrahan EO, Kies MS, Glisson BS *et al.* A Phase II Study of lonafarnib (SCH66336) in patients with chemorefractory, advanced squamous cell carcinoma of the head and neck. *Am. J. Clin. Oncol.* 32(3), 274–279 (2009).

67 Pivot X, Raymond E, Laguerre B *et al.* Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. *Br. J. Cancer* 85(5), 649 (2001).

68 Morrow P, Glisson B, Ginsberg L *et al.* A Phase I dose escalation study of pemetrexed in patients with advanced head and neck squamous cell cancer (HNSCC). *J. Clin. Oncol.* 25(Suppl. 18), 6055 (2007).

69 Urba S, van Herpen CM, Sahoo TP *et al.* Phase III study of pemetrexed in combination with cisplatin (Pem/Cis) versus placebo plus cisplatin (Cis) in patients with recurrent or metastatic squamous cell head and neck cancer. *Ann. Oncol.* 21(Suppl. 8), viii314–viii328 (2010).

70 Fury MG, Haque S, Stambuk H, Shen R, Carlson D, Pfister D. A Phase 2 study of pemetrexed plus gemcitabine every 2 weeks for patients with recurrent or metastatic head and neck squamous cell cancer. *Cancer* 117(4), 795–801 (2010).

71 Gibson MK, Li Y, Murphy B *et al.* Randomized Phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 23(15), 3562–3567 (2005).

72 Bollag DM, McQueney PA, Zhu J *et al.* Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. *Cancer Res.* 55(11), 2325–2333 (1995).

73 Burtness BA, Manola J, Axelrod R, Argiris A, Forastiere AA. A randomized Phase II study of ixabepilone (BMS-247550) given daily × 5 days every 3 weeks or weekly in patients with metastatic or recurrent squamous cell cancer of the head and neck: an Eastern Cooperative Oncology Group study. *Ann. Oncol.* 19(5), 977–983 (2008).

74 Fujii M, Tomita K, Nishijima W *et al.* Phase I/II study of s-1 plus cisplatin combination chemotherapy in patients with advanced/recurrent head and neck cancer. *Jpn. J. Clin. Oncol.* 40(3), 214–221 (2010).

75 Hong S, Cho B, Shin S *et al.* Induction docetaxel and S-1 followed by concomitant radiotherapy with low-dose daily cisplatin in locally advanced head and neck carcinoma. *J. Clin. Oncol.* 28(Suppl. 15), e16020 (2010).

76 Tahara M, Araki K, Okano S *et al.* Phase I trial of combination chemotherapy with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer. *Ann. Oncol.* 22(1), 175–180 (2010).

77 Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J. HPV-associated p16-expression and response to hypoxic modification of radiotherapy in head and neck cancer. *Radiother. Oncol.* 94(1), 30–35 (2010).

78 Rischin D, Young RJ, Fisher R *et al.* Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 Phase III trial. *J. Clin. Oncol.* 28(27), 4142–4148 (2010).

79 Psyrri A, Licitra L, Lacombe D *et al.* Strategies to promote translational research within the European Organisation for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Group: a report from the Translational Research Subcommittee. *Ann. Oncol.* 21(10), 1952–1960 (2010).

80 Ang KK, Harris J, Wheeler R *et al.* Human papillomavirus and survival of patients with oropharyngeal cancer. *N. Engl. J. Med.* 363(1), 24–35 (2010).