Primary Analysis of Phase 2 Results for Cemiplimab in Patients with Locally Advanced Basal Cell Carcinoma who Progress on or are Intolerant to Hedgehog Inhibitors

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Background

- Hedgehog inhibitors (HHIs), such as vismodegib and sonidegib, are approved for the treatment of patients with metastatic basal cell carcinoma (BCC) or locally advanced BCC (laBCC) who are not candidates for surgery or radiation.[1,2]
- However, for patients with laBCC, there is no standard regimen after first-line HHI therapy.[3]
- Cemiplimab is a high-affinity, highly potent, human programmed cell death (PD)-1 antibody, which has demonstrated anti-tumor activity in advanced solid tumors.[4–6]
- Cemiplimab is an established therapy approved for treatment of advanced cutaneous squamous cell carcinoma (CSCC) in patients who are not candidates for curative surgery or curative radiation.[7]
- Both BCC and CSCC are keratinocytic tumors with high mutational burden due to ultraviolet mutagenesis and are potentially amenable to immunotherapy.[3,8]
- We present the primary analysis of the laBCC cohort from the pivotal Phase 2 study of cemiplimab in the second-line (or greater) setting (NCT03132636).

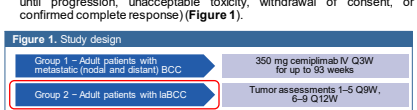
Objectives

- The primary objective was to evaluate objective response rate (ORR) by independent central review (ICR).
- Key secondary endpoints: duration of response (DOR), progression-free survival (PFS), overall survival (OS), complete response by ICR, and safety and tolerability.
  - ORR included two responses confirmed after the data cut-off date of February 17, 2020.

Methods

- In this pivotal Phase 2 study, patients with laBCC received cemiplimab 350 mg every 3 weeks (Q3W) intravenously (IV) (for up to 93 weeks or until progression, unacceptable toxicity, withdrawal of consent, or confirmed complete response) (**Figure 1**).

Figure 1. Study design



- Key inclusion criteria:
  - Histologically confirmed diagnosis of invasive BCC
  - Prior progression or intolerance to HHI therapy or no better than stable disease after 9 months on HHI therapy
  - At least one measurable baseline lesion
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Key exclusion criteria:
  - Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
  - Prior anti–PD-1 or anti–PD-ligand (L)1 therapy
  - Concurrent malignancy other than BCC and/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.

Results

Patient demographics and baseline characteristics

- As of February 17, 2020, 84 patients were enrolled; 66.7% were male; median age was 70 years (range: 42–89) (**Table 1**).
- The most common primary site of tumor location was head and neck (89.3%) (**Table 1**).
- Reasons for discontinuation of prior HHI therapy were progression of disease on HHI (71.4%), intolerant to prior HHI therapy (38.1%), and no better than stable disease after 9 months of HHI therapy (8.3%) (**Table 1**).
- Median follow-up was 15 months (range: 0.5–25).

Table 1. Patients demographics and baseline characteristics

	laBCC (N=84)
Median age, years (range)	70.0 (42–89)
Gender, % (n)	
Male	66.7 (56)
Female	33.3 (28)
ECOG performance status, % (n)	
0	60.7 (51)
1	39.3 (33)
Primary site of tumor, % (n)	
Head and neck	89.3 (75)
Extremity	2.4 (2)
Trunk	8.3 (7)
Reason for discontinuation of prior HHI, % (n)[†]	
Progression of disease on HHI	71.4 (60)
Intolerant to prior HHI therapy	38.1 (32)
Intolerant to vismodegib	38.1 (32)
Intolerant to sonidegib	4.8 (4)
No better than stable disease after 9 months on HHI therapy	8.3 (7)

[†]Sum is >84 because some patients had more than one reason for discontinuation.

Tumor response

- ORR per ICR was 31.0% (95% confidence interval [CI]: 21.3–42.0), including five complete responses and 21 partial responses (**Table 2**).
  - This includes two responses that emerged at the last tumor assessment prior to the data cut and were confirmed by ICR of tumor assessments after the data cut.

Table 2. Evaluation of response

n (%), unless otherwise stated	laBCC (N=84)
Objective response rate, % (95% CI)	31.0 (21.3–42.0)[†]
Complete response	5 (6.0)
Partial response	21 (25.0)
Stable disease	41 (48.8)
Progressive disease	9 (10.7)
Not evaluable[‡]	8 (9.5)

[†]Includes two patients whose partial responses were confirmed after the data cut-off date. [‡]Of the eight patients who were not evaluable, four did not have any post-baseline tumor assessments, three patients were not considered to have evaluable lesions by either photographic or radiologic assessment methods, and one patient had a second target lesion not imaged after baseline.

- The estimated Kaplan–Meier probability of DOR was 90.9% (95% CI: 68.3–97.6) and 85.2% (95% CI: 60.5–95.0) at 6 and 12 months, respectively.
- Median DOR per ICR had not been reached at the time of data cut-off.
- Time to response and durability of responses were observed (**Figure 2**).
- Reductions of externally visible BCC lesions during cemiplimab treatment have been observed (**Figure 3**).
- Median estimated PFS for all patients was 19.3 months (95% CI: 8.6–not evaluable [NE]) (**Figure 4**).
- Median OS had not been reached at the time of data cut-off.
- The estimated 12-month probability of survival was 92.3% (95% CI: 83.6–96.5) (**Figure 4**).

Figure 2. DOR in responding patients

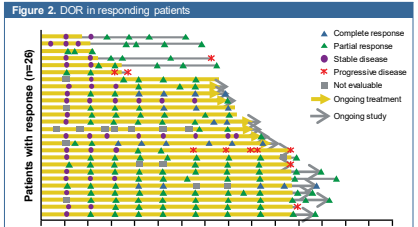
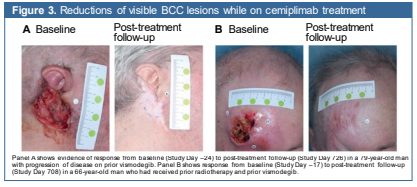
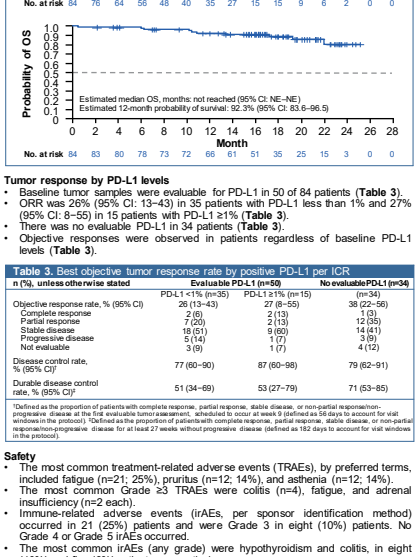


Figure 3. Reductions of visible BCC lesions while on cemiplimab treatment



Panel A shows evidence of response from baseline (study Day –24) to post-treatment follow-up (study Day +28) in a 79-year-old man with progression of disease on prior vismodegib. Panel B shows response from baseline (Study Day –17) to post-treatment follow-up (Study Day 708) in a 66-year-old man who had received prior radiotherapy and prior vismodegib.

Figure 4. PFS and OS in responding patients



Tumor response by PD-L1 levels

- Baseline tumor samples were evaluable for PD-L1 in 50 of 84 patients (**Table 3**).
- ORR was 26% (95% CI: 13–43) in 35 patients with PD-L1 less than 1% and 27% (95% CI: 8–55) in 15 patients with PD-L1 ≥1% (**Table 3**).
- There was no evaluable PD-L1 in 34 patients (**Table 3**).
- Objective responses were observed in patients regardless of baseline PD-L1 levels (**Table 3**).

Table 3. Best objective tumor response rate by positive PD-L1 per ICR

n (%), unless otherwise stated	Evaluable PD-L1 (n=50)		No evaluable PD-L1 (n=34)
	PD-L1 <1% (n=35)	PD-L1 ≥1% (n=15)	(n=34)
Objective response rate, % (95% CI)	26 (13–43)	27 (8–55)	38 (22–56)
Complete response	2 (6)	2 (13)	1 (3)
Partial response	7 (20)	2 (13)	12 (35)
Stable disease	18 (51)	9 (60)	14 (41)
Progressive disease	5 (14)	1 (7)	3 (9)
Not evaluable	3 (9)	1 (7)	4 (12)
Disease control rate, % (95% CI)[†]	77 (60–90)	87 (60–98)	79 (62–91)
Durable disease control rate, % (95% CI)	51 (34–69)	53 (27–79)	71 (53–85)

[†]Defined as the proportion of patients with complete response, partial response, stable disease, or non-partial response/non-progressive disease at the first evaluable tumor assessment, scheduled to occur at week 9 (defined as 56 days to account for visit windows in the protocol). Patients with complete response, partial response, stable disease, or non-partial response/non-progressive disease for at least 27 weeks without progressive disease (defined as 182 days to account for visit windows in the protocol).

Safety

- The most common treatment-related adverse events (TRAEs), by preferred terms, included fatigue (n=21; 25%), pruritus (n=12; 14%), and asthenia (n=12; 14%).
- The most common Grade ≥3 TRAEs were colitis (n=4), fatigue, and adrenal insufficiency (n=2 each).
- Immune-related adverse events (irAEs, per sponsor identification method) occurred in 21 (25%) patients and were Grade 3 in eight (10%) patients. No Grade 4 or Grade 5 irAEs occurred.
- The most common irAEs (any grade) were hypothyroidism and colitis, in eight (10%) and five (6%) patients, respectively.
- Grade 3 irAEs in >1 patient were colitis (n=3) and adrenal insufficiency (n=2).
- Adverse events of Grade 3 or greater, regardless of attribution, occurred in 51% of patients (**Table 4**).
- Seventeen percent of patients discontinued treatment due to TEAEs (**Table 4**).
- There were no treatment-related deaths (**Table 4**).
- The overall safety profile is generally consistent with previously reported experience with cemiplimab.

Table 4. TEAEs regardless of attribution

n (%)	laBCC (N=84)	
	Any grade	Grade ≥3
Any	82 (98)	43 (51)
Serious	29 (35)	22 (26)
Led to discontinuation	14 (17)	7 (8)
Associated with an outcome of death[†]	3 (4)	3 (4)
Occurred in ≥10% patients (any grade) or Grade 3 in ≥5% patients		
Fatigue	25 (30)	3 (4)
Diarrhea	20 (24)	0
Pruritus	18 (21)	0
Asthenia	17 (20)	1 (1)
Anemia	13 (16)	1 (1)
Decreased appetite	13 (16)	1 (1)
Headache	12 (14)	1 (1)
Nausea	12 (14)	1 (1)
Urinary tract infection	12 (14)	3 (4)
Arthralgia	11 (13)	0
Dyspnea	10 (12)	0
Blood creatinine increased	8 (10)	0
Dizziness	8 (10)	0
Cough	8 (10)	0
Hypothyroidism	8 (10)	0
Tumor hemorrhage	8 (10)	0
Hypertension	7 (8)	4 (5)

[†]Not considered treatment-related. TEAE, treatment-emergent adverse event.

Summary and Conclusion

- Cemiplimab is the first systemic therapy to show clinical benefit in patients with laBCC after HHI therapy with a 31.0% ORR per ICR. Among responders, the estimated 12-month DOR was 85.2%.
- The safety profile is generally consistent with other PD-1 antibodies and with previous reports of cemiplimab in other tumor types.
- Baseline PD-L1 expression is not associated with clinical activity.
- Combined with interim data from the mediastinal BCC cohort,[9] these results confirm that cemiplimab has substantial activity in advanced BCC tumors.

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