Phase 2 study of cemiplimab in patients with locally advanced basal cell carcinoma after hedgehog inhibitor therapy: Long-term follow-up

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Synopsis

- Basal cell carcinoma (BCC) is the most common human malignancy worldwide.[1] Most patients with BCC are cured by surgical excision, but a small proportion develop advanced BCC, which includes locally advanced (laBCC) and metastatic (mBCC) disease.[1,2]
- Hedgehog signaling pathway inhibitors (HHIs), such as vismodegib and sonidegib, are indicated for patients with mBCC or laBCC who are not candidates for curative surgery or radiotherapy.[3-5] Most patients with advanced BCC, however, progress on or are intolerant to HHI therapy.
- Cemiplimab is a high-affinity, fully human, hinge-stabilized immunoglobulin G4 anti–programmed cell death-ligand 1 (PD-L1) antibody that potently blocks the interaction of programmed cell death-1 (PD-1) with its ligand.[6]
- Cemiplimab (cemiplimab-rwlc in the US) is the first immunotherapy indicated for treatment of patients with mBCC and laBCC after HHI treatment or for whom HHIs are not appropriate.[7-11]
- In the primary analysis of the Phase 2 study (NCT03132636), cemiplimab demonstrated clinically meaningful activity and an acceptable safety profile in patients with laBCC after HHI therapy or for whom HHIs were not appropriate.[12] Here, we present the long-term follow-up data at approximately 40 months after the primary analysis of the first group in this study.

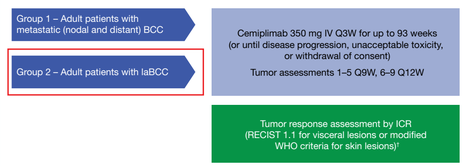
Objectives

- The primary objective is to evaluate objective response rate (ORR) by independent central review (ICR).
- Key secondary endpoints include ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), overall survival (OS), complete response rate, and safety and tolerability.

Methods

- In this open-label, multicenter, single-arm, Phase 2 trial, patients received cemiplimab 350 mg intravenously (IV) every 3 weeks (Q3W) for up to 93 weeks or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed complete response (**Figure 1**). The study design was previously reported in detail.[12]

Figure 1. Study design



†Or by composite response criteria for patient with both visceral and skin lesions, including ICR review of digital medical photography, radiology and pathology reports from on-treatment biopsies (if any).
BCC, basal cell carcinoma; ICR, independent central review; IV, intravenous; laBCC, locally advanced basal cell carcinoma; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

- Inclusion and exclusion criteria are provided in **Table 1**.
- Tumor assessments were done at the end of each treatment cycle, every 9 weeks (Q9W) for the first five cycles, and every 12 weeks (Q12W) for the subsequent four cycles.
- An updated analysis of the response was prespecified to be performed after all responding patients had been followed for a minimum of 12 months from onset of response.
- The data cutoff date was May 20, 2021.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion 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 • ECOG performance status of 0 or 1	• Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression • Prior anti–PD-1 or anti–PD-L1 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

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

Patients

- Eighty-four patients with laBCC were enrolled in this study, 66.7% were male, and median age was 70 years (range, 42–89). Patient characteristics are provided in **Table 2**.
- The primary site of tumor location was head and neck (89.3%).
- Most common reasons for discontinuation of HHI therapy were progression of disease on HHIs (71.4%), intolerance to prior HHIs (38.1%), and no better than stable disease after 9 months on HHIs (8.3%) (**Table 2**).
- Median duration of follow-up was 15.9 months (range, 0.5–39.7).

Table 2. Patient demographics and baseline characteristics

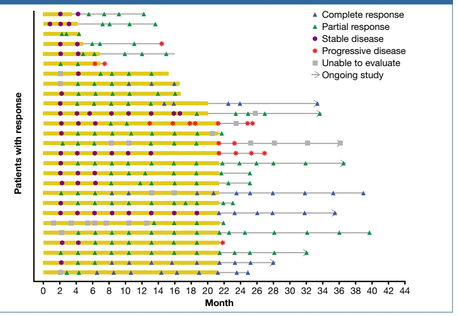
Characteristic	laBCC (N=84)
Age, median (range), years	70 (42–89)
≥65 to <75, n (%)	19 (22.6)
≥75, n (%)	34 (40.5)
Male, n (%)	56 (66.7)
ECOG performance status, n (%)	
0	51 (60.7)
1	33 (39.3)
Patients with prior cancer-related radiotherapy, n (%)	42 (50.0)
Patients with prior HHI therapy, n (%)	
Vismodegib	79 (94.0)
Sonidegib	14 (16.7)
Vismodegib + sonidegib	9 (10.7)
Reason for discontinuation of prior HHI, n (%)†	
Progression of disease on HHI	60 (71.4)
No better than stable disease after 9 months on HHI therapy	7 (8.3)
Intolerant to prior HHI therapy	32 (38.1)
Intolerant to vismodegib	32 (38.1)
Intolerant to sonidegib	4 (4.8)
Primary site of tumor, n (%)	
Head and neck	75 (89.3)
Trunk	7 (8.3)
Extremity	2 (2.4)
Duration of exposure, median (range), weeks	47.2 (2.1–97.9)
Median number of doses of cemiplimab administered (range)	15.0 (1–31)

†Sum is >84 because some patients had more than one reason for discontinuation.
ECOG, Eastern Cooperative Oncology Group; HHI, hedgehog inhibitor; laBCC, locally advanced basal cell carcinoma.

Clinical activity

- ORR per ICR was 32.1% (95% confidence interval [CI], 22.4–43.2) including six complete responses and 21 partial responses (**Table 3**).
  - Six (22.2%) responding patients had evidence of disease progression at the time of this analysis (**Figure 2**).
  - The disease control rate was 79.8% (95% CI, 69.6–87.7).
  - The durable disease control rate was 59.5% (95% CI, 48.3–70.1).

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



Each horizontal bar represents one patient. All patients completed treatment. Patients with confirmed complete response after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments.
DOR, duration of response; ICR, independent central review; laBCC, locally advanced basal cell carcinoma.

- As of data cutoff, median DOR had not been reached. Kaplan-Meier estimates of DOR were 83.8% (95% CI, 62.2–93.6) at 12 months and 56.6% (95% CI, 29.6–76.6) at 24 months (**Table 3**).

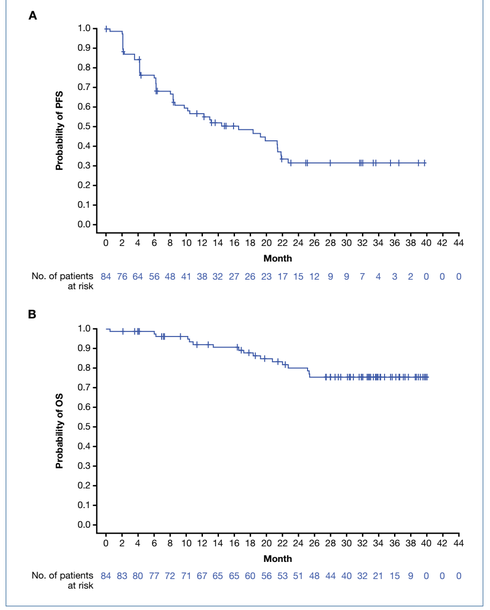
Table 3. Tumor response per ICR

Outcome	laBCC (N=84)
Duration of follow-up, median (range), months	15.9 (0.5–39.7)
Best overall response per ICR	
ORR, % (95% CI)	32.1 (22.4–43.2)†
Complete response, n (%)	6 (7.1)
Partial response, n (%)	21 (25.0)
Stable disease, n (%)	40 (47.6)
Non-complete response/non-progressive disease, n (%)	0
Progressive disease, n (%)	9 (10.7)
Not evaluable, n (%)‡	8 (9.5)
Observed DOR at 6 months, n (%)#	23 (85.2)
Disease control rate, % (95% CI)§	79.8 (69.6–87.7)
Durable disease control rate, % (95% CI)¶	59.5 (48.3–70.1)
Time to response, median (range), months#	4.3 (2.1–21.4)
Kaplan-Meier estimation of DOR, median (95% CI), months#	NR (15.5–NE)
6 months	88.5 (68.4–96.1)
12 months	83.8 (62.2–93.6)
24 months	56.6 (29.6–76.6)

†ORR per investigator assessment was 36.9% (95% CI, 26.6–48.1). ‡NE response includes the missing and unknown tumor response. §Defined as the proportion of patients with complete response, partial response, stable disease, or non-partial response/non-progressive disease. ¶Defined as the proportion of patients with complete response, partial response, stable disease, or non-partial response/non-progressive disease for ≥182 days without progressive disease. #Data shown are for patients with response.
CI, confidence interval; DOR, duration of response; ICR, independent central review; laBCC, locally advanced basal cell carcinoma; NE, not evaluable; NR, not reached; ORR, objective response rate.

- Median PFS was 16.5 months (95% CI, 8.6–21.4). Kaplan-Meier estimates of PFS were 56.7% (95% CI, 44.5–67.1) at 12 months and 31.7% (95% CI, 20.4–43.5) at 24 months (**Figure 3A**).
- Median OS had not been reached at the time these data were reported. Kaplan-Meier–estimated OS at 24 months was 80.3% (95% CI, 69.0–87.9) (**Figure 3B**).

Figure 3. Kaplan-Meier curves for PFS and OS



laBCC, locally advanced basal cell carcinoma; PFS, progression-free survival; OS, overall survival.

Safety

- Eighty-three (98.8%) patients experienced treatment-emergent adverse events (TEAEs) of any grade regardless of attribution.
- The most common TEAEs of any grade were fatigue (n=26, 31.0%), diarrhea (n=20, 23.8%), pruritus (n=18, 21.4%), asthenia (n=17, 20.2%) and arthralgia (n=16, 19.0%). Grade ≥3 TEAEs occurred in 44 (52.4%) patients (**Table 4**).
- Fifteen (17.9%) patients discontinued treatment due to TEAEs of any grade. Four (4.8%) patients died of TEAEs of any grade (**Table 4**).
- Treatment-related AEs (TRAEs) were reported in 66 (78.6%) patients, with the most common being fatigue (n=21, 25%), asthenia (n=12, 14.3%), diarrhea (n=11, 13.1%), pruritis (n=11, 13.1%), nausea (n=9, 10.7%), decreased appetite (n=8, 9.5%) and hypothyroidism (n=8, 9.5%).
- No Grade ≥3 TRAEs occurred in more than one patient or led to an outcome of death.
- Twenty-three (27.4%) patients experienced sponsor-identified immune-related AEs (irAEs) of any grade. Grade ≥3 irAEs occurred in nine (10.7%) patients.

Table 4. TEAEs†

	laBCC (N=84)	
TEAEs, n (%)	**Any grade**	**Grade ≥3**
Any	83 (98.8)	44 (52.4)
Serious	31 (36.9)	24 (28.6)
Led to discontinuation	15 (17.9)	9 (10.7)
Associated with an outcome of death‡	4 (4.8)	4 (4.8)
Occurring in ≥10% of patients or Grade ≥3 in ≥5% of patients§		
Fatigue	26 (31.0)	4 (4.8)
Diarrhea	20 (23.8)	0
Pruritus	18 (21.4)	0
Asthenia	17 (20.2)	1 (1.2)
Arthralgia	16 (19.0)	0
Decreased appetite	13 (15.5)	1 (1.2)
Anemia	13 (15.5)	1 (1.2)
Nausea	12 (14.3)	1 (1.2)
Headache	12 (14.3)	1 (1.2)
Urinary tract infection	12 (14.3)	3 (3.6)
Dyspnea	10 (11.9)	0
Cough	9 (10.7)	0
Tumor hemorrhage	9 (10.7)	0

†AEs were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 22.1. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. ‡None of the deaths were considered treatment related. §AEs are listed in descending order of frequency in any grade.
AE, adverse event; laBCC, locally advanced basal cell carcinoma; TEAE, treatment-emergent adverse event.

Conclusions

- This long-term follow-up analysis further confirms the safety and efficacy of cemiplimab in patients with laBCC after progression on or intolerance to HHI therapy.
- There were no new safety signals compared with previous analyses of cemiplimab in laBCC.[12]
- Combined with the primary analysis[12] in the laBCC cohort and interim analysis[13] from the mBCC cohort, these results confirm cemiplimab has substantial activity in advanced BCC tumors.

References

1. Puig S et al. *Clin Transl Oncol*. 2015;17:497–503.
2. Monroe M et al. *Otolaryngol Clin North Am*. 2021;54:271–280.
3. Sekulic A et al. *N Engl J Med*. 2012;366:2171–2179.
4. Migden MR et al. *Lancet Oncol*. 2015;16:716–728.
5. Basset-Seguin N et al. *Lancet Oncol*. 2015;16:729–736.
6. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870.
7. Regeneron Pharmaceuticals, Inc. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf. [Accessed January 22, 2022].
8. Regeneron Pharmaceuticals, Inc. Available at: https://www.prnewswire.com/news-releases/libtayo-cemiplimab-approved-by-the-european-commission-as-the-first-immunotherapy-indicated-for-patients-with-advanced-basal-cell-carcinoma-301319988.html. [Accessed January 22, 2022].
9. Health Canada. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions/libtayo-notice-compliance-conditions-218718.html. [Accessed January 22, 2022].
10. Ministry of Health Israel. Available at: https://israeldrugs.health.gov.il/#!/medDetails/164%2099%2036023%2000. [Accessed January 22, 2022].
11. Brazilian Health Authority - ANVISA. Available at: https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/libtayo-cemiplimabe-nova-indicacao. [Accessed January 22, 2022].
12. Stratigos AJ et al. *Lancet Oncol*. 2021;22:848–857.
13. Lewis K et al. *J Immunother Cancer*. 2020;8:Abstract 428.

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Disclosures

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