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Brief overview: cemiplimab for the treatment of advanced basal cell carcinoma: PD-1 strikes again

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***Abstract*:** Basal cell carcinoma (BCC) is the most common malignancy worldwide. Fortunately, most tumors are localized and easily amenable to surgical resection or locally destructive treatments. However, a subset of BCCs can become locally advanced or metastatic. The development of small-molecule inhibitors of smoothened, a protein in the hedgehog pathway, which is almost universally activated in BCCs, was a breakthrough in the treatment of patients with advanced BCC. However, these agents are associated with primary and secondary resistance and have a toxicity profile that makes long-term use difficult. The recent approval of cemiplimab for patients with advanced BCC who are resistant to or are intolerant of hedgehog inhibitor therapy fills a significant unmet need as these patients now have a viable, second-line systemic therapeutic option. This article summarizes the rationale and data leading to the approval for cemiplimab in advanced BCC.

Keywords: anti-PD-1, basal cell carcinoma, immunotherapy, skin cancer

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Introduction

The immune system likely plays a critical role in the surveillance and eradication of skin cancers, including basal cell carcinoma (BCC). This is exemplified by the long-known observation that the incidence of BCC, and non-melanoma skin cancer (NMSC) in general, is greatly increased in patients receiving immunosuppression for solid organ transplants. It is estimated that the risk of developing BCC is increased by a factor of 10 in patients with solid organ transplants.[1] The risk factors for developing NMSC in immunosuppressed patients are the same as those for the general population, including older age, male sex, and cumulative sun exposure.[2] Furthermore, these cancers tend to occur in sun-exposed areas, implicating ultraviolet radiation as a causative agent.[3] It has also long been known that ultraviolet radiation induces a local immunosuppressive environment.[4]

Imiquimod is an immune response modifier that works by binding toll-like receptors and inducing release of immune-modulating cytokines. This agent is approved for the treatment of superficial BCCs and has demonstrated an overall treatment success upward of 80%.[5] This is proof of concept that the immune system can be utilized to treat and, in some instances, irradicate BCCs.

BCC, being a UV-induced tumor, tends to harbor a high tumor mutation burden (TMB), and studies have demonstrated that approximately 60% of cutaneous BCCs have a TMB $\geqslant$10 mutations/megabase (Muts/Mb) (with the average across all solid tumor types examined being 13.3%).[6] Goodman *et al.*[7] reported in their analysis that for BCCs, the median TMB was 90 Muts/Mb compared with a median TMB of 4 Muts/Mb for all other tumors examined. There is some evidence that TMB may correlate with an antitumor immune response, with the hypothesis that the increased mutational burden leads to increased neoantigen production and a greater chance of the tumor being recognized by CD8 + T-cells.[6–8]

Immunotherapy now plays a critical role in the treatment of most cutaneous malignancies.

Checkpoint inhibitors (anti-CTLA4 antibody, anti-PD1 antibodies, and anti-PDL-1 antibodies) are approved treatments for advanced melanoma, cutaneous squamous cell carcinoma (cSCC), and Merkel cell carcinoma. Like BCC, these tumors share the characteristics of innate immune surveillance and a high TMB.[1,6]

BCCs almost universally harbor mutations in the hedgehog pathway. The hedgehog pathway inhibitors (HHIs), vismodegib and sonidegib, have demonstrated impressive results in clinical studies in patients with advanced BCC, and these agents have been Food and Drug Administration (FDA)-approved since 2012 and 2015, respectively, for this patient population.[9,10] However, these agents are associated with both primary and secondary resistance of the tumor as well as having significant toxicity, making long-term use of these agents difficult.[11] Up until recently, there was no approved second-line systemic therapy for advanced BCA.

Immunotherapy for BCC and the approval of cemiplimab

There have been several case reports published of patients with advanced BCC being treated with immune therapy demonstrating meaningful and durable responses.[7,12–14] In addition, Chang and colleagues published an open-label, proof-of-concept study of pembrolizumab ± vismodegib in 16 patients with advanced BCC.[15] This demonstrated an overall response rate of 38% without any concerning safety signals. Although not powered to detect this, the response rate of the pembrolizumab plus vismodegib group was not superior to the monotherapy group.

Study 1620 was an open-label, multi-center, phase II, non-randomized study that evaluated the efficacy of cemiplimab in 54 patients with metastatic BCC (mBCC) (group 1) and 84 patients with locally advanced BCC (laBCC) (group 2) who had progressed on HHI therapy, were intolerant to HHI therapy, or who had not had an objective response after 9 months of HHI therapy. Patients with laBCC could not be candidates for curative surgery or curative radiation. Patients were excluded if they had autoimmune disease that required systemic immunosuppression within 5 years; history of solid organ transplant; prior treatment with anti-PD-1 or PD-L1 therapy; infection with HIV, hepatitis B, or hepatitis C; or poor performance status (Eastern Cooperative Oncology Group (ECOG) ⩾2). The primary end point was confirmed objective response rate (ORR) by independent central review (ICR). Secondary end points included duration of response (DOR), progression-free survival (PFS), overall survival (OS), complete response (CR) rate, and safety and tolerability. Patients received cemiplimab 350 mg every 3 weeks for up to 93 weeks, or until disease progression or unacceptable toxicity.[16]

When the prespecified timing of the primary analysis was reached for group 2 (laBCC), group 1 (mBCC) data had not reached maturity and therefore were not included in the published results. A total of 84 patients with laBCC were enrolled, treated, and included in the analyses. Patients were a median age of 70 years, and the majority were men (67%) with primary tumors of the head and neck (89%). All patients had received prior HHI therapy, and the most common reason for discontinuing HHI therapy was disease progression (71%). Fifty percent of patients had received prior cancer-related radiation and 83% had received at least one prior cancer-related surgery.[16]

At the time of data cutoff, the median duration of follow-up was 15 months and the median duration of exposure to cemiplimab was 47 weeks. ORR by ICR was seen in 26 of 84 patients (31%), including 6% CR and 25% PR. Of note, CR was defined as the disappearance of all target lesions for ⩾4 weeks, CR of nontarget lesions, and without the appearance of any new lesions. A confirmatory biopsy was also required for patients with laBCC. PR was defined as a decrease of ⩾30% in the sum of target lesion diameters by RECIST 1.1 and ⩾50% reduction by World Health Organization (WHO) criteria for externally visible lesions. Seventy-nine percent of patients had an observed DOR of at least 6 months, and median DOR was not reached. Interestingly, the median time to response was 4.3 months compared with 1.9 months seen in Study 1540 which evaluated the use of cemiplimab in advanced cSCC.

Subgroup analysis showed no difference in ORR regardless of the baseline characteristics, and exploratory biomarker data showed no association between response and TMB, major histocompatibility class 1 (MHC-1) expression, or PD-L1 status.[16] For patients with an evaluable PD-L1 expression level ($n=50$), the ORR, disease-control rate, and durable disease-control rate were 26%, 77%, and 51% for those with a PD-L1 expression of <1% ($n=35$) compared with 27%, 87%, and

53% for those with a PD-L1 expression of ⩾1% ($n=15$).[16] Based on this, it is clear that patients with low PD-L1 expression may still derive benefit from cemiplimab, and therefore PD-L1 testing is not required prior to initiating treatment.

Treatment-emergent adverse events of any grade, regardless of attribution, occurred in 97% of patients, with the most common being fatigue (30%), diarrhea (24%), pruritus (21%), and asthenia (20%). Grade 3–4 adverse events occurred in 40 (48%) out of 84 patients. The most common were hypertension (5%), colitis (5%), fatigue (4%), urinary tract infection (4%), and visual impairment (4%). Serious adverse events considered related to treatment occurred in 11% of patients, with the most common being colitis (4%) and adrenal insufficiency (2%). There were no grade 4–5 immune-related adverse events and no treatment-related deaths. Eleven percent of patients discontinued treatment due to a treatment-related adverse events.

The prespecified interim analysis of the mBCC cohort was presented at the 2020 Society for Immunotherapy of Cancer (SITC) conference.[17] This analysis included 28 patients with nodal and/or distant metastatic disease with the opportunity to be followed for approximately 57 weeks. Objectives and study design were the same as discussed above for laBCC. Eighty-two percent were male and the median age was 65.5 years. Here, the majority of patients had primary tumors of the trunk (50%). Fifty-four percent of patients had both nodal and distant metastases, with 32.1% having distant-only and 14.3% having nodal-only metastases. The median duration of exposure was 38.9 weeks, with a median of 13 doses of cemiplimab administered. ORR by ICR was 21.4%, including 6 of 28 patients with a partial response and 0 of 28 patients with complete response. Median time to response was 3.2 months with an observed DOR of 9–23 months. All six responses had an observed DOR of at least 8 months; median DOR was not reached. Adverse events of any grade occurred in 92.9% of patients, with the most common (regardless of attribution) being fatigue (50%), diarrhea (35.7%), pruritus (25%), and constipation (25%). Grade ⩾3 adverse events occurred in 42.9% of patients, with hypertension being the only adverse event occurring in ⩾2 patients. Grade ⩾3 treatment-related adverse events occurred in 17.9% of patients, and the only grade ⩾3 immune-related adverse event (irAE) was colitis, which occurred in one patient (3.6%). There was one adverse event that led to death, which was deemed unrelated to study treatment.

Based on the combined laBCC and mBCC data, cemiplimab was FDA-approved fully for patients with laBCC and granted accelerated approval for patients with mBCC who were previously treated with HHI therapy or for whom an HHI is not appropriate.[18] The recommended dose of cemiplimab is 350 mg given as an intravenous infusion over 30 min every 3 weeks. No PD-L1 or TMB testing is required prior to starting treatment. In general, treatment should be withheld for grade ⩾3 immune-mediated adverse reactions and permanently discontinued for grade ⩾4 immune-mediated adverse reactions, recurrent severe immune-mediated adverse reactions that require systemic immunosuppressants, or an inability to reduce prednisone dose to ⩽10 mg per day within 12 weeks of initiating corticosteroids. No dose reduction is recommended for cemiplimab.

The results of Study 1620 demonstrate that cemiplimab is active in advanced BCC and is the first systemic therapy to show clinically meaningful antitumor activity in patients with locally advanced or metastatic BCC after progression on or intolerance to HHI therapy.[16,17]

Conclusion

In general, cutaneous malignancies have demonstrated meaningful response rates and durability to immunotherapy. Although the approval of HHI therapy, nearly a decade ago, was a breakthrough for patients with advanced BCC, these agents were often associated with primary and secondary resistance and, importantly, have a toxicity profile that makes long-term use difficult from a quality-of-life perspective. Study 1620 demonstrated the use of cemiplimab, a PD-1 antibody, resulted in meaningful response- and disease-control rates for patients with advanced BCC previously treated with an HHI. As noted above, time to response in this patient population can be delayed, with over half of the responses coming after the time of first assessment and 5 of the 26 responses coming after 6 months on therapy. The factors associated with this response pattern are not clear, and further study into these mechanisms are certainly warranted. However, from a clinical perspective, it is important to recognize this response pattern and maintain patients

on treatment in the absence of unequivocal progression or toxicity.

Like multiple other trials with PD-1 antibodies in patients with advanced malignancies, cemiplimab was generally well tolerated in patients with advanced BCC. There were no new or concerning safety signals identified. Although patients with advanced BCC generally present at an advanced age, often with associated co-morbidities, they often remain candidates for immunotherapy. In the 1620 study, all patients were over 60 years and 63% were 65 years and above.

Therefore, the approval of cemiplimab for advanced BCC addresses a significant unmet need as there was previously no systemic treatment options for this patient population.

Author contributions

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Christina Davis received speaking fees from Regeneron, Pfizer, and Sanofi and has received consulting fees from Array and Regeneron; Karl Lewis has received consulting fees from Regeneron, Merck, Roche/Genentech, Sun Pharma, Pfizer, and Iovance and received research funding from Regeneron, Merck, Roche/Genentech, Pfizer, Array, Iovance, SeaGen, Senhwa, Moderna, and Synlogic.

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