Rapid response to cemiplimab for advanced cutaneous squamous cell carcinoma

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INTRODUCTION

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer, with an estimated annual incidence of > 700,000 in the United States.[1,2] In >95% of patients, CSCC is cured, most commonly with excision or Mohs micrographic surgery. A small percentage of patients develop advanced CSCC (locally advanced CSCC [laCSCC] or metastatic CSCC [mCSCC]), which is associated with a high mortality rate and poor prognosis, with an estimated 3-year survival of 55%.[3,4] Traditional treatment options for advanced CSCC include cytotoxic chemotherapy and targeted therapy; eg, epidermal growth factor receptor inhibitors.[5] However, only 15%-25% of patients with advanced CSCC respond to these medications, and when responses do occur, they are rarely durable.

Cemiplimab is a highly-potent, fully human, hinge-stabilized, IgG4 monoclonal antibody directed against programmed cell death-1 (PD-1) protein.[6] Cemiplimab demonstrated substantial antitumor activity in phase 1 advanced CSCC expansion cohorts (NCT02383212) and in the pivotal phase 2 EMPOWER-CSCC 1 trial (NCT02760498).[7-9] Based on these trials, cemiplimab-rwlc is approved for treatment of advanced CSCC in the United States and Europe and is approved or under review by other health authorities.[6,10-12]

It is unclear, how quickly patients respond to therapy. In the clinical trials leading to cemiplimab's approval, the first assessment was performed 8 weeks after initiation of therapy.[7-9] Here, we report the case of a 61-year-old man with advanced CSCC treated with cemiplimab, for whom closer follow-up revealed a clinical sustained response only 3 weeks after initiation of therapy.

Abbreviations used:

CSCC:	cutaneous squamous cell carcinoma
laCSCC:	locally advanced cutaneous squamous cell carcinoma
mCSCC:	metastatic cutaneous squamous cell carcinoma

CASE REPORT

A 61-year-old otherwise healthy man from the CemiplimAb-rwlc Survivorship Epidemiology study (NCT03836105)[13] presented with a 1-year history of an enlarging growth on his left cheek. He had no health insurance and was evaluated at a volunteer-driven free medical clinic by one of the authors (JS).[14] Physical examination revealed a large, ulcerated, necrotic mass, with palpable extension in the underlying soft tissue, measuring 10.0 × 8.5 cm on the left cheek. There was no palpable lymphadenopathy. A biopsy revealed an infiltrating, moderately well-differentiated, invasive CSCC, with no perineural invasion noted, although the patient did describe localized pain. The mass was deemed surgically unresectable, and the patient was referred by dermatology to a medical and radiation oncologist, who determined that radiation would not be an

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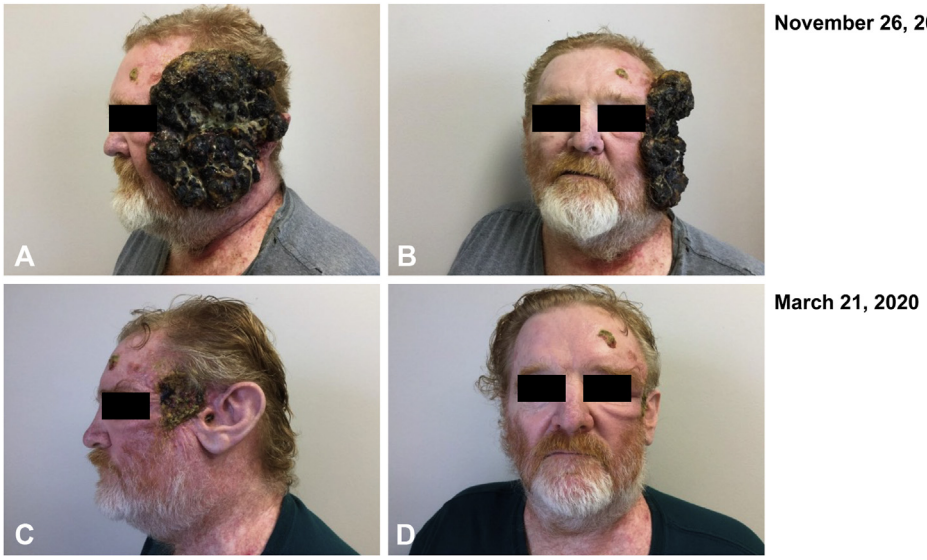

Fig 1. Rapid response to cemiplimab in a patient with advanced cutaneous squamous cell carcinoma. **A,** First clinical presentation revealed a 10.0 × 8.5-cm necrotic exophytic mass located on the left cheek. **B,** Clinical presentation 6 months after initial presentation with clear progression of tumor. The tumor measured 20.0 × 19.0 cm and extended from the left tragus to the left lateral canthus. **C,** Photographic documentation at 3 weeks, following the first cycle of cemiplimab, showed a reduction in tumor size, now measuring 15.0 × 12.0 cm. **D,** Photographic documentation after 4 cycles of treatment.

effective treatment option. Due to insurance status, further care was delayed for 6 months.

The patient returned 6 months later with tumor progression and a 20-lb weight loss. The tumor now measured 20.0 × 19.0 cm, extending from the left tragus to the left lateral canthus (Fig 1, *A* and *B*). The left eye was forced shut due to local swelling and ptosis. The remainder of the examination was notable for decreased hearing from his left ear and absence of lymphadenopathy. Positron emission tomography-computed tomography revealed an ^{18}F-fluorodeoxyglucose-avid mass in the right lung. There were 3 small (<1 cm) ^{18}F-fluorodeoxyglucose-avid nodular densities in the left lung that were too small for biopsy. A decision was made to monitor closely.

The patient received his first cycle of cemiplimab 350 mg every 3 weeks within the following month and was reassessed at 3-week intervals with photographic documentation. At the first reassessment, 3 weeks following the first administration, the tumor had shrunk by ~40% and measured 15.0 × 12.0 cm with some ulceration (Fig 1, *C*). The patient was able to open his left eye and reported improved hearing. After 5 treatment cycles, his tumor had decreased to 6.0 × 4.0 cm (Fig 1, *D*). The patient continued to experience progressive weight loss, but no other side effects were noted.

Repeat imaging revealed that 2 lung nodules had resolved; however, 1 nodule had enlarged from 6 mm to 2.5 cm. A lung biopsy was performed on this nodule. Tumor cells demonstrated a pattern consistent with poorly-differentiated squamous cell carcinoma. A presumptive diagnosis of metastatic squamous cell carcinoma was made.

While the primary tumor continued to have good response to cemiplimab, the medical oncologist was concerned about the pulmonary nodule that had enlarged during the treatment period. As this might be considered tumor progression, cemiplimab was discontinued after the fifth treatment cycle, and cetuximab, an epidermal growth factor receptor inhibitor, was initiated. After 4 months of therapy, the lung nodule, resolved, but the facial tumor, representing laCSCC, exhibited clinical progression, and the patient succumbed 18 months after his initial presentation.

DISCUSSION

Immune checkpoint inhibitors have led to a breakthrough in the management of advanced CSCC. In 2018, cemiplimab-rwlc became the first Food and Drug Administration-approved systemic therapy for advanced CSCC.[6] Cemiplimab approval was based on data from the phase 2 EMPOWER-CSCC 1 trial and 2 phase 1 expansion cohorts.[7-9]

Together, these trials included 108 patients (mCSCC, n = 75; laCSCC, n = 33). The overall objective response rate with cemiplimab was 47% for patients with mCSCC and 49% for patients with laCSCC; 61% of responders experienced a response of ≥ 6 months.[7-9] For patients with mCSCC without externally visible target lesions, the objective response rate was assessed per independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1; for patients with externally visible target lesions (mCSCC and laCSCC), the objective response rate was assessed according to a composite response that integrated independent central review assessments of radiological data according to Response Evaluation Criteria in Solid Tumors version 1.1 and digital medical photography as per the modified World Health Organization criteria.[15,16] Longer-term follow-up, and analyses of additional patients in the phase 2 study (combined N = 193) confirmed observations on initial efficacy and demonstrated durability of responses.[17,18] In expansion cohorts of the phase 1 study and the metastatic-disease cohort of the phase 2 study, the median observed time to response was 2.3 months (range, 1.7-7.3) and 1.9 months (range, 1.7-6.0), respectively.[7]

We report here the most rapid onset of clinical response to cemiplimab. A better understanding of the time to first response and maximum response is critical to evaluate treatment efficacy and may lead to optimization of treatment durations. Studies of patients with Hodgkin lymphoma treated with anti-PD−1 drugs suggest an early decrease in anatomic and metabolic tumor burden, which may represent a favorable predictive sign.

Cutaneous skin cancers are often managed by dermatologists based on both functional and quality-of-life status. In many circumstances, partial shrinkage of a tumor, with a lack of tumor growth, might be considered a clinical success by both the dermatologist and patient. This case illustrates the challenge of managing laCSCC. The decision to discontinue cemiplimab in our patient, despite a significant improvement in his primary cutaneous tumor, was due to an assumption of 'disease progression'. This assumption was made because a pulmonary nodule, representing mCSCC, was enlarging, despite an improvement in the large facial tumor, which was the patient's primary concern. Although the oncologist was focused on the nontarget finding, it is possible that the patient could have been treated, if he had been maintained on cemiplimab, while his lung nodule was addressed with stereotactic radiation therapy.

The reason for differences in response between the primary tumor and metastasis remains unclear.[19] One possibility is that the facial laCSCC had a moderately-differentiated histology type, and the pulmonary nodule had a poorly-differentiated type. As the decision was made to discontinue cemiplimab, the possibility of pseudoprogression, whereby immune infiltration of a tumor leads to the phenomenon of an initial increase in size followed by response in patients treated with immune checkpoint inhibitors, cannot be excluded.[19] This case illustrates significant early clinical response to cemiplimab and provides new insights into the kinetics of response to this medication. Further investigations are warranted to determine, whether differences in time to first response correlate with tumor burden, overall maximal response, and prognosis. Clearly, the management of immune checkpoint inhibitor therapy requires ongoing input by the dermatologist, the oncologist, and the patient, to determine treatment goals.

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Conflicts of interest

None disclosed.

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