Systemic Treatment of Recurrent/ Metastatic Squamous Cell Carcinoma of the Head and Neck

42

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Abstract

Most patients with recurrent or metastatic head and neck squamous cell cancers qualify for palliative treatment. The management of these patients includes supportive care only, mono- or multiagent chemotherapy, and more recently targeted therapies. While platinum-based combinations are superior to single-agent therapies in terms of response rate, they are more toxic and so far have not shown to lead to meaningful survival benefit. Attempts to improve on this by using other or additional cytotoxic drugs were unsuccessful in the last 30 years. It was therefore an urgent need to investigate the efficacy of novel anticancer therapies that specifically target the tumor cells in such patients. A recent randomized trial showed that adding cetuximab, an EGFR-directed monoclonal antibody, to a standard platinum-based chemotherapy regimen led to an important survival benefit. Despite the still dismal prognosis, the outcome of this latter trial has changed practice in this category of head and neck cancer patients. The next challenge will be to sort out how to incorporate the numerous targeted agents that are currently studied into the existing treatment strategies, also in consideration of an optimization of their therapeutic index. Human papillomavirus status with immunohistochemical p16 expression as its surrogate marker represents promising prognostic and possibly predictive biomarkers that need to be prospectively validated in future randomized trials.

Keywords

Head and neck • Recurrent • Metastatic • Targeted therapies • Platinum • Monoclonal antibodies • Tyrosine kinase inhibitors • Immunotherapy

42.1 Introduction

Approximately 60–65 % of patients with head and neck cancer can be cured with surgery and/or radiotherapy [1]. While a large proportion of patients presenting with stage I and II squamous cell carcinoma of the head and neck (SCCHN) will remain disease-free after single modality treatment (either surgery or radiotherapy), the majority of patients presenting in a more advanced disease stage, and treated with whatever combined modality approach, will eventually relapse either locoregionally and/or at distant sites. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only or, in addition single-agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents.

Treatment choice should be based on factors such as performance status, comorbidity, prior treatment, symptoms, patient preference, and logistics [2]. Goals of treatments in

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these circumstances are mainly symptom control and prevention of new cancer-related symptoms, improvement in quality of life (QoL), and, if assessable, objective tumor response (OR), disease stabilization (SD), or both combined (disease control; DC) and in addition prolongation of overall survival (OS) and progression-free survival (PFS). Unfortunately, correlation between objective tumor reduction (or DC) and subjective benefit (symptom control and QoL) has not been adequately studied, underscoring the importance of clinical trials in this patient group [3].

42.2 Associated Problems

Patients with R/M-SCCHN can have specific problems related to their social habits such as ongoing heavy tobacco and alcohol use or the use of other carcinogens, which may lead to poor cognitive function, comorbid medical conditions (cardiovascular and/or pulmonary diseases), and malnutrition. Moreover, typically disease-related problems may be present, such as infections (local, aspiration pneumonia, systemic), hypercalcemia, local pain, or bleeding (arterial, venous, capillary), which all can influence QoL and OS and may necessitate active supportive care [4].

42.3 Prognostic Factors

Several clinical prognostic factors have been proposed to define patients who are most likely to benefit from palliative chemotherapy and these can be categorized as patient related, tumor related, or treatment related. Already for a long time, it is known that the performance status is one of the most important prognostic factors that not only influences the incidence of response to chemotherapy but also affects the OS of these patients regardless of the response to the applied chemotherapeutic agents [4, 5]. Patients with only local recurrence with or without regional lymph node involvement and no bony erosion after definitive treatment have a better chance to respond to chemotherapy than do patients with systemic and visceral metastases. Other factors that have been reported to influence outcome are a good response to prior induction (neoadjuvant) chemotherapy or radiotherapy, a long interval between primary and recurrence, good organ functions, poorly differentiated histotype, and the response to palliative treatment [4, 6–8]. Data from two more recently conducted US trials in R/M-SCCHN (E1395 and E1393) were combined and analyzed for prognostic factors for response and survival. The median follow-up of the patients in these two trials was 4.7 years; survival rates at 1, 2, 3, and 5 years were 32, 12, 7, and 3.6 %, respectively, and median OS was 7.8 months. The OR rate was 32 %. On multivariate analysis, the investigators were able to identify one pathologic feature (tumor cell differentiation) and four clinical baseline characteristics (Eastern Oncology Cooperative Group (ECOG) performance status, weight loss, location of the primary tumor, and prior radiotherapy) as independent predictors of OS. They constructed a prognostic model for OS based on the presence of these five independent prognostic factors and were able to categorize the patients into two groups with significantly different outcome, i.e., one in which patients had only 0–2 adverse prognostic factors and another in which patients had ≥3 poor prognostic factors. The first group had a median survival that was nearly twice that of the second group (0.98 years vs. 0.52 years). In this study, 283 of the 399 patients included in the analysis had three or more adverse factors, explaining the median survival of only 7.8 months [9]. They also identified that the same variables and the presence of residual tumor at the primary site were independent predictors of response to chemotherapy. In fact, response to chemotherapy was found to be of prognostic significance. When the investigators added response to chemotherapy to the model, the location of the primary tumor lost its prognostic significance but all other parameters, including tumor cell differentiation, retained their significance as independent predictors of survival. Predictors of 2-year survivorship were the response to chemotherapy [complete response (CR) or partial response (PR) vs. no response], white race (vs. others), ECOG performance status of 0 (vs. 1), poor cell differentiation (vs. well/moderate), and no prior radiotherapy. Interestingly, all long-term survivors had locally recurrent disease at study entry. The findings in this study suggested that (1) there is an urgent need of better therapy for this category of patients; (2) response to systemic therapy has a major impact on survival; (3) patients with locally recurrent disease, but not the patients with distant metastases, who are primarily treated with chemotherapy, rarely will be cured from their disease; and (4) future trials in patients with R/M-SCCHN should take the five adverse prognostic factors into consideration.

R/M-SCCHN patients who fail the platinum-based first-line therapy do very poorly. León et al., in a retrospective analysis of the outcome of patients with R/M-SCCHN who were progressing while on platinum-based palliative chemotherapy, reported no responses using traditional chemotherapeutic agents and a median OS of 3.4 months [10]. More recently performed phase II/III trials, albeit with slightly better outcome, are in line with this [11–17] (Table 42.1). These data can be used as a reference when evaluating the effectiveness of new agent(s) in previously treated patients.

42.4 The Chemotherapeutic Approach

Squamous cell carcinoma of the head and neck is one of the more chemosensitive human neoplasms. Recent reports on induction chemotherapy in locoregionally advanced SCCHN have indicated that OR rates and CR rates approaching 90 %

Table 42.1 Second-line treatment in recurrent/metastatic SCCHN (phase II/III data)

Author (year)	Drug	Prior chemotherapy for R/M-SCCHN	Median PFS (months)	Median OS (months)
Pivot (2001) [11]	MTX	62 %	1.5	3.7
Stewart (2009) [12]	MTX	Unclear	N/A	6.7
Machiels (2011) [13]	BSC (MTX)[a]	83 % (17 %)[b]	1.9	5.2
Numico (2002) [14]	Docetaxel	61 %	4.0 (TTP)	6.0
Zenda (2007) [15]	Docetaxel	Unclear	1.7	4.6
Specenier (2011) [16]	Docetaxel	77 %	1.7	4.1
Argiris (2013) [17]	Docetaxel	Unclear	2.1 (TTP)	6.0

MTX methotrexate, *BSC* best supportive care, *PFS* progression-free survival, *N/A* not assessable, *TTP* time to progression, *OS* overall survival
[a]78 % of the patients received MTX
[b]17 % of the patients relapsed <6 months after chemoradiation

and 60 %, respectively, are achievable [3]. These data are far from what can be reached in the recurrent/metastatic disease setting in which a more unfavorable (resistant) phenotype has emerged. In fact, compiled results from 12 nonrandomized trials showed an OR rate of 50 % and a CR rate of 16 % [18]. Some investigators have indicated that reaching a CR, especially if confirmed histologically, is meaningful for survival benefit [4, 19, 20], while PRs might have much less impact on survival and merely indicate biological effectiveness [4]. This may certainly be so for long-term survival. In the earlier mentioned prognostic factor analysis of the two ECOG studies, ten times more CRs were observed in those alive at 2 years and beyond vs. those with a survival <2 years (37 % vs. 3 %). For OR (CR + PR), these percentages were 78 % vs. 25 %, suggesting that CR might be a surrogate marker for survival.

42.4.1 Single-Agent Chemotherapy

The four most extensively studied single cytotoxic agents in advanced or recurrent disease are bleomycin (average OR 21 %), methotrexate (average OR 31 %), 5-fluorouracil (5-FU) (average OR 15 %), and cisplatin (average OR 28 %). Response rates with these agents, but also with several other conventional agents of different classes [the platinum analog carboplatin (25 %), the alkylating agents ifosfamide (26 %) and cyclophosphamide (36 %), the anthracycline doxorubicin (24 %), and the vinca alkaloid vinblastine (29 %)], are generally in the 15–30 % range, while response duration is generally between 3 and 5 months [7, 21–29]. Similar response rates, mostly observed in phase II studies, were observed with newer agents such as paclitaxel, docetaxel, vinorelbine, irinotecan, edatrexate, pemetrexed, capecitabine, orzel, and S-1 [30–41] (Table 42.2).

As evident from the table, the taxanes, paclitaxel and docetaxel, are among the highest in activity in this disease setting. At the same time, it is clear from the table that there is a wide range of activity in different studies, most likely reflecting variations in patient characteristics. For most of the conventional agents, but also of the newer agents, no direct comparison has been made with the standard palliative agent methotrexate. The few exceptions to this are summarized in Table 42.3.

Table 42.2 New active[a] agents in recurrent/metastatic SCCHN

Drug	Response rates (%)	First author, year [references]
Edatrexate	6–21	Kuebler, 1994 [37]; Schornagel, 1995 [38]
Pemetrexed	26	Pivot, 2001 [32]
Vinorelbine	6–16	Testolin, 1994 [33]; Degardin, 1998 [34]
Irinotecan	21	Murphy, 2005 [36]
Capecitabine	8–24	Colevas, 2006 [3]; Martinez-Trufero, 2010 [35]
Orzel	21	Colevas, 2001 [41]
S-1	27	Park, 2008 [39]
Paclitaxel	20–43	Schrijvers, 2005 [30]; Grau, 2009 [31]
Docetaxel	20–42	Schrijvers, 2005 [30]; Hitt, 2006 [40]

[a]Activity defined as ≥15 % responses

Grose et al. [42] randomized 100 patients to be treated either with methotrexate or cisplatin. OR rates were 16 and 8 %, median durations of response were 18 and 8 weeks, and median durations of survival were 20 and 18 weeks, with methotrexate and cisplatin, respectively. A similar but smaller study was conducted by Hong et al. [25]. They found neither a difference in OR rate nor in median OS. However, mucositis occurred more frequently in the methotrexate group (38 % vs. 0 %; $p=0.001$), while vomiting occurred more frequently in the cisplatin group (87 % vs. 10 %; $p<0.0001$). These two randomized studies demonstrated that in the treatment of recurrent SCCHN, methotrexate and cisplatin are equally effective, although methotrexate appears to be better tolerated. Schornagel et al. [38] reported on an adequately sized European Organization for the Research and Treatment of Cancer (EORTC) trial, in which edatrexate (an analog of methotrexate) was compared with methotrexate. The originally favorable outcome in the phase II part of this protocol could not be confirmed in the phase III final results. There was strikingly more toxicity with edatrexate than with

Table 42.3 Single-agent treatment in recurrent/metastatic SCCHN: randomized trials

Author (year)	No. of patients	Drugs randomized	Response rate (%)	Median OS (months)
Grose (1985) [42]	100	Methotrexate	16	4.6
		Cisplatin	8	4.1
Hong (1983) [25]	38	Methotrexate	23	6.1
		Cisplatin	29	6.3
Schornagel (1995) [38]	264	Methotrexate	16	6.0
		Edatrexate	21	6.0
Vermorken (1999) [43]	95	Methotrexate	16	6.8
		Paclitaxel 3 h (vs. 24 h)	11 (−23)	6.5
Guardiola (2004) [44]	57	Methotrexate	15	3.9
		Docetaxel	27	3.7

OS overall survival

methotrexate (90 % vs. 45 % high-grade toxicity) and similar efficacy. As mentioned above, nonrandomized trials suggested a high activity with the use of taxanes in R/M-SCCHN patients. Direct comparisons were therefore of major interest. Vermorken et al. [43] compared paclitaxel 175 mg/m^2, administered either as a 3-h or a 24-h infusion, with standard-dose methotrexate (40–60 mg/m^2 weekly) in a randomized phase II study. The 24-h infusion regimen was considered too toxic due to a high incidence of febrile neutropenia. However, none of the regimens was superior with respect to response or survival. Weekly schedules of taxanes induce interesting response rates and may have a better therapeutic index than three weekly schedules. Guardiola et al. [44] randomized 57 patients between weekly docetaxel 40 mg/m^2 or weekly methotrexate 40 mg/m^2. The OR rate in this phase II trial was significantly higher with docetaxel (27 % vs. 15 %). However, there was no indication that OS or time to progression was any different between the two treatment arms. It is currently unclear if any of the cytotoxic agents prolongs survival when compared with supportive care alone as an adequately powered randomized controlled trial has never been performed. Only one small study in the past was designed to demonstrate clinical benefit over best supportive care only, using randomized controlled trial methodology. In that trial, 31 patients treated with single-agent cisplatin demonstrated prolonged survival compared with 26 patients treated with supportive measures only [45]. An interesting aspect in this trial was the demonstration that patients who respond do so quickly. Of the 16 responders, 75 % responded after the first cycle and the remaining 25 % after the second cycle [3, 45].

42.4.2 Combination Chemotherapy

42.4.2.1 Standard Platinum-Based Combinations

Combination chemotherapy is very often considered in patients who are young and in a good condition, in particular when favorable prognostic factors for response to chemotherapy are available [4]. The Wayne State University cisplatin/infusional 5-FU (PF) regimen gradually emerged as the most commonly used combination chemotherapy regimen in patients with SCCHN. With that regimen, nonrandomized trials suggested a better outcome than what was observed with single-agent treatment, at least with respect to OR rates and CR rates [18]. However, response rates were notably lower for the subsets of patients who had prior surgery and radiation and those who had metastatic disease [3]. In a number of adequately sized randomized trials performed in the 1990s, this PF regimen was shown to be superior to single-agent regimens, in terms of response rates but not in terms of meaningful survival advantage, and this gain in response rates was obtained at the cost of more toxicity [6, 7, 24] (Table 42.4).

Jacobs et al. [7] compared the PF regimen with either cisplatin alone or 5-FU alone in a randomized phase III trial which included 249 patients. The OR rate to PF (32 %) was superior to that of cisplatin (17 %) or 5-FU (13 %) ($p=0.035$). However, there was neither a difference in median time to progression nor in survival among the three groups. Forastiere et al. [6] randomized 277 patients to PF, carboplatin/5-FU

Table 42.4 Platinum-based combinations vs. single-agent chemotherapy: randomized trials

Author (year)	No. of patients	Agents	Response rate (%)	Median overall survival (months)
Jacobs (1992) [7]	249	PF	32*	5.5
		P	17	5.0
		F	13	6.1
Forastiere (1992) [6]	277	PF	32†	6.6
		CF	21	5.0
		M	10	5.6
Clavel (1994) [24]	382	CABO	34‡	7.3
		PF	31§	
		P	15	
Urba (2012) [49]	795	P + PEM	12	7.3
		P + placebo	8	6.3

P cisplatin, *C* carboplatin, *M* methotrexate, *B* bleomycin, *V* vincristine, *PEM* pemetrexed, *CABO* = P + M + B + V
*$p=0.035$, †$p<0.001$, ‡$p<0.001$, §$p=0.003$

(CF), or standard-dose methotrexate. Hematologic and nonhematologic toxicities were significantly worse with PF than with methotrexate ($p=0.001$). Toxicity with CF was intermediate between the two other regimens. The OR rates were 32 % for PF, 21 % for CF, and 10 % for methotrexate, respectively. The comparison of PF to methotrexate was statistically significant ($p<0.001$), and the comparison of CF to methotrexate was of borderline statistical significance ($p=0.05$). Median response durations and median survival times were similar for all three treatment groups. The CF combination also induced fewer responses than the PF regimen in a randomized phase III trial in the neoadjuvant setting [46]. Moreover, there was no difference in response rate in a randomized comparison of carboplatin plus methotrexate vs. single-agent methotrexate [47]. Taken together, these data clearly suggest that carboplatin is less active than cisplatin in the treatment of SCCHN.

Clavel et al. [48] in a first prospective trial randomized 185 patients between CABO, which consisted of cisplatin, methotrexate, bleomycin, and vincristine, and ABO (CABO without cisplatin). Although the OR rate was higher with CABO (50 % vs. 28 %; $p=0.003$), this did not lead to a better survival. In a next phase III study Clavel et al. [24] compared PF with CABO and with cisplatin alone in 382 patients with R/M-SCCHN. The OR rate was 31 % with PF, 34 % with CABO, and 15 % with cisplatin alone. The two combination regimens were significantly better in that respect than cisplatin alone ($p<0.001$ and 0.003, respectively). In addition, the CR rate with CABO (9.5 %) was higher than with cisplatin alone (2.5 %) ($p=0.02$) or with PF (1.7 %) ($p=0.01$). However, although perhaps expected differently, these higher response rates (and CR rates) did not translate into an improved median survival, which was 7.3 months in all three arms. The median time to progression among the assessable patients was 19 weeks in the CABO arm, 17 weeks in the PF arm, and 12 weeks in the cisplatin arm (log rank $p=0.02$). Both combination regimens were associated with more toxicity.

In the largest phase III trial ever conducted in R/M-SCCHN, 795 patients were randomly assigned to receive either cisplatin plus pemetrexed or cisplatin plus placebo [49] (Table 42.4). For the whole intention-to-treat population, no survival advantage was observed. However, among patients with performance status 0 or 1, a preplanned subgroup analysis revealed a significant increase in OS and PFS with the cisplatin–pemetrexed regimen (8.4 vs. 6.7 months; $p=0.026$; 4.0 vs. 3.0 months; $p=0.044$, respectively). Moreover, the investigators demonstrated efficacy of the cisplatin–pemetrexed combination in patients with oropharyngeal cancers (OS, 9.9 vs. 6.1 months; $p=0.002$; PFS, 4.0 vs. 3.4 months; $p=0.047$) but they did not provide any data on human papillomavirus (HPV) status which could possibly have influenced the results. As expected, the cisplatin–pemetrexed arm exhibited a higher rate of adverse events including drug-related deaths and grades 3–4 hematologic toxicities and fatigue. Taken together, the potential benefit of the doublet therapy is promising in good performance patients and warrants further study.

42.4.2.2 Platinum–Taxane Combinations

Of the newer agents, the taxanes have been studied most extensively in combination chemotherapy regimens [30, 50–54]. More recently, the carboplatin–docetaxel combination was evaluated in a phase II study conducted by the Southwest Oncology Group [53]. Sixty-eight patients were treated with docetaxel 65 mg/m^2 and carboplatin AUC 6 every 21 days. The OR rate was 25 %. Sixty-one percent of the patients experienced grade 3/4 neutropenia. The median PFS was 3.8 months and the median OS 7.4 months.

The paclitaxel plus cisplatin (PP) combination was directly compared to the PF regimen in the Intergroup trial E1395 conducted by ECOG [54]. Patients received either paclitaxel 175 mg/m^2 (over 3 h) and cisplatin 75 mg/m^2, both on day 1, or the classical PF regimen. The OR rate was 26 % with PP and 30 % with PF ($p=0.84$). The overall grade 3/4 toxicity rate was similar between the two groups. However, grade 3/4 mucositis (31 %) was only observed in the PF arm, while the occurrence of neurotoxicity was similar in the two groups. Median OS was 8.7 months in the PF group and 8.1 months in the PP group. Considering the more favorable toxicity profile, PP may be a valuable alternative to PF.

42.4.2.3 Two-Drug and Three-Drug Platinum–Taxane Combinations

The response rates of two-drug or three-drug combinations with paclitaxel or docetaxel in nonrandomized trials are summarized in Table 42.5. With TPF (docetaxel 80 mg/m^2 day 1, cisplatin 40 mg/m^2 days 2 and 3, and 5-FU 1000 mg/m^2 by continuous infusion days 1–3, repeated every 28 days), Janinis et al. [55] observed an OR rate of 44 %, a median time to progression of 7.5 months, and a median OS of 11 months. Despite the use of granulocyte colony-stimulating factor (G-CSF), febrile neutropenia occurred rather frequently

Table 42.5 Platinum–taxane combinations in recurrent/metastatic SCCHN: two vs. three drugs

	Response rates (complete response rates) (%) with	
	Paclitaxel	Docetaxel
Two drugs		
Cisplatin	32–39 (0)	33–52 (9–11)
Carboplatin	33–33 (4–8)	25 (NR)
Three drugs		
Cisplatin/5-FU	31–38 (13)	44 (12)
Cisplatin/ifosfamide	58 (17)	–
Carboplatin/ifosfamide	59 (17)	–

NR not reported
Based on data from refs. [30, 50–52, 54]

(in 15 % of the patients). Benasso et al. [56] treated 47 patients with PPF (paclitaxel 160 mg/m^2 on day 1 and cisplatin 25 mg/m^2/day and 5-FU 250 mg/m^2/day, both on days 1–3), every 3 weeks. The OR rate was 31 % with 13.3 % complete responders. Median PFS and OS were 4.1 months and 7.9 months, respectively. Forty-eight percent of the patients experienced grade 3/4 neutropenia. The TIP and TIC regimens were tested in R/M-SCCHN by Shin et al. [51, 52]. The TIP regimen consisted of paclitaxel 175 mg/m^2 on day 1, ifosfamide 1000 mg/m^2 (by 2-h infusion) on days 1–3, mesna 600 mg/m^2 on days 1–3, and cisplatin 60 mg/m^2 on day 1, repeated on day 22 [51]. Ninety percent of the patients experienced grade 3 or 4 neutropenia, and the rate of febrile neutropenia was unacceptably high (27 %). The OR rate was 58 % with 17 % complete responders. In the TIC regimen, similar doses of paclitaxel and ifosfamide were used as in TIP, but cisplatin was replaced by carboplatin AUC 6 [52]. Also TIC was repeated every 3 weeks. TIC induced febrile neutropenia in 30 % of the patients and one patient died of neutropenic sepsis. The OR rate was 59 % with 17 % complete responders. The median duration of the responses was 3.7 months. Overall, it can be concluded that taxane-containing triplets induce high response rates, also in the recurrent/metastatic disease setting. However, they are associated with substantial hematologic toxicity and a high complication rate. As these triplets have never been directly compared with PF in a randomized phase III study in this setting, they should not be recommended outside clinical trials. Moreover, as none of the combination chemotherapy regimens demonstrated an OS benefit when compared to single-agent methotrexate, cisplatin, or 5-FU, the use of combination chemotherapy preferably is used in younger patients with a good performance status and with symptomatic disease who require prompt symptom relief.

42.4.2.4 Cytotoxic Chemotherapy in R/M-SCCHN: Summary

For patients who are not in the condition to be treated with the more aggressive platinum-based combination chemotherapy regimens, single-agent methotrexate is still a standard palliative therapy.

Platinum-based combinations are superior to single-agent therapies in terms of response rate (at the cost of more toxicity) but do not lead to meaningful survival benefit.

In first-line setting, median survival ranges between 6–9 months and 1-year survival rates vary from 20 to 40 %.

Once platinum resistance occurs, the outlook is very poor.

The reference arm for testing new single cytotoxic agents, preferably in a randomized trial design, is single-agent methotrexate.

There is thus clearly an urgent need of novel anticancer therapies that target the tumor cells specifically while minimizing the toxic side effects, and R/M-SCCHN patients should preferably be invited to participate in phase I/II clinical trials investigating such experimental therapeutics.

42.5 Targeted Therapies in R/M-SCCHN

Several biological therapies have been chosen in head and neck cancer patients because of their different mechanism of action, greater selectivity (target of action is overexpressed as compared to normal tissue), and different toxicity profiles or because they play a role in carcinogenesis [2, 57]. These include drugs that target growth factors and their receptors, signal transduction, cell cycle control, prostaglandin synthesis, protein degradation, hypoxia, and angiogenesis (Fig. 42.1). More recently, EGFR antisense oligonucleotides, antibody-based immunoconjugates, peptides, affibodies, and nanobodies

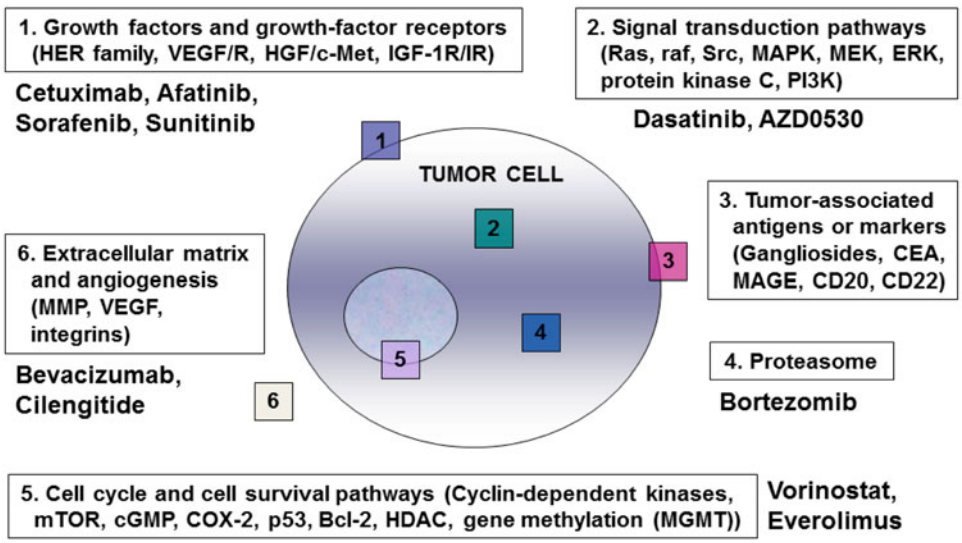

Fig. 42.1 Potential therapeutic targets in SCCHN

have entered preclinical and clinical investigations [58, 59]. Based on practice-changing results in patients with melanoma, immunotherapy targeting specific co-signaling pathways to enhance antitumor immunity represents an interesting approach also in R/M-SCCHN [60]. In this chapter, only those data will be highlighted that have presently some relevance for the treatment of patients with R/M-SCCHN.

42.5.1 Epidermal Growth Factor Receptor and ErbB2

The epidermal growth factor receptor (EGFR, otherwise known as ErbB1 or HER1) inhibitors are of particular interest, because EGFR and its ligand TGF-α (alpha) are overexpressed in the vast majority of cases of SCCHN. In contrast, ErbB2 (HER2/neu) expression in SCCHN ranges between 40 and 60 % [61]. EGFR overexpression and increased EGFR copy number have been related to poor prognosis in patients with SCCHN [62, 63]. Its prognostic role is more specifically related to the treatment received, such as radiotherapy [62, 64] and chemotherapy [65]. Recently, it was found, however, that both EGFR expression by immunohistochemistry and EGFR gene copy number by fluorescence in situ hybridization (FISH) were not predictive for response to anti-EGFR therapy with cetuximab [66, 67].

Two of the potential EGFR-targeting strategies are currently in clinical use: the monoclonal antibodies (MoAbs) directed at the extracellular domain of the receptor and the small molecule and adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs). Table 42.6 is summarizing some important EGFR inhibitors under clinical investigation in R/M-SCCHN. EGFR-activated signaling pathways and the effect of activation on cell proliferation and survival are well documented [68]. Ligand binding to the EGFR is followed by stimulation of a number of different signal transduction cascades, including the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway. The MoAbs and TKIs act at different points on the pathway to disrupt signaling. However, it is likely that the effects of these agents are not mediated by disruption of EGFR signaling pathways alone. Also, antibody-dependent cellular cytotoxicity (ADCC) is thought to be an important mechanism of action, but for a long time, it was thought that this only referred to immunoglobulin G_1 (IgG1) MoAbs [69, 70]. However, very recently it was discovered that also human IgG2 MoAbs against EGFR effectively trigger ADCC but, in contrast to IgG1, only by cells of the myeloid lineage [71]. The ability of many EGFR inhibitors to enhance the effects of radiation and/or chemotherapy has been demonstrated both in vitro and in vivo [72]. In vitro and in vivo data suggest that the combined use of an EGFR-targeted MoAb and a TKI increases the impact of either agent alone on downstream signaling, apoptosis, proliferation, and tumor (xenograft) growth [73, 74], and this may be of interest for the clinical situation, in particular for the recurrent/metastatic disease setting (see below).

42.5.1.1 Monoclonal Antibodies

Cetuximab

The best-studied monoclonal antibody thus far is cetuximab, which is a human–murine chimeric IgG_1 monoclonal antibody, which competitively binds to the extracellular domain of the EGFR. Cetuximab has been tested in R/M-SCCHN, either in second-line after failure of platinum-based chemotherapy or in first-line in combination with platinum-based chemother-

Table 42.6 Selection of relevant EGFR-targeting agents under clinical investigation in SCCHN

Monoclonal antibodies				Toxicity
Cetuximab	IMC225	Chimeric human–murine	IgG1	Skin
Matuzumab	EMD72000	Humanized mouse	IgG1	Skin
Nimotuzumab	h-R3	Humanized mouse	IgG1	Systemic/hemodynamic
Zalutumumab	2F8	Human	IgG1	Skin
Panitumumab	ABX-EGF	Human	IgG2	Skin

Tyrosine kinase inhibitors				
Gefitinib	ZD1839	Reversible	EGFR	Skin/gastrointestinal (GI)
Erlotinib	OSI-774	Reversible	EGFR	Skin/GI
	PKI-166	Reversible	EGFR/ERbB2	Skin/GI/systemic/hepatic
Lapatinib	GW-572016	Reversible	EGFR/ERbB2	Skin/GI/systemic
Afatinib	BIBW-2992	Irreversible	Pan Her[a]	Skin/GI/systemic
Dacomitinib	PF-00299804	Irreversible	Pan Her[a]	Skin/oral/GI/systemic

Based on data from refs. [57, 59]
[a]EGFR/Her2/Her4

apy. Moreover, it has been tested as part of the combined modality treatment for locoregionally advanced SCCHN. This latter application is beyond the scope of this chapter.

Cetuximab in Second-Line Therapy

Three phase II trials examined the role of cetuximab in platinum-refractory or platinum-resistant disease. All patients received cetuximab intravenously at an initial loading dose of 400 mg/m^2 followed by weekly 250 mg/m^2.

Baselga et al. [75] added weekly cetuximab to platinum-based chemotherapy in 96 patients with truly platinum-refractory SCCHN. The OR rate (primary end point) was 10 %. The DC rate (CR + PR + SD) was 53 %. The median time to progression and OS were 85 and 183 days, respectively.

Herbst et al. [76] studied the combination of cetuximab and chemotherapy in a rather heterogeneous population of 130 patients with R/M-SCCHN. The patients had either SD after two cycles or had progressed under cisplatin-based chemotherapy. After cetuximab was added to the same regimen, 13 % of the patients responded. The DC rate in the patients with progressive disease at study entry was 55 %. Median duration of response was about 4 months in the cohort of patients with progressive disease at study entry and 7.4 months in the cohort of patients with SD at study entry.

Vermorken et al. [77] conducted an open-label, uncontrolled, multicenter phase II study, with a two-phase design. In the first phase, 103 patients with platinum-refractory R/M-SCCHN received single-agent cetuximab. A PR was documented in 13 % of the patients. The DC rate was 46 %. The median duration of response was 126 days. The median time to progression was 70 days. Fifty-three patients (51 %) who experienced progression while receiving single-agent cetuximab continued treatment with cetuximab but then again in combination with a platinum compound. No objective responses were observed in this second phase. Responses in the latter three studies were remarkably similar, irrespective of whether the cetuximab was administered as a single agent or added to a platinum-based regimen. This suggests that the observed responses were attributable to cetuximab alone rather than to the reversal of platinum resistance by cetuximab.

Interestingly, the survival of around 6 months achieved with cetuximab in platinum-refractory disease was found similar to that seen with first-line therapy and represented an increase in survival of 2.5 months compared with platinum-refractory historical controls [10]. Based on these results and particularly considering the fact that about 50 % of the patients showed DC, cetuximab monotherapy seems to be a good option for patients with R/M-SCCHN who have progressed on platinum-based chemotherapy.

Cetuximab in First-Line Therapy

The feasibility of the combination of cetuximab with cisplatin or carboplatin and 5-FU was demonstrated in a phase I/II study [78]. In addition, it was shown that cetuximab could be easily combined with weekly paclitaxel [79] and with the combination of a platinum and a taxane [80]. The second step was to evaluate whether the addition of cetuximab to platinum-based chemotherapy in first-line for recurrent/metastatic disease would benefit patients in terms of survival gain. Up to this moment, this has been studied only in two randomized multicenter phase III trials [81, 82] (Table 42.7).

Burtness et al. [81] assigned 117 patients to cisplatin 100 mg/m^2 every 4 weeks either with weekly cetuximab or with weekly placebo. The primary end point of this study was PFS. The study was designed to detect a difference in median PFS of 2 months, i.e., 2 months with cisplatin plus placebo and 4 months with the experimental arm. However, the observed median PFS in the control arm was longer than expected (2.7 months). The median PFS in the cetuximab arm was 4.2 months and that difference did not reach statistical significance ($p=0.09$). In fact, the actual power to detect a 2-month difference in this situation was only 50 %. The OR rate was 26 % in the experimental arm vs. 10 % in the control arm ($p=0.03$). Median OS was not significantly different (9.2 vs. 8 months, $p=0.21$). Development of cetuximab-related skin toxicity was associated with an improved OS (hazard ratio 0.42, $p=0.01$).

In the EXTREME study [82], 442 patients were randomized to receive either chemotherapy alone (cisplatin 100 mg/m^2 or carboplatin AUC 5 mg/ml/min on day 1 followed by 5-FU 1000 mg/m^2/day for 4 days) or the same regimen com-

Table 42.7 First-line treatment with EGFR inhibitors in recurrent/metastatic SCCHN: randomized trials

Study, author (year)	*N*	Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
ECOG 5397 Burtness (2005) [81]	117	P + cetuximab	26*	4.2	9.2
		P + placebo	10	2.7	8.0
EXTREME Vermorken (2008) [82]	442	PF^1 + cetuximab	36*	5.6*	10.1*
		PF^1	20	3.3	7.4
SPECTRUM Vermorken (2013) [90]	657	PF^2 + panitumumab	36*	5.8*	11.1
		PF^2	25	4.6	9.0

P cisplatin, *PF^1* cisplatin or carboplatin plus 5-fluorouracil, *PF^2* cisplatin plus 5-fluorouracil, *significant differences, *PFS* progression-free survival, *OS* overall survival

bined with weekly cetuximab (initial loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2). Cycles were repeated every 3 weeks for a maximum of six cycles. Thereafter, in the combined arm, cetuximab was continued as a single agent until disease progression or unacceptable toxicity whatever came first. No crossover was permitted in this study. Excluded were patients who had received prior chemotherapy except when this had been part of their primary treatment provided this chemotherapy was ended at least 6 months before inclusion in the study. The primary end point was OS. The addition of cetuximab to platinum/5-FU significantly prolonged the median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95 % confidence interval, 0.64–0.99; $p=0.04$) (Fig. 42.2).

The addition of cetuximab also prolonged the median PFS time from 3.3 to 5.6 months (hazard ratio for progression, 0.54; $p<0.001$) and increased the OR rate from 20 to 36 % ($p<0.001$) with 0.9 % CR in the control arm compared to 6.8 % CR in the investigational arm. The beneficial effect was evident both in the patients treated with cisplatin/5-FU and the patients treated with carboplatin/5-FU, although also in this study response rates with carboplatin/5-FU were below those obtained with cisplatin/5-FU independent from the treatment arm (Fig. 42.3). Moreover, protocol-defined subgroup analyses showed that the beneficial effects of adding cetuximab to platinum/5-FU chemotherapy on OS and PFS were evident in nearly all subgroups analyzed. The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19 and 13 %, respectively), neutropenia (23 and 22 %), and thrombocytopenia (11 % in both groups). Sepsis occurred in nine patients in the cetuximab group and in one patient in the chemotherapy-alone group ($p=0.02$). There were 11 cases of grade 3 or 4 hypomagnesemia in the cetuximab group,

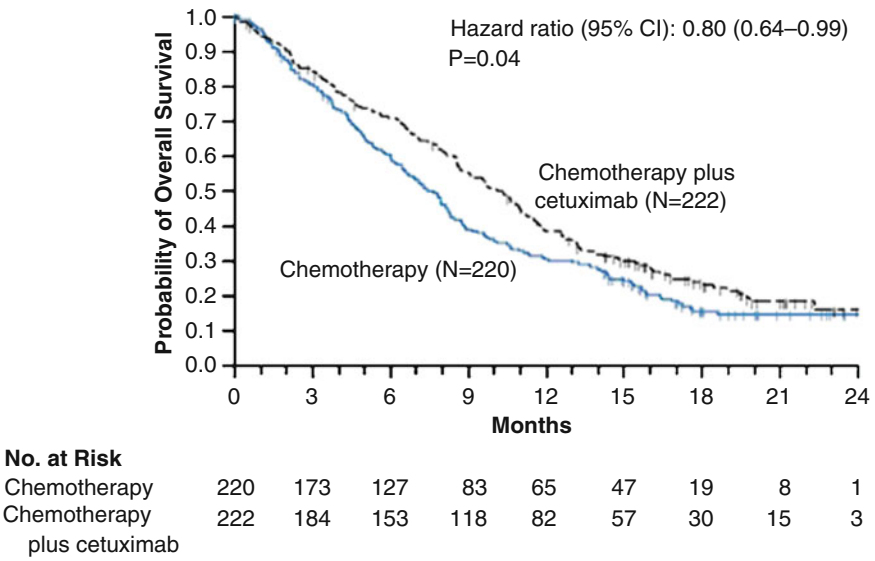

Fig. 42.2 Overall survival with platinum/5-FU combination chemotherapy with or without cetuximab (reprinted from Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116–27. Copyright 2008 Massachusetts Medical Society. All rights reserved)

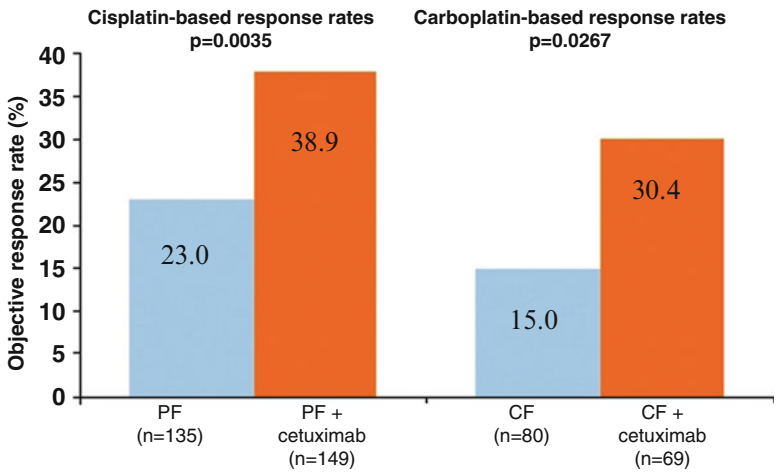

Fig. 42.3 Response rates: cisplatin/5-FU (PF)-based therapy vs. carboplatin/5-FU (CF)-based therapy

as compared with three cases in the chemotherapy-alone group ($p=0.05$). Of the 219 patients receiving cetuximab, 9 % had grade 3 skin reactions and 3 % had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths. The long-term follow-up data of this study were presented in 2014 [83]. Thirty-one (14 %) patients in the cetuximab arm and 25 (11 %) in the chemotherapy arm of the intention-to-treat population lived more than 2 years. At 5 years, 8 patients (6 and 2, in both arms, respectively) were still known to be alive. During the cetuximab maintenance period, the frequency of grade 3–4 toxicity decreased from 81 to 49 % when compared with the initial treatment period with platinum-based regimen plus cetuximab. Despite the markedly low 5-year survival figures, the long-term benefit with the addition of cetuximab has been confirmed.

This is the first time in over 30 years that superiority (in terms of survival) of a new regimen over standard platinum-based combination chemotherapy has been observed. Cetuximab and platinum-based chemotherapy is now considered as a new standard for the treatment of R/M-SCCHN for those who are able to tolerate platinum-based combination chemotherapy regimens [84].

Based on the results of several phase II studies with taxane/cetuximab combinations demonstrating OR rates above 50 % and manageable toxicity, future randomized trials should further explore the promising role of taxanes and their intriguing interaction with cetuximab [79, 80, 85] (Table 42.8). This, in fact, is taking place with the regimen that was originally reported by Guigay et al. in 2012 [85]. That so-called TPEx regimen (supported by G-CSF) induced in phase II an OR rate of 54 % in 54 R/M-SCCHN patients, a median PFS of 7.1 months and a median OS of 15.3 months. After four 3-weekly cycles of this TPEx combination (docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1 every 21 days, and weekly cetuximab), maintenance therapy was applied with biweekly single-agent cetuximab which was continued until disease progression or unacceptable toxicity. Since 2014, the GORTEC 2014-01 trial is ongoing in France, Germany, and Spain. This study compares the cisplatin/5-FU plus cetuximab regimen from the EXTREME trial with the TPEx regimen mentioned above. The primary end point is OS. Ancillary studies will provide data on QoL, cost-effectiveness, and HPV/p16 tumor status.

In contrast, disappointing results were obtained with a pemetrexed/cisplatin/cetuximab combination in 66 R/M-SCCHN patients out of which 35 had received prior cytotoxic chemotherapy [86]. In this phase II study, a relationship between the higher-than-expected rate of deaths (7.6 %), due to frequent grade 4 neutropenia (10.4 %) and pemetrexed, was suspected, thus hampering efforts to further develop this regimen in patients with R/M-SCCHN.

Panitumumab

Panitumumab (ABX-EGF) is a fully human IgG2 antibody with a very strong binding to the receptor [57, 87]. It blocks ligand binding and induces internalization of the receptor but no receptor degradation. Side effects include pruritus, skin rash, dyspnea, fatigue, abdominal pain, asthenia, and diarrhea. Panitumumab at a weekly dose of 2.5 mg/kg has an acceptable tolerability and encouraging clinical activity in patients with a variety of tumor types. Its pharmacokinetic profile allows a more convenient three weekly administration (9 mg/kg). Three studies with panitumumab in the recurrent/metastatic disease setting are of interest, i.e., the PRISM study, the PARTNER study, and the SPECTRUM study. The PRISM study is a phase II study with single-agent panitumumab in the second-line setting that enrolled 52 patients. Primary efficacy results showed a 4 % PR rate and a 39 % DC rate [88].The PARTNER study is a randomized phase II study in the first-line setting studying docetaxel plus cisplatin with or without panitumumab [89]. Data, although not statistically significant, indicated longer median PFS and higher OR rate (6.9 vs. 5.5 months and 44 % vs. 37 %, respectively) but shorter median OS (12.9 vs. 13.8 months) in the panitumumab arm. The interpretation of the decreased OS with the addition of panitumumab is hampered by crossover trial design allow-

Table 42.8 Chemotherapy plus cetuximab in recurrent/metastatic SCCHN showing promising results with taxane-based regimens

Author (year)	Phase	*N*	Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
Burtness (2005) [81]	III	117	P + cetuximab	26*	4.2	9.2
			P + placebo	10	2.7	8.0
Vermorken (2008) [82]	III	442	PF[1] + cetuximab	36*	5.6*	10.1*
			PF[1]	20	3.3	7.4
Buentzel (2007) [80]	II	23	Paclitaxel + Carboplatin + cetuximab	56	5.0 (TTP)	8.0
Hitt (2012) [79]	II	46	Paclitaxel + cetuximab	54	4.2	8.1
Guigay (2012) [85]	II	54	Docetaxel + P + cetuximab	54	7.1	15.3

P cisplatin, *PF[1]* cisplatin or carboplatin plus 5-fluorouracil, *significant differences, *PFS* progression-free survival, *TTP* time to progression, *OS* overall survival

ing patients who initially received docetaxel plus cisplatin to switch to panitumumab monotherapy upon disease progression. In the panitumumab arm, increments in PFS and OR rate were noted in the overall population and also in the p16-positive and p16-negative subgroups. The SPECTRUM trial is a phase III trial in which patients in the first-line recurrent/metastatic disease setting were randomized to be treated with cisplatin/5-FU with or without panitumumab [90]. Differences with the EXTREME trial included: being a global versus a European trial, not allowing carboplatin/5-FU to start with, not allowing performance status 2 patients to start with, and no compulsory maintenance therapy. Activity of panitumumab in this trial was observed in terms of an improved OR rate (36 % vs. 25 %; $p=0.0065$) and an improved PFS (5.8 vs. 4.6 months, $p=0.0036$). However, this did not translate into a significant OS benefit, albeit that there was a 2.1 months' benefit in median OS over a 9.0 months' median survival in the control arm (Table 42.7). The planned subanalysis of this study by p16 status will be described below.

Zalutumumab

Zalutumumab [57] is also a fully human IgG1 EGFR-directed monoclonal antibody. The frequency of acneiform rashes with this compound increases with the dose administered. Zalutumumab so far is the only anti-EGFR MoAb that has been tested in a phase III trial in the second-line setting in patients who failed standard platinum-based chemotherapy vs. best supportive care (BSC) alone [13] (Table 42.9). Patients in the BSC arm were allowed to receive single-agent methotrexate, if so wished by the investigator or patient. Despite significantly enhanced PFS with the zalutumumab regimen and the fact that the tail of the survival curve suggested that at 12 months a double amount of patients was alive in the zalutumumab arm, no significant impact on OS was found. Frequent grade 3–4 side effects were as follows: rash (21 % vs. 0 % in the zalutumumab vs. control arm, respectively), anemia (6 % vs. 5 %), and pneumonia (5 % vs. 2 %). Tumor hemorrhage (nine cases), pneumonia (five cases), and lung abscess (two cases) led most commonly to zalutumumab withdrawal.

Matuzumab

Matuzumab is a humanized IgG1 monoclonal antibody that in a phase I dose escalation study in stage III/IV larynx and hypopharynx cancer showed that fever and transient elevations of liver enzymes were the most frequently observed treatment-related adverse events [91]. A weekly dose of 200 mg, based on pharmacokinetic findings, was selected for further studies. No data of randomized trials in R/M-SCCHN are available.

Nimotuzumab

Nimotuzumab [57] is also a humanized IgG1 mouse antibody. Preliminary data suggest that therapeutic levels of nimotuzumab can be achieved without eliciting skin toxicity, which is the most common side effect of the other anti-EGFR-directed antibodies. Nimotuzumab has a lower receptor affinity than, e.g., panitumumab, cetuximab, or matuzumab, and there seems to be a relationship between receptor affinities and incidence of acneiform rash for anti-EGFR MoAbs [92]. It has been hypothesized that higher binding and internalization of MoAbs in the tumor together with a lower level of internalization in noncancerous tissues is obtained with intermediate affinity constant (K_d) values between 10^{-9} and 10^{-8} M, as is the case for nimotuzumab. Moreover, recent experimental observations have demonstrated that in contrast to other anti-EGFR antibodies, the intrinsic properties of nimotuzumab requires bivalent binding for stable attachment to cellular surfaces, which leads to a greater selectivity of nimotuzumab to bind to cells that express moderate to high EGFR levels, such as in SCCHN. At present, there is no clinical evidence that higher affinity to the receptor leads to greater efficacy, though stronger binding clearly leads to higher toxicities. A phase IIB clinical study in Indian patients with SCCHN showed very few skin reactions, including urticaria and pruritus, but did show some headache, hypertension, and fluctuation in blood pres-

Table 42.9 Second-line treatment with EGFR inhibitors in recurrent/metastatic SCCHN: randomized trials

Study, author (year)	*N*	Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
IMEX Stewart (2009) [12]	486	Gefitinib (250 mg)	2.7	ND	5.6
		Gefitinib (500 mg)	7.6	ND	6.0
		MTX	3.9	ND	6.7
ECOG 1302 Argiris (2013) [17]	270	D + Gefitinib	12.5	3.5 (TTP)	7.3
		D + placebo	6.2	2.1 (TTP)	6.0
ZALUTE Machiels (2011) [13]	286	Z + BSC	6.3	2.3*	6.7
		BSC (optional MTX)	1.1	1.9	5.2
LUX-Head & Neck 1 Machiels (2015) [102]	483	Afatinib	10.2	2.6*	6.8
		MTX	5.6	1.7	6.0

MTX methotrexate, *D* docetaxel, *Z* zalutumumab, *BSC* best supportive care, *PFS* progression-free survival, *ND* no data, *TTP* time to progression, *significant differences, *OS* overall survival

sure [93]. Nimotuzumab is presently approved for use in SCCHN, glioma, and nasopharyngeal cancer in various countries and is granted orphan drug status for glioma in the USA and for glioma and pancreatic cancer in Europe.

42.5.1.2 Tyrosine Kinase Inhibitors

The TKIs compete with ATP for the cytoplasmatic catalytic domain of EGFR. Gefitinib and erlotinib are reversible specific EGFR TKIs and belong to the group of quinazoline TKIs. This group also comprises PD153035 and GW 572016 (lapatinib), which are reversible dual EGFR/HER-2 inhibitors; EKB-569, which irreversibly inhibits the EGFR and HER-2 tyrosine kinase; and the irreversible pan-ErbB TKIs BIBW-2992 (afatinib) and PF-00299804 (dacomitinib) (see Table 42.6). PKI-166 (dual EGFR/ErbB-2) belongs to the pyrrolotriazine TKIs, which also include AEE788 (dual EGFR/ErbB-2) and BMS 599626. ARRY-334543 (dual EGFR/ErbB-2) and PD1578 belong to the pyridopyrimidine TKIs [57].

Single-Agent Use

Until very recently, the results with reversible oral TKIs have been disappointing [12, 94–98] (Table 42.10). Single-agent trials with reversible TKIs published in peer-reviewed journals showed OR rates ranging from 0 to 11 % and a median PFS of approximately 2.5 months [94–98]. Drug toxicity was generally mild, consisting of skin rash and diarrhea, more frequent at higher dosages. It has been suggested, based on some of these single-arm studies, that outcome might not only be related to the occurrence and severity of the skin reaction but also related to the dose used. This latter aspect was tested in a large phase III trial (1839 IL/0704; IMEX) in which 482 patients with R/M-SCCHN, unresponsive to platinum or unfit for platinum, were randomized in a three-armed study to receive either gefitinib 250 or 500 mg/day or methotrexate 40 mg/m^2 intravenously weekly [12]. Neither gefitinib 250 nor 500 mg/day improved survival compared with single-agent methotrexate. OR rates were 2.7, 7.6, and 3.9 %, respectively, and median OS was 5.6, 6, and 6.7 months, respectively (see also Table 42.9). Tumor bleeding was observed more frequently in patients treated with gefitinib than with methotrexate. Single-agent lapatinib (1500 mg/day) was associated with disappointing activity (no objective responses) in a phase II study in 42 patients with recurrent and/or metastatic disease, 15 of whom had previously received treatment with an EGFR inhibitor [98]. Cohen et al. [99] reviewed individual patient data from five clinical trials of erlotinib, lapatinib, or gefitinib to determine if there are clinical characteristics that are associated with clinical benefit. Performance status ($p=0.04$), older age ($p=0.02$), and development of rash ($p<0.01$), diarrhea ($p=0.03$), or oral side effects ($p=0.02$) were independently associated with clinical benefit. Older age, better performance status, and development of rash were associated with longer PFS and OS. EGFR mechanistic toxicities that developed during therapy were also highly associated with benefit and suggest a relationship between drug exposure and outcome.

To date, the only TKI that so far has shown activity comparable to that of cetuximab is afatinib, an irreversible HER family blocker. This was shown in a randomized phase II study in patients failing previous platinum therapy [100]. Dacomitinib showed comparable activity (13 %) but in a non-randomized study in patients without prior platinum [101]. Very recently afatinib was compared with methotrexate in a phase III trial (LUX-HN1) in patients failing first-line platinum-based chemotherapy [102] (Table 42.9). Patients were randomized 2:1 to 40 mg/day afatinib or 40 mg/m^2/week methotrexate. The primary end point of PFS and secondary end point of delayed deterioration in global health status, pain, and swallowing were met in favor of the afatinib arm. Of particular interest was the observation in the p16-negative cohort. However, neither response nor OS was significantly improved.

Combinations with Chemotherapy

A phase I/II trial of erlotinib and cisplatin performed by the Princess Margaret Hospital phase II consortium and the National Cancer Institute of Canada Clinical Trials Group in a population of platinum-sensitive R/M-SCCHN patients revealed an OR rate of 21 % and a median OS of 7.9 months [103]. These data are similar to those reported by Burtness et al. [81] with the combination of cisplatin and cetuximab

Table 42.10 TKIs inhibiting EGFR in recurrent/metastatic SCCHN: data from peer-reviewed journals

Drug	Author (year)	Phase	Prior palliative chemotherapy	Response rate (%)
Erlotinib	Soulieres (2004) [94]	II	0–1 lines	4
Gefitinib	Cohen (2003) [95]	II	0–1 lines	11
	Cohen (2005) [96]	II	0–5 lines	1
	Kirby (2006) [97]	II	0–1 lines	9
	Stewart (2009) [12]	III	P+/P–	3–8
Lapatinib	De Souza (2012) [98]	II	Unclear	0
Afatinib	Seiwert (2014) [100]	II	Prior P	16[a]/8[b]
Dacomitinib	Abdul Razak (2013) [101]	II	No prior P	13

P platinum-based regimen
[a]By investigator review
[b]By independent central review

in similar patients, albeit that these latter data were obtained in a randomized trial setting. Combinations of the TKIs with cisplatin plus docetaxel (in Europe with gefitinib, in the USA with erlotinib) have shown interesting results in small groups of patients and did not cause more hematologic toxicity than normally observed with cisplatin plus docetaxel alone [104, 105]. However, ECOG [17] conducted a randomized, placebo-controlled trial of docetaxel 35 mg/m^2 on days 1, 8, and 15 every 28 days, with or without gefitinib 250 mg/day in R/M-SCCHN patients. Although the combination was well tolerated and improved the time to progression from 2.0 to 3.5 months ($p=0.03$), this did not translate into an improved OS (see Table 42.9). Based on preliminary data, the combination of lapatinib and capecitabine yielded a 24 % OR rate in the early report of 34 evaluable patients, which corresponds with that reported for capecitabine alone [35, 106]. No data on OS were available in that latter study.

42.5.1.3 Overcoming Resistance to Anti-EGFR Therapy

Due to the existence of various receptor signaling pathways consisting of mesenchymal–epithelial transition factor (c-Met), PI3K-Akt, ErbB2/HER2, or ErbB3/HER3, aurora A kinase, phosphorylated signal transducer and activator of transcription 3 (STAT3), vascular endothelial growth factor (VEGF), primary or acquired resistance to cetuximab will usually develop. Apart from various combination regimens with either classic cytotoxic drugs or targeted agents, novel promising approaches include dual targeting MoAbs, mixture of MoAbs, and therapeutics blocking multiple HER receptors. The latter group comprises lapatinib, afatinib, or dacomitinib which were mentioned earlier [58, 59, 107]. An example of dual targeting MoAbs is the IgG1 antibody MEHD7945A which simultaneously inhibits both EGFR and HER3 and also regulates ADCC in vitro and in vivo. A 2014 randomized phase II study of MEHD7945A vs. cetuximab in second-line treatment of R/M-SCCHN failed to demonstrate any significant survival or response differences [108]. Catumaxomab (anti-EpCAM and anti-CD3) and ertumaxomab (anti-HER2/neu and anti-CD3) further expand the armamentarium of dual targeting MoAbs. Finally, Sym004 represents a mixture of two MoAbs aiming at nonoverlapping epitopes on the EGFR [109].

42.5.2 Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor

Activation of the VEGF–VEGFR axis triggers a cascade of signaling processes that promote tumor angiogenesis and lymphangiogenesis. The majority of the studies, although not all, examining the prognostic significance of VEGF expression did observe a worse outcome in patients with SCCHN expressing VEGF and VEGFR-2 [110, 111]. Anti-VEGF strategies include neutralizing antibodies to VEGF or VEGFR and VEGFR TKIs.

42.5.2.1 Bevacizumab

Bevacizumab is a humanized VEGF-A-directed antibody that is in clinical development in a wide variety of tumors including non-small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, and brain tumors. Seiwert et al. [112] integrated bevacizumab 10 mg/kg every 2 weeks into an alternating regimen of infusional 5-FU, hydroxyurea, and daily radiation as treatment for newly diagnosed or recurrent SCCHN requiring local control. Because of neutropenia, the originally planned chemotherapy doses (5-FU 800 mg/m^2, hydroxyurea 1000 mg/m^2) needed to be decreased (5-FU 600 mg/m^2, hydroxyurea 500 mg/m^2). Three thrombotic events and two fatal bleedings as well as late complications including five patients with fistula formation (11.6 %) and four with ulceration/tissue necrosis (9.3 %) were observed, for which a relation to bevacizumab was suspected. A phase II study demonstrated activity of a combination of bevacizumab and pemetrexed in first-line treatment of R/M-SCCHN [113]. In fact, the authors reported an OR rate of 30 % and a median OS of 11 months among 37 evaluable patients. However, bleeding complications were relatively high, with four grade 3 and two fatal bleeding events. Currently, a phase III trial (NCT00588770) investigating the role of a platinum doublet with or without bevacizumab in R/M-SCCHN is ongoing.

42.5.2.2 Tyrosine Kinase Inhibitors and Other Anti-angiogenic Agents

The complications mentioned above are regularly reported in different studies, not only with bevacizumab but also with the TKIs [57]. Early data on semaxanib (a small molecule TKI that interferes with angiogenesis by selectively inhibiting the VEGFR-2 receptor) and the multikinase inhibitor sorafenib [which is both an inhibitor of Raf-1 and B-Raf kinases and protein tyrosine kinases associated with VEGFR-2 and VEGFR-3 as well as the platelet-derived growth factor receptor B (PDGFR-B)] are summarized in two recent reviews, showing only modest activity and a higher-than-expected thromboembolic events [57, 72]. Recently, a high incidence of fatal and nonfatal hemorrhagic complications and fistulization in R/M-SCCHN was reported with sunitinib, a multitargeted TKI of REarranged during Transfection (RET), VEGFR, PDGFR, and c-KIT [114]. The severity of these complications highlights the importance of improved patient selection for future studies with these compounds in head and neck cancer. Use outside clinical trials is not recommended. In contrast, promising results were achieved with sorafenib, a multikinase Raf, VEGFR, and PDGFR inhibitor, combined with carboplatin and paclitaxel in a phase II study [115]. In that study, a DC rate of 84 % was reported, while PFS and OS were 8.5 and 22.6 months,

respectively. Despite favorable preclinical data and clinical phase I results, the addition of the selective integrin inhibitor cilengitide did not add any survival advantage when combined with the cisplatin/5-FU/cetuximab (as in EXTREME) regimen in a randomized phase II study [116].

42.5.3 Combined Targeting of EGFR and VEGFR

Based on preclinical data, combined targeting seems of interest and may be particularly of interest for patients with R/M-SCCHN when tolerance of such an approach proves to be good. Cohen et al. [117] combined erlotinib 150 mg/day and bevacizumab in patients with R/M-SCCHN. In the phase I portion of the study, no dose-limiting toxic effects were observed at the highest dose level of bevacizumab (15 mg/kg every 3 weeks). Forty-eight patients were treated at that dose level. The most common toxic effects were rash and diarrhea. Three patients had serious bleeding events of grade 3 or higher. The OR rate was 14.6 % with 8.3 % CR. The median time of OS and PFS was 7.1 months (95 % confidence interval 5.7–9.0) and 4.1 months (2.8–4.4), respectively. Argiris et al. [118] presented data on the combined treatment with weekly cetuximab and bevacizumab 15 mg/kg every 3 weeks in patients with R/M-SCCHN. Best response in 45 evaluable patients was 16 % PR and 58 % SD. The median PFS was 2.8 months and median OS 7.5 months. Toxicity was manageable. Only rarely serious toxicities were observed.

42.5.4 Other Targets Including Immunotherapy

Other targets, such as those along the EGFR downstream pathways (RAS-RAF-MAPK, PI3K-Akt-mTOR, STAT, phospholipase-C gamma, and protein kinase-C), aurora A, insulin-like growth factor-1 receptor (IGF-1R), proteasome, histone deacetylases (HDACs), toll-like receptor 8, epithelial cellular adhesion molecule (Ep-CAM), and cyclooxygenase-2, are all of interest but not being at the level of having relevance for daily practice, as yet [58, 59, 119] (Table 42.11). Similarly, immunotherapy represents an emerging field of research interest but also without any randomized clinical data available so far. In addition, clinical implementation of immunotherapy is hampered by the fact that the host immune response to the tumor in its immediate microenvironment is highly complex and remains poorly understood [120]. Notwithstanding this limitation, there is a rapidly evolving subset of MoAbs targeting T-cell immune checkpoint molecules like cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed death-1 (PD-1), and its ligand PD-L1. Currently, the largest body of clinical evidence exists for metastatic melanoma, albeit antitumor properties of the T-cell checkpoint inhibitors have been demonstrated in a variety of malignancies including renal cell carcinoma and non-small cell lung cancer [121]. In SCCHN, a gene expression signature study revealed a T-cell-inflamed microenvironment similar to melanoma in 33–47 % of the examined samples. PD-L1 expression and the presence of tumor-infiltrating lymphocytes were strongly correlated with mesenchymal phenotype of SCCHN, thus indicating a potential benefit from immunotherapy [122]. According to the recently presented, preliminary results from a phase Ib study, pembrolizumab (anti-PD-1 MoAb) produced a 20 % OR rate in 56 evaluable patients with R/M-SCCHN. Subgroup analysis based on HPV status found similar OR rates, while median PFS and OS were longer in HPV-positive than HPV-negative patients (17.2 vs. 8.1 weeks and median OS not reached vs. 9.5 months, respectively). The most frequent drug-related toxicities observed were fatigue (18 %), pruritus (10 %),

Table 42.11 Overview of promising immunotherapies in SCCHN

Targeting tumor antigens: tumor antigen-specific monoclonal antibodies – Cetuximab[a], panitumumab, nimotuzumab, onartuzumab, AV-203, MM-121, cixutumumab
Enhancing ADCC to tumor antigen-specific monoclonal antibodies – e.g., IL-12, VTX-2337
Restoring STAT1/STAT3 signaling balance – Ruxolitinib, SAR302503, BMS911543, pegylated interferon-γ
Targeting immunosuppressive cytokines – Bevacizumab, ficlatuzumab, rilotumumab (AMG 102), siltuximab
T-cell checkpoint inhibitors – Ipilimumab, tremelimumab, MED14736, MPDL5280A, BMS-936558, nivolumab, pembrolizumab
Therapeutic cancer vaccines – HPV 16 E6 and E7 peptide vaccine, MAGE-3 and HPV-16 vaccine, HPV pNGVL4a-CRT/E7 (Detox) DNA vaccine, TG4001 vaccine, Lm-LLO-E7 vaccine, multi-epitope p53 vaccine

ADCC antibody-dependent cellular cytotoxicity, *STAT* signal transducer and activator of transcription, *HPV* human papillomavirus, *MAGE-3* melanoma-associated antigen 3, *DNA* deoxyribonucleic acid
Based on data from ref. [119]
[a]FDA approved for SCCHN

and nausea (8 %) [123, 124]. A prospective phase III trial of pembrolizumab vs. standard treatment (methotrexate, docetaxel, or cetuximab) in platinum-resistant R/M-SCCHN (NCT02252042) is ongoing.

42.5.5 Targeted Therapy in R/M-SCCHN: Summary

After decades without real progress, a recent randomized trial showed that adding cetuximab, the first clinically available EGFR-directed monoclonal antibody, to a standard chemotherapy regimen (platinum/5-FU) led to an important survival benefit in patients with R/M-SCCHN, and this has changed practice. So far, the data on the monoclonal antibodies against EGFR seem to be more promising in their interaction with cytotoxic agents than the small molecule TKIs. However, combined targeting either with different anti-EGFR approaches or with both anti-EGFR and anti-VEGF(R) approaches seems an interesting field of research. There is a plethora of targeted therapies in various stages of preclinical and clinical development. The next challenges will be to sort out which of those agents have clinically meaningful activity and to find out how to incorporate them into the existing treatment strategies for those suffering from this devastating disease. The most promising but also demanding approach is to identify reliable prognostic and predictive biomarkers which successfully pass prospective validation in a phase III trial setting. HPV and p16 status may become a stratification element for future randomized trial design [89, 100, 125–128] (Table 42.12 and Fig. 42.4). HPV may be of particular interest when testing single-agent activity of newer targeted therapies [100, 108].

Table 42.12 Relationship between human papillomavirus (HPV)/p16 status and treatment outcomes in recurrent/metastatic SCCHN

Study group	Phase	Drugs	HPV/p16	
			Prognostic	Predictive
EXTREME [82, 125]	III	PF ± cetuximab	Yes	No
SPECTRUM [90, 126]	III	PF ± panitumumab	Yes	Yes
ECOG 1395 [54, 127]	III	PF vs. PP	Yes	NR
ECOG 3301 [127, 128]	II	Irinotecan + docetaxel	Yes	NR
PARTNER [89]	II	Docetaxel + cisplatin ± panitumumab	Yes ?	No
PoC 1200.28 [100]	II	Afatinib vs. cetuximab	NR	Yes

PF platinum plus 5-fluorouracil in EXTREME, cisplatin plus 5-fluorouracil in SPECTRUM and ECOG 1395, *PP* paclitaxel plus cisplatin, *NR* not reported

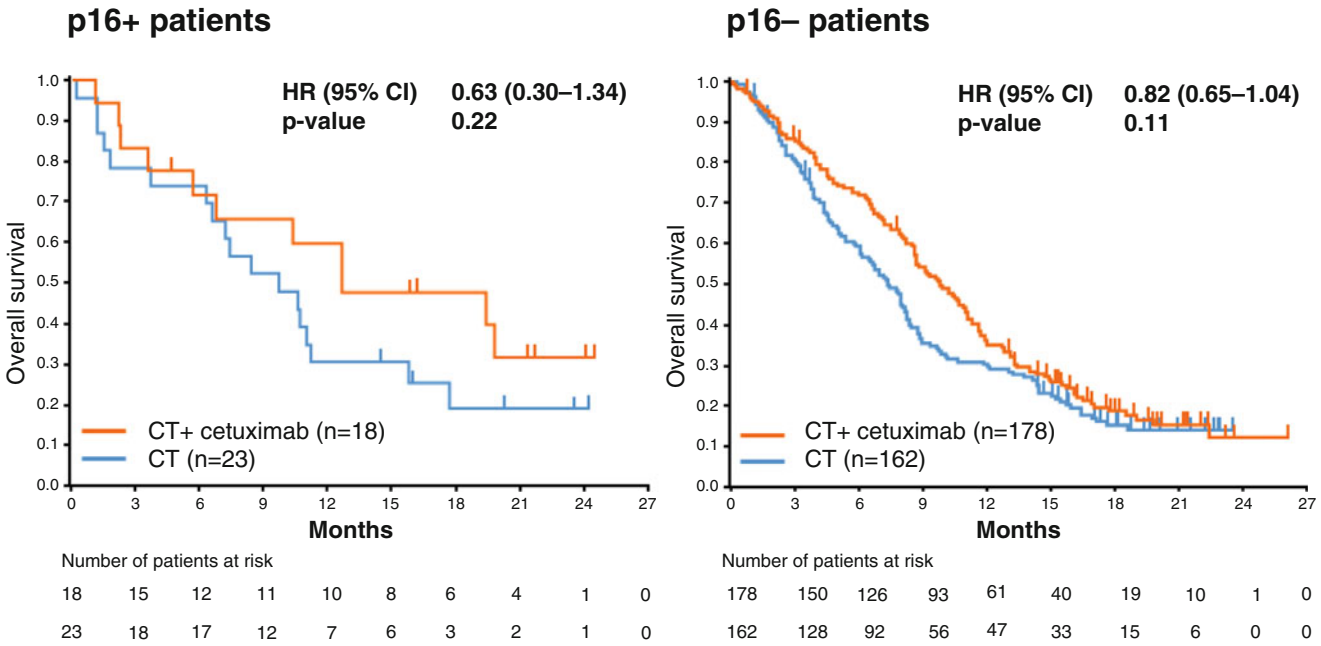

Fig. 42.4 Overall survival in the EXTREME trial by p16 status (presented by Vermorken JB at the 4th International Conference on Innovative Approaches in Head and Neck Oncology (ICHNO), Barcelona, Spain, February 7–9, 2013 (abstract SP-006)) (courtesy of Jan B. Vermorken)

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