REVIEW ARTICLE

Medical treatment of advanced cutaneous squamous-cell carcinoma

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Abstract
Considering the rising incidence, cutaneous squamous-cell carcinoma (cSCC) has a high clinical relevance. In patients with localized cSCC, complete surgical resection is indicated. Radiotherapy should be performed in patients with non-resectable tumours or in patients who are not suitable for surgery. Systemic therapy is reserved for cSCC that are neither surgically nor radiotherapeutically curable due to their extensive local spread and/or local or distant metastasis. In the absence of prospective randomized phase 3 trials to evaluate and compare the efficacy and safety of chemotherapeutics, epidermal growth factor receptor (EGFR) inhibitors and anti-PD-1 antibodies, no final recommendation for systemic therapy can be given for patients with locally advanced or metastatic cSCC. Anti-PD-1 antibodies currently show promising results with response rates of up to 50% in both locally advanced and metastatic cSCC. Anti-PD-1 antibodies appear to achieve higher response rates compared with EGFR inhibitors, and the duration of response appears to be superior to both chemotherapy and EGFR inhibitors. Compared with chemotherapy, the side effect profile of anti-PD-1 antibodies appears to be favourable. Altogether, PD-1 inhibitors are expected to become the new standard of care for patients with locally advanced and metastatic cSCC. Currently, placebo-controlled clinical trials are investigating the adjuvant use of cemiplimab and pembrolizumab in patients undergoing resection and radiotherapy of high-risk cSCC. Patients not eligible for anti-PD-1 treatment, e.g. in organ transplant recipients, or in patients refractory to anti-PD-1 may be offered EGFR inhibitors and/or chemotherapies. Chemotherapies appear to be superior to EGFR inhibitors in terms of response rates, whereas EGFR inhibitors have a more favourable toxicity profile. EGFR inhibitors are therefore more suitable for multimorbid and/or frail elderly patients. By combining EGFR inhibitors with local therapy such as surgery or radiotherapy, response rates and duration of response may be improved.

Conflict of interest
F.F. Gellrich: Honoraria for advice: Sanofi-Aventis. T. Eigentler: Honoraria for advice: Sanofi-Aventis; Research Support: Regeneron Pharmaceuticals. R. Gutzmer: Research Support: Pfizer, Johnson&Johnson, Novartis, Amgen, MerckSerono; Honoraria for lectures and advice: Roche Pharma, Bristol-MyersSquibb, Novartis, MSD, Almirall-Hermal, Amgen, Merck-Serono, SUN, Pierre-Fabre, Sanofi 4SC; Travel and meeting support: Roche Pharma, Bristol-MyersSquibb, Merck-Serono, SUN, Pierre-Fabre. S. Hüning, S. Beissert, E. Stockfleth, and F. Meier have no conflict of interest.

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Introduction
Cutaneous squamous-cell carcinoma (cSCC) has a high clinical relevance. After basal cell carcinoma, it is the second most frequent malignant skin tumour and mainly affects older patients.1 The incidence has increased steadily over the last decades.1 Because of demographic change, a further increase in incidence can be assumed in the future. Due to the frequent comorbidities of older patients, it can be expected that tolerable systemic therapies will become more important in the future.
Complete surgical excision is indicated for patients with localized cSCC.\textsuperscript{2} Radiotherapy should be performed in patients with non-resectable tumours or in patients who are not eligible for surgery.\textsuperscript{3}

Systemic therapy is reserved for squamous cell carcinomas which cannot be treated with curative intention either by surgery and/or radiotherapy due to extensive local spread and/or local or distant metastasis. There are no controlled or randomized studies regarding the benefit of systemic therapy in metastatic cSCC. Systemic therapies should preferably be performed in the setting of clinical trials. The indication and selection of a systemic therapy should be discussed by the interdisciplinary tumour board.\textsuperscript{5}

Various systemic therapies are applied in the treatment of advanced cSCC. Chemotherapeutics, interferon-alpha and 13-cis-retinoic acid have been used mainly in the past (Table 1). In particular with regard to early reports from the chemotherapeutic era, the case series are often small, it is not clear if this was a selection of patients and which response criteria were used. Thus, the efficacy data have to be interpreted with caution. Clinical studies with epidermal growth factor receptor (EGFR) inhibitor have been published since 2011 (Table 2). Since 2018, data have been available on the therapy of squamous cell carcinoma with anti-PD-1 antibodies (Table 3).\textsuperscript{2}

**Methods**

The literature selection is based on the systematic literature search conducted for the development of the German S3 guideline ‘Actinic keratoses and cutaneous squamous-cell carcinoma’ version 1.0 including phase 2 studies for the treatment of locally advanced and metastatic cSCC and case series.\textsuperscript{4} A systematic review summarizing 28 studies with 119 patients was also included.\textsuperscript{5} Data related to anti-PD-1 have been updated including new data presented at the 2019 ASCO Annual Meeting.

**Clinical studies with chemotherapeutics, interferon-alpha and 13-cis-retinoic acid**

Several case series and phase 2 studies investigated the efficacy of different combinations of chemotherapeutic agents, interferon-alpha and 13-cis-retinoic acid (13-cRA) for the treatment of locally advanced and metastatic squamous cell carcinoma (Table 1).

In 1990, Guthrie et al.\textsuperscript{6} investigated 12 patients with advanced squamous cell carcinoma receiving cisplatin 75 mg/m\textsuperscript{2} and doxorubicin 50 mg/m\textsuperscript{2} every 3 weeks. The patients were treated with curative or neoadjuvant intent ahead of excision and radiotherapy. Of 12 patients, 4 (33%) achieved complete remission and 7 (58%) responded to therapy. Combination of systemic therapy with local therapy achieved even higher response rates. Two patients who received only chemotherapy remained in remission. The median duration of response was 8.6 months (4–13 months). Toxicities were manageable. Five patients had to discontinue therapy due to side effects (gastrointestinal toxicities, renal failure and cardiac toxicities).

The combination of cisplatin, 5-fluorouracil (5-FU) and bleomycin\textsuperscript{7} achieved a response in 11 out of 13 patients (84%). Four patients (30%) showed a complete remission, and seven patients (54%) showed a partial remission. The median duration of response was 11.7 months. Local control after definitive radiotherapy and/or surgery was achieved in seven patients. Six patients died of disease during follow-up. Various side effects such as nausea, vomiting, transient skin changes and haematologic abnormalities were reported. In one case, pulmonary fibrosis led to death.

First-line therapy with cisplatin and 5-fluorouracil\textsuperscript{8} showed responses in 6 of 7 patients (86%) with 3 complete remissions (43%) and 3 partial remissions (43%). The median duration of response was 11.8 months (3 and 24). Five out of 7 patients (71%) had mild to severe nausea, some of them with vomiting and diarrhoea.

In a retrospective study, 14 patients received oral monotherapy with 5-fluorouracil.\textsuperscript{9} The cSCC were not suitable for surgery, radiotherapy or topical therapy. The dose was 175 mg/m\textsuperscript{2} for 3 weeks every 5 weeks. On average, 2 to 6 cycles were administered. The therapy was well tolerated, only gastrointestinal side effects occurred. No complete remissions were achieved, two patients (14.3%) showed partial remissions with a median response time of 30 months.

### Table 1 Clinical studies with chemotherapeutics, interferon-alpha and 13-cis-retinoic acid

| Therapy | Line of therapy | Number of evaluable patients | Overall response rate (ORR) | Duration of response (DOR) | Complete remission (CR) |
|---------|----------------|-----------------------------|----------------------------|--------------------------|------------------------|
| Cisplatin and doxorubicin\textsuperscript{5} | partly neoadjuvant | 12 | 58% | 8.6 months | 33% |
| Cisplatin, 5-fluorouracil and bleomycin\textsuperscript{7} | pretreated | 13 | 84% | 11.7 months | 30% |
| Cisplatin and 5-fluorouracil\textsuperscript{8} | first-line | 7 | 86% | 11.8 months | 43% |
| Oral 5-fluorouracil\textsuperscript{7} | first-line | 14 | 14% | 30 months | 0% |
| IFN-alpha and 13-cRA\textsuperscript{10} | first line | 28 | 68% | 5 months | 25% |
| IFN-alpha and 13-cRA and cisplatin\textsuperscript{11} | first-line | 35 | 34% | 9 months | 17% |
| Radiotherapy (70 gray) and carboplatin\textsuperscript{12} | only locally advanced including regional lymph node metastases | 19 | 100% | 24 months (overall survival) | 53% |
Retinoids (vitamin A derivatives) and interferon-alpha (IFN-alpha) are potent regulators of tumour cell differentiation and proliferation, and both have immune modulatory and antiangiogenic activity. Thirty-two patients with heavily pretreated, advanced, inoperable cSCC received a combination therapy of 13-cRA (1 mg/kg per day) and recombinant human IFN-alpha 2a (3 million IU per day) for at least 2 months. Nineteen of 28 evaluable patients (68%) responded to therapy. Seven patients achieved complete remissions (25%). Patients with locally advanced cSCC responded more frequently (93%) to therapy than patients with distant metastases (25%). The median duration of response was 5 months. There were no life-threatening side effects. Dose reductions due to side effects were required in 18 patients, mainly due to fatigue.

Shin et al. investigated the combination of IFN-alpha (5 Mio IU, 3 × weekly), 13-cRA (1 mg/kg daily) and cisplatin (20 mg/m² weekly) in a phase 2 study. Thirty-five patients were evaluable. The overall response rate (ORR) was 34% whereupon 17% of patients achieved a complete remission. The median duration of response was 5 months. There were no life-threatening side effects. Dose reductions due to side effects were required in 18 patients, mainly due to fatigue.

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A systematic review of systemic therapies for locally advanced cSCC summarized 28 studies with 119 patients. These were uncontrolled studies with small patient numbers. Overall, cSCC was showing chemosensitivity to platinum-based chemotherapy with response rates above 50%. In combination with 5-FU, higher response rates were observed, although monotherapies with 5-FU only show low response rates. Complete remissions with the combination occurred in up to 33% of cases. The median duration of response was 42 weeks. Increased toxicity is more frequently observed with polychemotherapy including nausea, vomiting and diarrhoea. In addition to the pronounced side effects of chemotherapy, there are also the side effects of radiotherapy. Interferon-alpha and 13-cis-retinoic acid show lower response rates and a shorter duration of response. Local advanced cSCC appears to respond better to this therapy than metastatic cSCC. The spectrum of side effects differs from platinum-based chemotherapies with fatigue being the most frequent side effect.

### Clinical studies with EGFR inhibitors

| Therapy          | Line of therapy | Number of evaluable patients | Overall response rate (ORR) | Duration of response (DOR) | Complete remission (CR) |
|------------------|-----------------|------------------------------|----------------------------|---------------------------|-------------------------|
| Cetuximab        | First-line      | 36                           | 28%                        | 6.8 months                | 6%                      |
| Panitumumab15    | First-line/second-line | 16                      | 31%                        | 8 months                  | 12%                     |
| Gefitinib16      | Neoadjuvant     | 22                           | 45%                        | 64% (2-year-PFS)          | 18%                     |
| Erlotinib17      | First-line/second-line | 29                      | 10%                        | 4.7 months (PFS)          | 0%                      |
| Erlotinib and radiation 18 | T4 primary tumours | 15                       | –                          | 60% (2-year-PFS)          | –                       |
| Lapatinib19      | Neoadjuvant     | 10                           | 25%                        | –                         | 0%                      |

### Clinical studies with anti-PD-1 antibodies

| Therapy          | Line of therapy | Number of evaluable patients | Overall response rate (ORR) | Duration of response (DOR) | Complete remission (CR) |
|------------------|-----------------|------------------------------|----------------------------|---------------------------|-------------------------|
| Cemiplimab phase 1 locally advanced or metastatic22 | Any | 26                           | 50%                        | –                         | –                       |
| Cemiplimab phase 2 metastatic23 | Any | 59                           | 49%                        | Not reached (median PFS = 18.4 months) | 17%                     |
| Cemiplimab phase 2 locally advanced24 | Any | 78                           | 44%                        | Not reached               | 13%                     |
| Pembrolizumab phase 2 metastatic26 | Any | 10                           | 40%                        | Not reached               | 10%                     |
| Pembrolizumab phase 2 metastatic27 | First-line | 19                           | 42%                        | 7 months (median PFS)     | 5%                      |
role in signal-transduction pathways that regulate key cellular functions involved in cell proliferation, invasion, angiogenesis and metastasis. Therefore, EGFR appears to be a suitable therapeutic target for the treatment of cSCC.13 (Table 2).

Cetuximab is a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR). In 2011, 36 patients with locally advanced cSCC received cetuximab as first-line therapy with an initial dose of 400 mg/m², followed by weekly doses of 250 mg/m² for 6 weeks.14 The response rate was 28%, including 2 (6%) complete remissions and 8 (22%) partial remissions. In patients with complete or partial remission, the median duration of response was 6.8 months. Grade 1–2 adverse events, classified according to Common Terminology Criteria for Adverse Events (CTCAE version 3.0), included acne-like rash in 78% of patients. There were two grade 4 infusion reactions and one grade 3 interstitial pneumopathy.

The monoclonal antibody panitumumab directed against EGFR was investigated in 16 patients with advanced cSCC.15 About 31% of patients showed a response with 2 complete remissions (12%) and 3 partial remissions (19%). Median progression-free survival was 8 months and overall survival 11 months. Five patients developed CTCAE (version 3.0) grade 3 and 4 side effects, including severe skin reactions in four cases. Minor side effects (grade 1 and 2) occurred in the remaining patients.

In a phase 2 study, the small-molecule EGFR inhibitor gefitinib was evaluated for neoadjuvant treatment of 23 patients with locally advanced, metastatic or recurrent cSCC not suitable for curative therapy.16 About 45% of patients responded to therapy, 18% of patients with complete remission and 27.3% of patients with partial remission. Grade 2–3 toxicities were observed in 59.1% of patients experiencing class-specific effects during induction therapy. Following induction, patients underwent surgery or radiotherapy or were treated with radiotherapy plus gefitinib or with surgery plus radiotherapy plus gefitinib therapy. Two-year overall, disease-specific and progression-free survival rates were 72.1%, 72.1% and 63.6%, respectively.

A phase 2 study published in 2018 evaluated the EGFR-targeted small-molecule inhibitor erlotinib for the treatment of patients who are not eligible for curative surgical resection. Twenty-nine patients were evaluable for response. The overall response rate was 10% with no complete response. Median progression-free and overall survival was 4.7 months and 13 months, respectively. Adverse events were reported for all patients enrolled in this study. CTCAE grade 3 adverse events were fatigue, acne-like rash and dehydration.17

In 2013, 15 patients with locally advanced and metastatic cSCC were treated with erlotinib in combination with radiotherapy.18 The response rate and 2-year survival rates were 83% and 65%. The disease-free survival was 73% after one year and 60% after 2 years. The median time to recurrence was 10.5 months (1–14 months), and the recurrence rate after 2 years was 26.7%. Skin reactions occurred in all patients, mucositis in 87% of patients and diarrhoea in 20% of patients.

Neoadjuvant therapy with the small-molecule EGFR inhibitor lapatinib was investigated in 10 patients with cSCC.19 The patients received 1500 mg lapatinib daily for a period of 14 days before definitive surgery. Therapy was continued for another 42 days. A reduction in tumour size was seen in 2 of 8 evaluable patients after 2 weeks of treatment. Two patients had to discontinue therapy prematurely due to side effects (pancreatitis and diarrhoea). There was one grade 3 adverse event (diarrhoea).

Epidermal growth factor receptor inhibitors achieved lower response rates (25–45%) compared with chemotherapy with response rates of 58–86%. The side effects of EGFR inhibitors appear to be more tolerable than the toxicity of platinum-based chemotherapy. Frequently acne-like rash occurs. Since cSCC mainly affects older patients, comorbidities and frailty must be taken into account when selecting systemic therapies. EGFR inhibitors may be more suitable for maintaining quality of life than platinum-based chemotherapy.

**Clinical studies with anti-PD-1 antibodies**

Immune checkpoint inhibitors, in particular anti-PD-1 antibodies such as pembrolizumab and cemiplimab have shown promising results in phase 2 studies for patients with locally advanced and/or metastatic cSCC (Table 3). cSCC have a very high mutational load, which is positively associated with PD1 inhibitor response in other tumour entities. In 2016, the clinical experience with anti-PD-1 antibodies in five patients with locally advanced and/or metastatic cSCC was reported. The heavily pretreated patients were given either nivolumab or pembrolizumab, which resulted in partial responses or stabilization of the disease.20

Cemiplimab is a monoclonal antibody directed against the programmed cell death-1 receptor (anti-PD-1).21 The U. S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved cemiplimab for the treatment of patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or radiotherapy.

The approval of cemiplimab was based on the data of the R2810-ONC-1540 trial (NCT02760498). Patients with locally advanced cSCC and patients with metastatic cSCC were treated with cemiplimab 3 mg/kg every 2 weeks. In both patients with locally advanced cSCC and patients with metastatic cSCC, cemiplimab induced a response in up to 50% of patients. In the metastatic-disease cohort of the phase 2 study, the median follow-up was 7.9 months. In this cohort, 82% of patients continued to have a response and to receive cemiplimab at the time of data cut-off.22

Updated data for cemiplimab were presented at the 2019 ASCO annual meeting. In the phase 2 study of 59 patients with metastatic cSCC, the median follow-up was 16.5 months.23 The overall response rate (ORR) by central review was 49.2% (95%
Median duration of response has not been reached, observed duration of response exceeded 12 months in 75.9% of patients. Median progression-free survival was 18.4 months. Median overall survival has not been reached, Kaplan–Meier estimation of overall survival at 24 months was 70.6% (95% CI 57.0–80.6%). The most common treatment-related adverse events were diarrhoea, fatigue and nausea. In 13.6% of patients, grade ≥ 3 immune-related adverse events were observed. In the phase 2 study of 78 patients with locally advanced cSCC, the median follow-up was 9.3 months.24 ORR by central review was 43.6%, investigator-assessed ORR was 52.6%. Median duration of response, progression-free survival and overall survival have not been reached. The Kaplan–Meier estimated progression-free probability at 12 months was 58.1% (95% CI, 43.7–70%), and the estimated probability of survival at 12 months was 93.2% (95% CI, 84.4–97.1%). The most common treatment-related adverse events were fatigue, diarrhoea, pruritus and nausea. Grade ≥ 3 immune-related adverse events were observed in 10.3% of patients.

The immune-mediated side effects differ from the side effects of platinum-based chemotherapy or EGFR inhibitors. Timely interdisciplinary management of side effects with early diagnosis and initiation of therapy especially for immune-mediated phenomena is relevant for a safe and successful treatment. It should be noted that immune checkpoint inhibitors can lead to rejection reactions in organ transplant patients.25

Kuchchadkar et al.26 evaluated the clinical activity of the anti-PD-1 antibody pembrolizumab in metastatic cSCC patients not curable by surgery or radiotherapy. Patients were treated with pembrolizumab 200 mg every 3 weeks for up to 2 years. Overall response rate was 40%, with 10% complete response and 30% partial response. Two grade 3 related adverse events were noted, hepatitis and pneumonitis. The median PFS and OS was not reached at the time of publication of the study (February 2018).

First-line therapy with pembrolizumab was investigated in 19 chemotherapy-naive patients.27 Two hundred milligram pembrolizumab was administered every 3 weeks for a period of up to 24 months. Overall response rate was 42% corresponding to 7 partial remissions (37%) and 1 complete remission (5%). Median progression-free survival was 7 months and median overall survival was not reached at the time of publication. One patient discontinued pembrolizumab due to grade 2 colitis. Therapy-related adverse events occurred in 63% of patients and included rash (32%), pruritus (16%), fatigue (26%), dyshidrotic (10%) and diarrhoea (10%).

Anti-PD-1 antibodies are currently showing promising results with response rates of up to 50% in both locally advanced and metastatic cSCC. Anti-PD-1 antibodies appear to achieve higher response rates compared with EGFR inhibitors, and the duration of response appears to be superior to both chemotherapy and EGFR inhibitors. Compared with chemotherapy, the side effect profile of anti-PD-1 antibodies appears to be favourable. Altogether, PD-1 inhibitors are expected to become the new standard of care for patients with locally advanced and metastatic cSCC. Currently, placebo-controlled clinical studies investigate the adjuvant use of cemiplimab and pembrolizumab in patients after resection and radiotherapy of high-risk cSCC.

Patients not eligible for anti-PD-1 treatment, e.g. in organ transplant patients, or being progressive thereunder might be offered EGFR inhibitors and/or chemotherapies. Chemotherapies appear to be superior to EGFR inhibitors in terms of response rates, whereas EGFR inhibitors have a more favourable toxicity profile. EGFR inhibitors are therefore more suitable for multimorbid and/or frail elderly patients. By combining EGFR inhibitors with local therapy such as surgery or radiotherapy, response rates and duration of response can be improved.

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