Primary analysis of Phase 2 results for cemiplimab in patients with metastatic basal cell carcinoma who progressed on or were intolerant to hedgehog inhibitors

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Background

- In the US, basal cell carcinoma (BCC) is the most common non-melanoma skin cancer, with approximately 2.8 million cases per year, leading to >3000 deaths annually.[1,2]
- Hedgehog inhibitors (HHIs), such as vismodegib and sonidegib, are approved for the treatment of patients with locally advanced BCC (laBCC) or metastatic BCC (mBCC) who are not candidates for surgery or radiation.[3,4]
- Until recently, there were no approved agents for the treatment of BCC in patients who experienced progression of disease on HHI therapy, or who were intolerant to prior HHI therapy.
- Cemiplimab, an immunoglobulin G4 monoclonal antibody derived using VelocImmune® technology, is a fully human, hinge-stabilized, high-affinity, high-potency blocker of programmed cell death-1 (PD-1).[5]
- In a pivotal Phase 2 study of patients with advanced BCC who discontinued HHI therapy due to progressive disease, intolerance, or no better than stable disease after 9 months (NCT03132636), cemiplimab became the first systemic therapy to show clinical benefit in patients with laBCC after HHI therapy, with estimated duration of response (DOR) exceeding 1 year in 85% of responders.[6]
- Cemiplimab is approved in the US (generic name: cemiplimab-rwlc) for treatment of mBCC or laBCC in patients previously treated with an HHI or for whom HHI therapy is not appropriate. Cemiplimab-rwlc is approved in the US in certain patients with advanced cutaneous squamous cell carcinoma (CSCC).[7]
- In Europe, Canada, and Brazil, cemiplimab is also approved in certain patients with advanced BCC and CSCC.[8–11]

Objective

- Here, we present primary data analysis of patients in the mBCC cohort from the pivotal Phase 2 study of cemiplimab in advanced BCC.

Key takeaways

- Cemiplimab provided clinically meaningful antitumor activity, including durable responses, in patients with mBCC who had progressed on or were intolerant to HHI therapy.
- The safety profile was generally consistent with that previously described for cemiplimab and other PD-1 inhibitors.

Conclusion

- These results complement those previously reported for the laBCC cohort,[6] and together indicate that cemiplimab is highly active in advanced BCC tumors.

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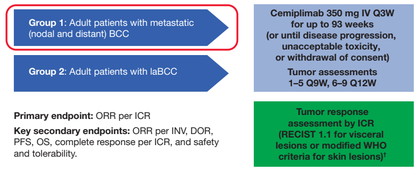
Disclosure

Karl D Lewis reports grants and personal fees from Regeneron Pharmaceuticals, Inc., during the conduct of the study; consulting or advisory roles from Array BioPharma, Merck, Roche, Regeneron Pharmaceuticals, Inc., Sanofi, and Iovance Biotherapeutics; travel, accommodations, and expenses from Merck, Roche/Genentech, Regeneron Pharmaceuticals, Inc., Neon Therapeutics, and Alkermes; honoraria from Array BioPharma and Iovance Biotherapeutics; institutional research funding from Roche/Genentech, Merck, Array BioPharma, Incyte, NeKtar, Iovance Biotherapeutics, Bristol-Myers Squibb, Kartos Therapeutics, OncoSec, Regeneron Pharmaceuticals, Inc., Alkermes, Neon Therapeutics, Ultimovacs, Senhwa Biosciences, Replimune, and Amgen; and uncompensated relationships at Roche/Genentech and Regeneron Pharmaceuticals, Inc.

Methods

- After a screening period of up to 28 days, patients received cemiplimab 350 mg every 3 weeks for 93 weeks, followed by four 12-week cycles or until disease progression, unacceptable toxicity, or withdrawal of consent (**Figure 1**).

Figure 1. Study design



†Or by composite response criteria for patient with both visceral and skin lesions.
BCC, basal cell carcinoma; DOR, duration of response; ICR, independent central review; INV, investigator assessment; IV, intravenous; laBCC, locally advanced basal cell carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; WHO, World Health Organization.

- Inclusion and exclusion criteria are provided in **Table 1**.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 years • ECOG performance status of 0 or 1 • Histologically confirmed diagnosis of invasive BCC • Progression of disease on or intolerance to previous HHI therapy or having no better than stable disease after 9 months on HHI therapy • At least one measurable baseline lesion[12]	• Ongoing or recent (within 5 years) evidence of substantial autoimmune disease requiring systemic immunosuppression • Previous treatment with an anti–PD-1 or an anti–PD-L1 drug • Untreated brain metastases that may be considered active • Concurrent malignancy other than BCC or history of malignancy other than BCC within 3 years of date of first planned dose of cemiplimab, except for tumors with negligible risk of metastasis or death

BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; HHI, hedgehog inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1.

Results

Patient demographics and baseline characteristics

- As of data cutoff (May 20, 2021), 54 patients were enrolled; median age was 63.5 years (range, 38–90) and 70.4% of patients were male (**Table 2**).
- The most common primary tumor sites were the trunk (46.3%) and the head and neck (40.7%) (**Table 2**).
- The most common reasons for discontinuation of HHI therapy were progression of disease on HHI (75.9%) or intolerance to HHI (33.3%) (**Table 2**).

Table 2. Patient demographic and baseline characteristics

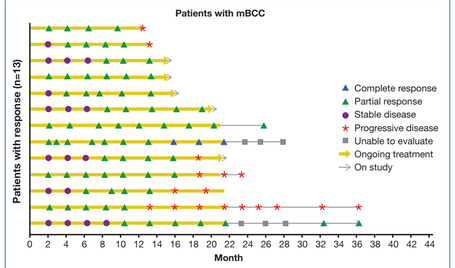
Characteristic	mBCC (N=54)
Age, median (range), years	63.5 (38–90)
≥65 years, n (%)	27 (50.0)
Male, n (%)	38 (70.4)
ECOG performance status, n (%)	
0	36 (66.7)
1	18 (33.3)
Number of patients with prior HHI therapy, n (%)	
Vismodegib	52 (96.3)
Sonidegib	9 (16.7)
Vismodegib + sonidegib	7 (13.0)
Reason for discontinuation of prior HHI, n (%)†	
Progression of disease on HHI	41 (75.9)
Intolerant to prior HHI therapy	18 (33.3)
Intolerant to vismodegib	19 (35.2)
Intolerant to sonidegib	5 (9.3)
No better than stable disease after 9 months on HHI therapy	7 (13.0)
Primary tumor site, n (%)	
Head and neck	22 (40.7)
Trunk	25 (46.3)
Extremity	6 (11.1)
Anogenital	1 (1.9)
Metastatic status, n (%)	
Distant only	19 (35.2)
Distant and nodal	29 (53.7)
Nodal only	5 (9.3)

†Sum is >54 because some patients had more than one reason for discontinuation.
ECOG, Eastern Cooperative Oncology Group; HHI, hedgehog inhibitor; mBCC, metastatic basal cell carcinoma.

Tumor response

- Median duration of follow-up was 8.4 months (range, 1.5–36.2).
- Objective response rate (ORR) per independent central review (ICR) was **24.1% (95% confidence interval [CI], 13.5–37.6)**; with one complete response and 12 partial responses (**Figure 2, Table 3**).
  - ORR per investigator assessment (INV) was 25.9% (95% CI, 15.0–39.7), with two complete responses and 12 partial responses.

Figure 2. Time to and duration of response in responding patients per ICR



Each horizontal bar represents one patient. A gray arrow indicates a patient still on study. Patients with confirmed complete response after a minimum of 48 weeks of treatment could elect to discontinue treatment and continue with all relevant study assessments.
ICR, independent central review; mBCC, metastatic basal cell carcinoma.

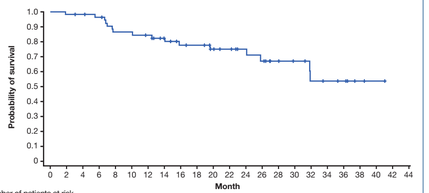
Table 3. Tumor response per ICR

Response	mBCC (N=54)
Best overall response	
ORR, % (95% CI)	24.1 (13.5–37.6)#
Complete response, n (%)	1 (1.9)
Partial response, n (%)	12 (22.2)
Stable disease, n (%)	16 (29.6)
Non-complete response/non-progressive disease, n (%)	5 (9.3)
Progressive disease, n (%)	16 (29.6)
NE,† n (%)	4 (7.4)
Disease control rate, % (95% CI)‡	63.0 (48.7–75.7)
Durable disease control rate, % (95% CI)§	42.6 (29.2–56.8)
Time to response, median (range), months¶	4.0 (2.0–10.5)
KM estimation of DOR, median (95% CI), months	16.7 (9.8–NE)
6 months	100 (NE–NE)
12 months	53.5 (21.2–77.7)
KM estimation of PFS, median (95% CI), months	8.3 (4.2–15.9)

†NE response includes missing and unknown tumor response.
‡Defined as the proportion of patients with complete response, partial response, stable disease or non-complete response/non-progressive disease.
§Defined as the proportion of patients with complete response, partial response, stable disease, or non-complete response/non-progressive disease for ≥182 days without progressive disease.
¶Data shown are for patients with response.
#ORR per investigator assessment was 25.9% (15.0–39.7).
CI, confidence interval; DOR, duration of response; ICR, independent central review; KM, Kaplan-Meier; mBCC, metastatic basal cell carcinoma; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival.

- Among responders, median time to response was 4.0 months (range, 2.0–10.5) per ICR.
- Estimated median duration of response (DOR) per ICR was 16.7 months (95% CI, 9.8–not evaluable [NE]).
- Median overall survival (OS) was not reached (95% CI, 25.7–NE) (**Figure 3**). The 12-month Kaplan-Meier (KM) estimation of OS was 84.4% (95% CI, 71.3–91.9).
- Median KM estimation of progression-free survival (PFS) was 8.3 months (95% CI, 4.2–15.9) per ICR (**Figure 4**).

Figure 3. KM curve for OS

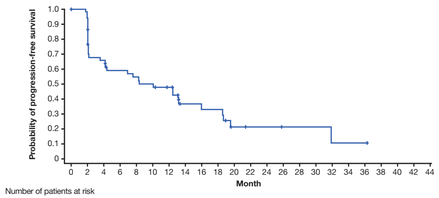


KM, Kaplan-Meier; mBCC, metastatic basal cell carcinoma; OS, overall survival.

Safety

- The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (42.6%; n=23), diarrhea (37.0%; n=20), constipation (22.2%; n=12), and hypertension (20.4%; n=11) (**Table 4**).
- Immune-related adverse events (irAEs) of any grade occurred in 61.1% (n=33) of patients.
- Grade ≥3 irAEs were seen in 9.3% (n=5) of patients; the only Grade ≥3 irAEs occurring in more than one patient was colitis.
- Two patients (3.7%) had a serious TEAE resulting in death: staphylococcal pneumonia (n=1) and hemoptysis (n=1).
- There were no treatment-related deaths.

Figure 4. KM curve for PFS per ICR



Patients with confirmed complete response after a minimum of 48 weeks of treatment could elect to discontinue treatment and continue with all relevant study assessments.
ICR, independent central review; KM, Kaplan-Meier; mBCC, metastatic basal cell carcinoma; PFS, progression-free survival.

Table 4. TEAEs regardless of attribution†

	mBCC (N=54)	
n (%)	Any grade	Grade ≥3
Any TEAE	51 (94.4)	23 (42.6)
Serious TEAEs	16 (29.6)	15 (27.8)
TEAEs leading to treatment discontinuation	4 (7.4)	3 (5.6)
TEAEs associated with an outcome of death‡	2 (3.7)	2 (3.7)
Any TEAE occurring in ≥10% patients§		
Fatigue	23 (42.6)	0
Diarrhea	20 (37.0)	0
Constipation	12 (22.2)	0
Hypertension	11 (20.4)	6 (11.1)
Arthralgia	9 (16.7)	0
Pruritus	8 (14.8)	0
Pyrexia	8 (14.8)	1 (1.9)
Weight increased	8 (14.8)	0
Vomiting	7 (13.0)	0
Edema peripheral	6 (11.1)	0
Pain in extremity	6 (11.1)	1 (1.9)
Decreased appetite	6 (11.1)	1 (1.9)
Headache	6 (11.1)	1 (1.9)
Nausea	6 (11.1)	0
Anemia	6 (11.1)	0
Hyperglycemia	6 (11.1)	1 (1.9)

†Adverse events were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 22.1.
The severity of adverse events was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
‡Adverse events leading to death were staphylococcal pneumonia and hemoptysis, deemed unrelated to treatment.
§Events are listed in descending order of frequency in any grade.
mBCC, metastatic basal cell carcinoma; TEAE, treatment-emergent adverse event.

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