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ORIGINAL ARTICLE

Final analysis of phase II results with cemiplimab in metastatic basal cell carcinoma after hedgehog pathway inhibitors

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Background: Metastatic basal cell carcinoma (mBCC) is a rare condition with no effective second-line treatment options. Cemiplimab is an immune checkpoint inhibitor that blocks the binding of programmed cell death-1 (PD-1) to its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). Here, we present the final analysis of cemiplimab in patients with mBCC after first-line hedgehog pathway inhibitor (HHI) treatment (NCT03132636).

Patients and methods: In this open-label, single-arm, phase II study, adults with mBCC and Eastern Cooperative Oncology Group performance status $\leq$1, post-HHI treatment, received cemiplimab 350 mg intravenously every 3 weeks for $\leq$93 weeks or until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) by independent central review (ICR). Duration of response (DOR) was a key secondary endpoint. Other secondary endpoints were ORR per investigator assessment, progression-free survival (PFS), overall survival (OS), complete response rate, safety, and tolerability.

Results: Fifty-four patients were enrolled: 70% were male and the median age of patients was 64 [interquartile range (IQR) 57.0-73.0] years. The median duration of follow-up was 8 months (IQR 4-21 months). The ORR per ICR was 22% [95% confidence interval (CI) 12% to 36%], with 2 complete responses and 10 partial responses. Among responders, the median time to response per ICR was 3 months (IQR 2-7 months). The estimated median DOR per ICR was not reached [95% CI 10 months—not evaluable (NE)]. The disease control rate was 63% (95% CI 49% to 76%) per ICR and 70% (95% CI 56% to 82%) per investigator assessment. The median PFS per ICR was 10 months (95% CI 4-16 months); the median OS was 50 months (95% CI 28 months-NE). The most common treatment-emergent adverse events were fatigue [23 (43%)] and diarrhoea [20 (37%)]. There were no treatment-related deaths.

Conclusions: Cemiplimab demonstrated clinically meaningful antitumour activity, including durable responses, and an acceptable safety profile in patients with mBCC who had disease progression on or intolerance to HHI therapy.

Key words: cemiplimab, metastatic basal cell carcinoma, immunotherapy, PD-1, hedgehog inhibitor

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INTRODUCTION

The incidence of basal cell carcinoma (BCC) is rising in the United States and worldwide, possibly attributable to increased exposure to ultraviolet B radiation.[1,2] In the United States, BCC is the most common nonmelanoma skin cancer, with ∼2.8 million cases per year, leading to >3000 deaths annually.[3,4] For most patients with BCC, surgery is a curative option; however, a small fraction of patients develop either metastatic BCC (mBCC) or locally advanced BCC (laBCC) that requires systemic therapy.[5] Historically, population-based data have been limited on the natural course of mBCC, but cases from 1981 to 2011 do not suggest a trend for improvement in median survival.[6]

More recent development of new treatments for advanced BCC has led to greater understanding of the disease. Virtually all cases of BCC are characterised by aberrant signalling of the hedgehog signalling pathway, most commonly due to sporadic loss-of-function mutations in the tumour suppressor gene, patched homologue (*PTCH*). A *PTCH* mutation results in loss of patched-mediated inhibition of the G-protein-coupled receptor Smoothened (SMO), thereby enhancing downstream signalling that results in uncontrolled cellular proliferation.[7,8] Recognition of the oncogenic role of SMO in BCC led to the development of vismodegib and sonidegib, orally available inhibitors of SMO, referred to as hedgehog inhibitors (HHIs).[8,9] Vismodegib (150 mg orally once daily) is an approved therapy for mBCC, leading to an objective response rate (ORR) of 33% with a median duration of response (DOR) of 7.6 months per central review in the primary analysis.[10] However, some patients are resistant to, or develop resistance after an initial response to, HHI therapy due to SMO mutations, noncanonical cell identity switching, and noncanonical pathway crosstalk causing hedgehog pathway activation.[11]

Cemiplimab, an immunoglobulin G4 monoclonal antibody to the programmed cell death-1 (PD-1) receptor, became the first agent approved in the United States (generic name cemiplimab-rwlc) for the treatment of patients with advanced BCC who were previously treated with an HHI or for whom HHI therapy is not appropriate.[12,13] Regulatory approvals for BCC indications were based on primary data in patients with laBCC and interim data in patients with mBCC from a pivotal phase II study (ClinicalTrials.gov identifier NCT03132636).[14,15]

Here, we present the final analysis from the pivotal phase II study of cemiplimab treatment from patients in the mBCC cohort.

METHODS

Study design

This was an open-label, multicentre, single-arm, phase II trial comprising 38 study sites in Canada, Europe, and the United States. Patients enrolled in the study were stratified by clinical disease presentation as either mBCC or laBCC. The results of the final analysis for the mBCC cohort are reported here.

Participants

Enrolled patients were not candidates for further HHI therapy because of disease progression, intolerance to previous HHI therapy, or having no better than stable disease after 9 months on HHI therapy. Intolerance to HHI therapy was defined as any grade 3 or 4 adverse event deemed related to an HHI, or any of the following HHI-related events in patients with at least 3 months of exposure to HHI therapy: grade 2 muscle spasms or myalgias; grade 2 dysgeusia or anorexia, if accompanied by grade ≥1 weight loss; or grade 2 nausea or diarrhoea despite medical management. All patients were ≥18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a histologically confirmed diagnosis of invasive BCC. Patients were also required to have at least one baseline lesion measurable by digital medical photography per modified World Health Organization (WHO) criteria or by radiologic imaging (computed tomography or magnetic resonance imaging) as per the RECIST version 1.1 criteria.[16]

Key exclusion criteria were ongoing or recent (within 5 years) evidence of substantial autoimmune disease requiring systemic immunosuppression, previous treatment with an anti—PD-1 or anti—programmed death-ligand 1 (anti-PD-L1) drug, previous treatment with other systemic immune-modulating agents (such as vaccines or cytokine treatments) within 28 days before the first dose of cemiplimab, untreated brain metastases that may be considered active, and concurrent malignancy other than BCC or a history of malignancy other than BCC within 3 years before the date of the first planned dose of cemiplimab, except for tumours with negligible risk of metastasis or death. Institutional review boards at each participating study site approved the study protocol, and the study was conducted in accordance with the principles of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All patients provided written informed consent before enrolment.

Procedures

Detailed procedures were previously reported.[14] In brief, following a screening period of up to 28 days, patients received cemiplimab 350 mg every 3 weeks in an outpatient setting by 30-min intravenous infusion (±10 min) for 93 weeks (five 9-week treatment cycles, followed by four 12-week cycles) or until disease progression, unacceptable toxicity, or withdrawal of consent.

Response after disease progression was not counted as response per RECIST; however, no patients met this criterion for treatment of a tumour. Reasons for permanent discontinuation of study drug included grade ≥3 infusion-related reaction, patient nonadherence, patient withdrawal of consent, pregnancy, or investigator determination of any medical condition that could jeopardise the patient's safety if study treatment were to continue. Tumour assessments were made after each treatment cycle (every

9 weeks for 5 weeks, then every 12 weeks). Assessments included radiologic imaging (computed tomography or magnetic resonance imaging) or digital medical photography for externally visible lesions. Patients who discontinued study treatment because of disease progression had a follow-up visit 30 days after the last cemiplimab treatment and were followed for survival status after the end-of-study visit.

Outcomes

The primary endpoint was ORR by independent central review (ICR), evaluated by RECIST version 1.1.[16] Clinical response criteria were used for patients with externally visible target lesions if all metastatic lesions were not measurable by RECIST, such as with bone-only metastases. Secondary endpoints were DOR (defined as the time between the first measurement of complete response or partial response and the first date of recurrent or progressive disease or death) per ICR and investigator assessment, ORR per investigator assessment, progression-free survival (PFS; defined as the time between the start of treatment and the first date of recurrent or progressive disease or death from any cause) per ICR and investigator assessment, overall survival (OS; defined as the time between the start of treatment and death from any cause), complete response rate by ICR, safety and tolerability of cemiplimab, and immunogenicity of cemiplimab.

Procedures for central review of efficacy in this study were previously described.[14] In brief, radiologic assessments were reviewed by an independent radiologic review committee per RECIST version 1.1, and digital medical photography assessments were reviewed by an independent photographic review committee per modified WHO criteria. For patients followed by both scans and photos, the overall response assessment was adjudicated by an independent composite review committee.

Statistical analysis

For the primary endpoint, the statistical hypothesis was that cemiplimab-treated patients had an ORR representing clinically meaningful response, defined as a $>$15% response rate. The null hypothesis (non—clinically meaningful ORR of $\leq$15%) could be excluded using the lower limit of a two-sided 95% confidence interval (CI) if the observed ORR was $\geq$28%. A patient sample size of 50 provided $\geq$85% power to reject a null hypothesis of an ORR of 15% at a two-sided significance level of 5% if the true ORR was 34% of patients. The sample size was increased by $>$5% to 54 patients to allow for patients who withdrew prematurely from the study. For the efficacy analysis, 95% CIs were calculated by the Clopper—Pearson method,[17] based on the binomial exact CI approach to determine whether the lower limit of a two-sided 95% CI excluded a historical control ORR that was not deemed clinically meaningful.

There was no hypothesis test for secondary endpoints. Descriptive summaries of time-to-event data and the secondary analyses of efficacy as measured by DOR, PFS, and OS were estimated by the Kaplan—Meier method. Patients who were deemed not evaluable (NE) by RECIST version 1.1 were considered as not reaching partial or complete response for ORR. Statistical analyses were carried out using the Statistical Analysis System (SAS version 9.4; SAS Institute Inc., Cary, NC).

Role of the funding source

The study was sponsored by Regeneron Pharmaceuticals, Inc., and Sanofi, and was designed by employees of Regeneron Pharmaceuticals, Inc., in collaboration with the investigators. Data from the study were collected by investigators, analysed by statisticians employed by the sponsors, and interpreted by the authors, including employees of the sponsors. The first draft of the manuscript was prepared by a medical writer funded by the sponsors according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M15-0288) and was based on authors' comments on the manuscript outline, which was also prepared by the medical writer. Thereafter, the first draft was critically reviewed and revised by the authors, including employees of the sponsors.

RESULTS

Between 29 June 2017 and 20 June 2023, 54 patients with mBCC were enrolled, with an ECOG performance status of 0 [36 (67%) patients] or 1 [18 (33%) patients], who had discontinued prior HHI treatment and were treated with cemiplimab. The median age was 64 years [interquartile range (IQR) 57-73], and most patients were male (70%; Table 1). The primary tumour site in most patients was the trunk (46%) or the head and neck (41%). The most common sites of metastases were the lung (59%), soft tissue (46%), and lymph nodes (30%; Table 1). Patients could have multiple reasons for discontinuation of prior HHI therapy (Table 1). Intolerance to HHI therapy was cited as the sole reason for discontinuation in eight (15%) patients, with the following adverse events reported: rhabdomyolysis ($n = 1$); muscle spasms/myalgias ($n = 4$); ischaemic cardiopathy ($n = 1$); dry mouth and taste disturbance and muscle spasms/myalgias ($n = 1$); and muscle spasms/myalgias and dysgeusia/anorexia ($n = 1$). The median duration of HHI therapy among these eight patients who discontinued HHI therapy due to intolerance was 41.3 weeks (IQR 19-73 weeks). Many patients received multiple HHI treatments; 19 (35%) patients were intolerant to vismodegib and 5 (9%) were intolerant to sonidegib. The median duration of exposure to cemiplimab was 34 weeks (IQR 18-87 weeks), with patients receiving a median of 11 doses (IQR 5-24 doses). The median duration of follow-up was 8.4 months (IQR 4-21 months). Further therapies after cemiplimab treatment were only reported for two patients: one underwent a rhinoplasty and blepharoplasty (reconstructive procedures in the area of prior cancer-related surgeries), and another underwent a skin neoplasm excision (secondary primary BCC). The final database lock date was 20 June 2023.

Table 1. Patient demographics and baseline characteristics

Demographic variables	mBCC (n = 54)
Age	
Median (IQR), years	64 (57-73)
≥65 years, n (%)	27 (50)
Mean (SD), years	64 (11)
Male, n (%)	38 (70)
Population, n (%)	
White	47 (87)
Not reported	1 (2)
Missing	6 (11)
Clinical variables	
ECOG performance status, n (%)	
0	36 (67)
1	18 (33)
Patients with prior HHI therapy, n (%)	
Vismodegib	52 (96)
Sonidegib	9 (17)
Vismodegib and sonidegib	7 (13)
Reason for discontinuation of prior HHI[a], n (%)	
Progression of disease on HHI	41 (76)
Intolerant to prior HHI therapy	18 (33)
Intolerant to vismodegib	19 (35)
Intolerant to sonidegib	5 (9)
No better than stable disease after 9 months on HHI therapy	7 (13)
Primary tumour site, n (%)	
Trunk	25 (46)
Head and neck	22 (41)
Extremity	6 (11)
Anogenital area	1 (2)
Metastatic status, n (%)	
Distant and nodal	29 (54)
Distant only	19 (35)
Nodal only	5 (9)
Site of metastasis[b], n (%)	
Lung	32 (59)
Soft tissue	25 (46)
Lymph node	16 (30)
Bone	14 (26)
Liver	4 (7)
Other	10 (19)
Duration of exposure, median (range), weeks	34 (18-87)
Number of doses administered, median (range)	11 (5-24)

ECOG, Eastern Cooperative Oncology Group; HHI, hedgehog inhibitor; IQR, interquartile range; mBCC, metastatic basal cell carcinoma; SD, standard deviation.
[a]Sum is >54 because some patients had more than one reason for discontinuation.
[b]Some patients had more than one site of metastasis.

Table 2. Tumour response and duration of response by independent central review or investigator assessment[a]

	Independent central review (n = 54)	Investigator assessment (n = 54)
Best overall response		
Objective response rate	12 (22; 12-36)	14 (26; 15-40)
Complete response	2 (4)	2 (4)
Partial response	10 (19)	12 (22)
Stable disease	17 (32)	24 (44)
Noncomplete response/ nonprogressive disease	5 (9)	N/A
Progressive disease	16 (30)	14 (26)
NE[b]	4 (7)	2 (4)
Disease control rate[c]	34 (63; 49-76)	38 (70; 56-82)
Durable disease control rate[d]	23 (43; 29-57)	23 (43; 29-57)
Time to response (months), median (IQR)[e]	3 (2-7)	3 (2-4)
Kaplan–Meier estimation of duration of response (months), median (95% CI)[e]	NR (10-NE)	NR (10-NE)
6	100 (100-100)	93 (59-99)
12	58 (27-80)	79 (47-93)
24	50 (21-74)	61 (29-82)
Kaplan–Meier estimation of progression-free survival (months), median (95% CI)	10 (4-16)	7 (4-8)

CI, confidence interval; IQR, interquartile range; NE, not evaluable; NR, not reached.
[a]Data are n (%; 95% CI) or n (%), unless otherwise specified.
[b]NE response includes missing and unknown tumour response.
[c]Defined as the proportion of patients with complete response, partial response, stable disease, or noncomplete response/nonprogressive disease.
[d]Defined as the proportion of patients with complete response, partial response, stable disease, or noncomplete response/nonprogressive disease for ≥182 days without progressive disease.
[e]Data shown are for patients with response.

The ORR per ICR was 22% (95% CI 12% to 36%; n = 12), which included two (4%) complete responses and 10 (19%) partial responses (Table 2). The ORR per investigator assessment was 26% (95% CI 15% to 40%; n = 14), including 2 (4%) complete responses and 12 (22%) partial responses (Table 2). Of the eight patients who were intolerant to prior HHI therapy and had response data, three (38%) had stable disease per ICR. Among responders (patients with complete or partial response), the median time to response was 3 months (IQR 2-7 months) per ICR and 3 months (IQR 2-4 months) per investigator assessment. The disease control rate was 63% (95% CI 49% to 76%) per ICR and 70% (95% CI 56% to 82%) per investigator assessment. The durable disease control rate (defined as the proportion of patients with complete response, partial response, or stable disease for ≥182 days without evidence of progression) was 43% (95% CI 29% to 57%) by both ICR and investigator assessment. The median DOR (patients with complete or partial response) estimated by the Kaplan–Meier method was not reached (95% CI 10 months-NE) (Table 2) per ICR and per investigator assessment. Among responders (patients with complete or partial response), Kaplan–Meier estimation of DOR by ICR was 58% (95% CI 27% to 80%) at 12 months and 50% (95% CI 21% to 74%) at 24 months (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.10.123). By investigator assessment, Kaplan–Meier estimation of DOR was 79% (95% CI 47% to 93%) at 12 months and 61% (95% CI 29% to 82%) at 24 months. Among patients who progressed on or did not respond to prior HHI therapy (n = 46), ORR was 26% (95% CI 14% to 41%), DCR was 65% (95% CI 50% to 79%), and the median Kaplan–Meier estimation of DOR was not reached (95% CI 10 months-NE). Among patients who were intolerant to prior HHI therapy (n = 8), ORR per ICR was 0% (95% CI 0% to 37%), and DCR per ICR was 50% (95% CI 16% to 84%). There were not enough data to draw any significant conclusions regarding correlation of sites of metastasis with tumour response.

The depth of radiographic tumour regressions is illustrated in Figure 1. Each bar in the figure represents the color-coded best overall response of a patient. In addition to 10 patients with responses in the waterfall plot (green bars), there were two responders who do not appear in the figure. In both of these patients, the radiologic response assessment was noncomplete response and nonprogressive disease, but the overall assessment, which included digital medical photography, was partial response according to the independent composite review committee. These responses

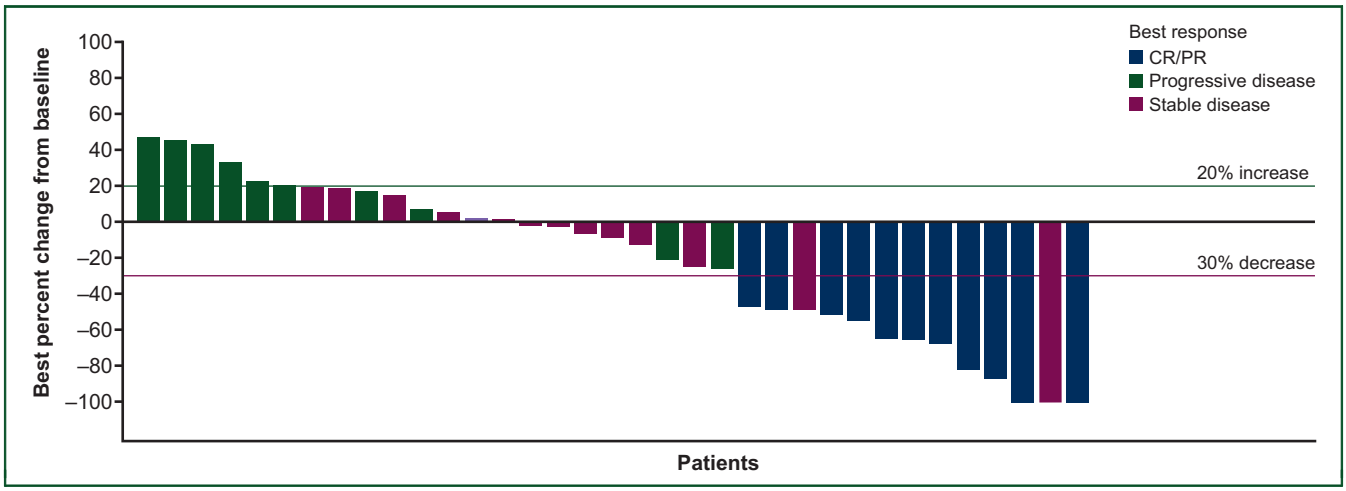

Figure 1. Waterfall plot of the best percent change from baseline in target lesions per RECIST 1.1 by independent central review[a].
CR, complete response; PR, partial response.
[a]Shown is the best percentage change from baseline in the sum of target lesion diameters during the study period. Lesion measurements after progression are excluded. Increase in the sum of target lesion diameters >100% is reported as 100%. Nineteen patients are not depicted because they did not have measurable disease (per RECIST version 1.1) in any postbaseline assessments, per independent central review.

are depicted in the waterfall plot of tumour assessments carried out with digital medical photography according to modified WHO criteria (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.10.123). Figure 1 also depicts two patients with tumour regressions of >30% who were classified as having stable disease (blue bars). Second from right is a patient with complete regression of target lesions, who was classified as having stable disease due to noncomplete response and nonprogressive disease status of nontarget lesions. Tenth from right is a patient who, despite >30% regression of target lesions, was assessed as having stable disease by the independent composite review committee that also assessed digital medical photography performed for this patient.

The median Kaplan–Meier estimation of PFS was 10 months (95% CI 4-16 months) by ICR (Table 2, Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.10.123). The median Kaplan–Meier estimation of OS was 50 months (95% CI 28 months-NE). The 12-month Kaplan–Meier estimated probability of OS (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2023.10.123) was 83% (95% CI 70% to 91%).

Treatment-emergent adverse events (TEAEs) of any grade, regardless of cause, were reported in 51 (94%) patients, with the most common including fatigue ($n = 23$, 43%), diarrhoea ($n = 20$, 37%), constipation ($n = 12$, 22%) and hypertension ($n = 12$, 22%) (Table 3). Grade ≥3 TEAEs, regardless of attribution, occurred in 23 (43%) patients, of which only hypertension ($n = 6$, 11%) occurred in more than two patients. Of the 54 patients with mBCC, four (7%) discontinued treatment due to TEAEs. Serious TEAEs were reported in 16 (30%) patients, including two (4%) patients who experienced serious TEAEs resulting in death: one patient died from staphylococcal pneumonia and one patient died from haemoptysis. Neither death was considered related to study treatment. Immune-related TEAEs of any grade occurred in 33 (61%) patients, the most common of which included pruritus ($n = 6$, 11%), fatigue ($n = 6$, 11%), diarrhoea ($n = 5$, 9%), hyperthyroidism ($n = 5$, 9%), hypothyroidism ($n = 4$, 7%), and maculo-papular rash ($n = 4$, 7%). Immune-related TEAEs of grade ≥3 occurred in five (9%) patients, including two cases each of colitis and immune-mediated myocarditis, and one case each of increased gamma-glutamyl transferase, pancytopenia, pneumonitis, pleural effusion, autoimmune pericarditis, and lymphoproliferative disorder. Treatment-related adverse events and TEAEs of special interest are summarized in Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2023.10.123.

DISCUSSION

In this multicentre study, cemiplimab provided the first demonstration of clinically meaningful efficacy for patients with mBCC after first-line HHI therapy. Cemiplimab achieved an ORR per ICR of 22% (95% CI 12% to 36%). The median DOR was not reached among patients with mBCC. Per investigator assessment, ORR was 26% and the median DOR was not reached. The ORR with cemiplimab in the second-line setting (22%) was comparable to that achieved previously with first-line HHI therapies for patients with mBCC, which ranged from 17% to 37%.[9,10,18,19]

Before this study, there were no standard therapeutic options for patients with mBCC after HHI therapy. Small pilot studies of experimental agents in the second-line BCC setting after HHI therapy did not provide efficacy signals or an acceptable safety profile to warrant further development.[20,21] Cemiplimab produced a durable partial response in a patient with mBCC in the dose-escalation portion of the first-in-human study,[22] and there have been other case reports and case series of BCC tumour responses with immune checkpoint blockade.[23-26] The current report is the first prospective multicentre study of PD-1 blockade for this patient population.

Table 3. TEAEs, regardless of attribution[a]

Patients with events (n = 54)	Grade 1-2	Grade 3	Grade 4	Grade 5
Serious, *n* (%)	1 (2)	12 (22)	1 (2)	2 (4)[c]
Leading to treatment discontinuation, *n* (%)	1 (2)	3 (6)	0 (0)	0 (0)
Sponsor-identified irAEs, *n* (%)	11 (20)	4 (7)	0 (0)	0 (0)
irAEs by investigator assessment, *n* (%)	28 (52)	4 (7)	1 (2)	0 (0)
Any TEAE[b], *n* (%)	28 (52)	20 (37)	1 (2)	2 (4)[c]
Fatigue	23 (43)	0 (0)	0 (0)	0 (0)
Diarrhoea	20 (37)	0 (0)	0 (0)	0 (0)
Constipation	12 (22)	0 (0)	0 (0)	0 (0)
Hypertension	6 (11)	6 (11)	0 (0)	0 (0)
Arthralgia	9 (17)	0 (0)	0 (0)	0 (0)
Pruritus	8 (15)	0 (0)	0 (0)	0 (0)
Pyrexia	7 (13)	1 (2)	0 (0)	0 (0)
Weight increased	8 (15)	0 (0)	0 (0)	0 (0)
Vomiting	7 (13)	0 (0)	0 (0)	0 (0)
Oedema peripheral	6 (11)	0 (0)	0 (0)	0 (0)
Pain in extremity	4 (7)	1 (2)	0 (0)	0 (0)
Decreased appetite	5 (9)	1 (2)	0 (0)	0 (0)
Headache	5 (9)	1 (2)	0 (0)	0 (0)
Nausea	6 (11)	0 (0)	0 (0)	0 (0)
Anaemia	6 (11)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	5 (9)	1 (2)	0 (0)	0 (0)
Asthenia	4 (7)	1 (2)	0 (0)	0 (0)
Urinary tract infection	5 (9)	0	0	0
Dizziness	5 (9)	0	0	0
Weight decreased	5 (9)	0	0	0
Back pain	3 (6)	2 (4)	0	0
Dry skin	5 (9)	0	0	0
Rash maculopapular	5 (9)	0	0	0
Eczema	5 (9)	0	0	0
Fall	3 (6)	2 (4)	0	0
Hyperthyroidism	5 (9)	0	0	0
Dyspnoea	4 (7)	0	0	0
Cough	4 (7)	0	0	0
Blood creatinine increased	4 (7)	0	0	0
Hypothyroidism	4 (7)	0	0	0
Abdominal pain	4 (7)	0	0	0
Blood creatine phosphokinase increased	4 (7)	0	0	0
Rash	4 (7)	0	0	0
Hypokalaemia	2 (4)	2 (4)	0	0
Haematuria	4 (7)	0	0	0
Neck pain	3 (6)	1 (2)	0	0
Infusion-related reaction	4 (7)	0	0	0
Actinic keratosis	3 (6)	0	0	0
Atrial fibrillation	2 (4)	1 (2)	0	0
Basal cell carcinoma	3 (6)	0	0	0
Upper respiratory tract infection	3 (6)	0	0	0
Alanine aminotransferase increased	3 (6)	0	0	0
Muscle spasms	3 (6)	0	0	0
Anxiety	3 (6)	0	0	0
Dry mouth	3 (6)	0	0	0
Myalgia	5 (9)	0	0	0
Colitis	1 (2)	2 (4)	0	0
Pain	3 (6)	0	0	0

AE, adverse event; irAE, immune-related adverse event; mBCC, metastatic basal cell carcinoma; TEAE, treatment-emergent adverse event.

[a]Data are from all treated patients. AEs were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 23.1. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. A patient is counted only once for multiple occurrences within a preferred term.

[b]Events are listed in the descending order of frequency in any grade. TEAEs regardless of attribution, of any grade or of grade ≥3, occurring in ≥5% of patients are shown.

[c]AEs leading to death: staphylococcal pneumonia and haemoptysis deemed unrelated to treatment.

In the primary analysis of patients with laBCC treated with cemiplimab in the HHI refractory setting, ORR was 31% per central review and median DOR was not reached.[14] The results of the final analysis for patients with mBCC in the current report (ORR 22%, median DOR not reached), although clinically meaningful, are consistent with prior observations that mBCC is more refractory to treatment than laBCC. The ORR in patients with mBCC treated with vismodegib was considerably less than in patients with laBCC: 30% versus 43% per central review.[8] In the open-label STEVIE study, patients with mBCC treated with vismodegib had an ORR of 37%, compared with 69% in the laBCC group, per investigator review.[18] In the BOLT trial of sonidegib 200 mg orally daily, the ORR per central review was again lower for mBCC than for laBCC in the primary analysis: 15% versus 43%.[9]

Although the rate of HHI-related discontinuation due to toxicity is considerable in the first line of therapy, cemiplimab did not exceed this toxicity-related discontinuation rate in the second line and so remains a viable option after HHI therapy. In the STEVIE trial, adverse event—related discontinuations occurred in 31% of patients on vismodegib[18]; 15% of patients on vismodegib in the ERIVANCE study discontinued treatment due to adverse events by 39 months.[27] In the BOLT study, 30% of patients on sonidegib had adverse event—related discontinuations by 42 months.[28] In the current study, 7% of patients discontinued due to TEAEs (Table 3). Of note, while one patient reported ischaemic cardiomyopathy as the reason for discontinuation of prior HHI therapy, this type of adverse event is rarely related to HHI therapy, and it is possible that this was a concurrent event not due to HHI therapy.

Limitations of this study are the relatively small size of the patient population and the open-label single-arm design. Clinical activity with cemiplimab was nevertheless established in a population of patients who had disease progression on or were not candidates for HHI therapy, and consequently had no other treatment options.

A fundamental question for future research is to better understand immune evasion mechanisms in patients with advanced BCC. Despite the fact that BCC has a tumour mutation burden similar to cutaneous squamous cell carcinoma (CSCC),[29] the efficacy of cemiplimab appears lower in patients with advanced BCC. In patients with advanced CSCC who were not candidates for surgery or radiation, the ORR for cemiplimab was ∼45% to 51% and the median DOR was not reached.[30,31] The median time to response with cemiplimab was ∼2 months in advanced CSCC, versus ∼3 months in advanced BCC per central review. The differences between the efficacy of cemiplimab in these two keratinocyte carcinomas may be related to the fact that cemiplimab data in advanced BCC are in the second line of therapy, whereas the cemiplimab data in advanced CSCC include mostly patients receiving first-line therapy. Immunological differences between BCC and CSCC tumours may also provide an explanation; these include differences in immune cell infiltration between BCC and CSCC tumours, reduced expression of major histocompatibility complex class I molecules,

overexpression of regulatory T cells, and overexpression of immunosuppressive cytokines in BCC tumours.[32]

The findings reported here complement those of the previously reported laBCC cohort,[14] and together support the use of cemiplimab as a treatment option in the first- and second-line settings for patients with laBCC or mBCC who have disease progression on or are intolerant to HHI therapy.

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DATA SHARING

Qualified researchers may request access to study documents (including the clinical study report, study protocol

with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymised participant data will be considered for sharing once the product and indication have been approved by major health authorities (e.g. US Food and Drug Administration, European Medicines Agency, Pharmaceuticals and Medical Devices Agency, etc), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Requests should be submitted to https://vivli.org/.

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