Interim Analysis of Phase 2 Results for Cemiplimab in Patients with Metastatic Basal Cell Carcinoma (mBCC) who Progressed on or are Intolerant to Hedgehog Inhibitors (HHIs)

Karl D. Lewis,[1] Ketty Peris,[2] Aleksandar Sekulic,[3] Alexander J. Stratigos,[4] Lara Dunn,[5] Zeynep Eroglu,[6] Anne Lynn S. Chang,[7] Michael R. Migden,[8] Siyu Li,[9] Suk-Young Yoo,[9] Kosalai Mohan,[10] Ebony Coates,[10] Emmanuel Okoye,[10] Jean-François Baurain,[11] Oliver Bechter,[12] Axel Hauschild,[13] Marcus O. Butler,[14] Leonel Hernandez-Aya,[15] Lisa Licitra,[16] Rogerio I. Neves,[17] Emily S. Ruiz,[18] Frank Seebach,[10] Israel Lowy,[10] Timothy Bowler,[10] Matthew G. Fury[10]

[1]Division of Medical Oncology, University of Colorado Hospital, Aurora, CO, USA; [2]Institute of Dermatology, Catholic University of the Sacred Heart, Rome, Italy and Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy; [3]Department of Dermatology, Arizona Mayo Clinic, Scottsdale, AZ, USA; [4]Department of Dermatology-Venereology, Andreas Sygros Hospital-National and Kapodistrian University of Athens, Athens, Greece; [5]Department of Medicine, Head and Neck Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA; [7]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA; [8]Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; [10]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [11]University Catholic of Louvain, Brussels, Belgium; [12]Department of General Medical Oncology, University Hospitals, Leuven, Belgium; [13]Department of Dermatology, Schleswig-Holstein University Hospital, Kiel, Germany; [14]Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada; [15]Division of Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA; [16]Medical Oncology Head and Neck Cancer Department, Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [17]Penn State Cancer Institute, Hershey, PA, USA; [18]Department of Dermatology, Dana-Farber Cancer Institute, Boston, MA, USA

Synopsis

- Basal cell carcinoma (BCC) is the most common type of skin cancer[1] and ultraviolet exposure is a major risk factor.[2]
- Surgery is a curative option for most patients, but systemic therapy is indicated for a small percentage of patients who develop advanced BCC.[3]
- Vismodegib is a hedgehog signalling pathway inhibitor (HHIs) that is approved for treatment of patients with metastatic BCC (mBCC) or locally advanced BCC (laBCC) who are not candidates for curative surgery or curative radiotherapy. Sonidegib is another HHI that is approved for the treatment of laBCC only.
- There are no available data for patients who progress on or are intolerant to HHIs.
- Cemiplimab is a fully human antibody, derived using VelocImmune technology,[4–5] which is a high-affinity, highly potent, hinge-stabilized, immunoglobulin G4 monoclonal antibody directed against programmed cell death-1 (PD-1).[6]
- Cemiplimab has recently been shown to have profound clinical activity as monotherapy in first-line non-small cell lung cancer with ≥50% PD-ligand 1 expression.[7]
- Cemiplimab is approved for treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[8]
- In a pivotal Phase 2 study of patients with advanced BCC who discontinued HHI therapy due to disease progression, intolerance, or no better than stable disease after 9 months, 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.[9]
  - Cemiplimab produced an objective response rate (ORR) of 31% in patients with laBCC after treatment with HHI therapy; the safety profile was acceptable and consistent with that previously reported for cemiplimab in other tumor types.[9]
- Here, we present the prespecified interim analysis of the mBCC cohort from the pivotal Phase 2 study (NCT03132636).

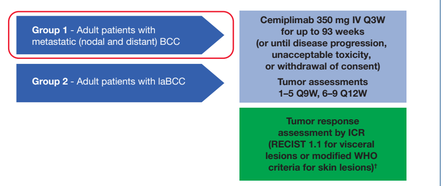
Objectives

- The primary objective is ORR by independent central review (ICR).
- Secondary objectives include ORR according to investigator review; duration of progression-free survival (PFS) by central and investigator review; overall survival (OS); complete response rate by central review; and safety and tolerability of cemiplimab.
- Interim analysis included patients with the opportunity to be followed for approximately 57 weeks to provide an ORR with 95% confidence interval (CI).

Methods

- This is a Phase 2, non-randomized, multi-center study of cemiplimab in patients with either mBCC or laBCC (**Figure 1**).

Figure 1. Study design



†Or by composite response criteria for patient with both visceral and skin lesions.
IV, intravenously; 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.

- After a screening period of up to 28 days, patients received cemiplimab 350 mg IV Q3W; therapy consisted of five 9-week treatment cycles followed by four 12-week treatment cycles (**Figure 1**).
- Inclusion and exclusion criteria are provided in **Table 1**.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Patients with histologically confirmed diagnosis of BCC with at least one measurable lesion ≥10 mm in maximal diameter according to RECIST 1.1 criteria • Patients with metastatic disease that does not meet target lesion criteria per RECIST 1.1, but have externally visible BCC with bi-dimensional measurements that must both be ≥10 mm • Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1 • Must have been deemed unlikely to benefit from further therapy with a HHI due to any of the following: – Prior progression of disease on HHI therapy – Intolerance to prior HHI therapy – No better than stable disease after 9 months on HHI therapy	• Patients were excluded if they had ongoing or recent (within 5 years) evidence of significant autoimmune disease requiring treatment with systemic immunosuppressive treatments • Prior treatment with an anti–PD-1/PD-ligand 1 therapy • Untreated brain metastases • Immunosuppressive corticosteroid doses within 4 weeks prior to the start of cemiplimab

- An independent composite review committee reviewed digital medical photography, radiology, and pathology reports from on-treatment biopsies (if any) to adjudicate response status for each tumor assessment.
- For patients followed by RECIST 1.1-only criteria, an independent radiology review committee reviewed the radiology for each tumor assessment.
- The data cut-off date for the results reported here was February 17, 2020.

Results

Patients

- As of data cut-off, 28 patients with mBCC had sufficient follow-up to be considered evaluable for clinical activity; 82.1% were males and median age was 65.5 years (range 38–90) (**Table 2**).

Table 2. Patient demographics and baseline characteristics

Characteristics	mBCC (N=28)
Median age, years (range)	65.5 (38–90)
≥65 years, n (%)	15 (53.6)
Male, n (%)	23 (82.1)
ECOG PS status, n (%)	
0	16 (57.1)
1	12 (42.9)
Number of patients with prior HHI therapy, n (%)	
Vismodegib	28 (100)
Sonidegib	3 (10.7)
Vismodegib + sonidegib	3 (10.7)
Reason for discontinuation of prior HHI, n (%)†	
Progression of disease on HHI	21 (75.0)
Intolerant to prior HHI therapy	10 (35.7)
Intolerant to vismodegib	11 (39.3)
Intolerant to sonidegib	2 (7.1)
No better than stable disease after 9 months on HHI therapy	5 (17.9)
Primary tumor site, n (%)	
Head and neck	11 (39.3)
Trunk	14 (50.0)
Extremity	2 (7.1)
Anogenital	1 (3.6)
Metastatic status, n (%)	
Distant only	9 (32.1)
Distant and nodal	15 (53.6)
Nodal only	4 (14.3)
Median duration of exposure, weeks (range)	38.9 (3.0–93.4)
Median number of doses administered (range)	13 (1–30)

†Sum is >28 because some patients had more than one reason for discontinuation.

Clinical activity

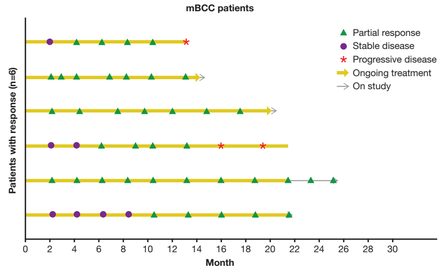
- ORR per ICR was 21.4% (95% CI, 8.3–41.0), with six patients showing a partial response.
- ORR per investigator assessment was 28.6% (95% CI, 13.2–48.7) (**Table 3**, **Figure 2**).

Table 3. Tumor response and duration of response per independent central review

n (%), unless otherwise stated	mBCC (N=28)
Best overall response	
Objective response rate, % (95% CI)	21.4 (8.3–41.0)†
Complete response	0
Partial response	6 (21.4)
Stable disease	10 (35.7)
Non-complete response/non-progressive disease	3 (10.7)
Progressive disease	7 (25.0)
Not evaluable‡	2 (7.1)
Disease control rate, % (95% CI)§	67.9 (47.6–84.1)
Durable disease control rate, % (95% CI)¶	46.4 (27.5–66.1)
Median (range) time to response, months#	3.2 (2.1–10.5)
Kaplan–Meier estimation of duration of response, median (95% CI), months#	Not reached (9.0–NE)
6 months	100 (NE)
12 months	66.7 (19.5–90.4)
Probability of progression-free survival, % (95% CI)	
6 months	58.1 (37.1–74.3)
12 months	49.8 (29.5–67.1)

†ORR per investigator was 28.6% (95% CI, 13.2–48.7).
‡Of the two patients who were not evaluable, one patient had no post-baseline assessment and one patient had no target or non-target lesions.
§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).
¶Defined as the proportion of 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).
#Data shown are for patients with response.
NE, not evaluable.

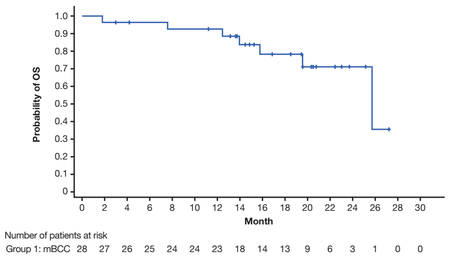
Figure 2. Time to and duration of response in responding patients by independent central review



Each horizontal bar represents one patient. 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.

- The disease control rate was 67.9% (95% CI, 47.6–84.1).
- The durable disease control rate was 46.4% (95% CI, 27.5–66.1).
- Among responders, median time to response per ICR was 3.2 months (range, 2.1–10.5). Observed DOR was 9–23 months. All six responses were ongoing at 1 year of treatment, and all six had observed duration of at least 8 months.
- Median DOR had not been reached.
- Median Kaplan–Meier estimation of OS was 25.7 months (95% CI, 19.5–NE) (**Figure 3**).

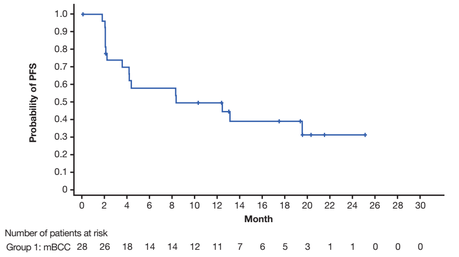
Figure 3. Kaplan–Meier curve for overall survival by independent central review



Median OS was 25.7 months (95% CI, 19.5–NE).

- Median Kaplan–Meier estimation of PFS was 8.3 months (95% CI, 3.6–19.5) (**Figure 4**).

Figure 4. Kaplan–Meier curve for progression-free survival by independent central review



Median PFS was 8.3 months (95% CI, 3.6–19.5). 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.

Safety

- Treatment-emergent adverse events (TEAEs) of any grade occurred in 26 (92.9%) patients. The most common TEAEs regardless of attribution were fatigue (50.0%), diarrhea (35.7%), pruritus (25.0%), and constipation (25.0%) (**Table 4**).
- Grade ≥3 TEAEs were observed in 12 (42.9%) patients. Hypertension (n=2) was the only Grade ≥3 TEAE regardless of attribution occurring in ≥2 patients.
- TEAEs leading to death occurred in one (3.6%) patient who died from staphylococcal pneumonia, considered unrelated to study treatment.
- Treatment-related adverse events (TRAEs) of any grade occurred in 22 (78.6%) patients. The most common TRAEs regardless of attribution were fatigue (42.9%), pruritus (25.0%), and arthralgia (17.9%).
- Grade ≥3 TRAEs were observed in five (17.9%) patients.
- Sponsor-identified immune-related adverse events (irAEs) of any grade occurred in eight (28.6%) patients. The most common sponsor-identified irAEs regardless of attribution were autoimmune hepatitis, colitis, hypothyroidism, and pneumonitis (each 7.1%).
- Grade ≥3 sponsor-identified irAEs were observed in one (3.6%) patient. The only Grade ≥3 sponsor-identified irAE was colitis (3.6%).

Table 4. Treatment-emergent adverse events regardless of attribution†

	mBCC (N=28)	
n (%)	Any grade	Grade ≥3
Any TEAE	26 (92.9)	12 (42.9)
Serious TEAEs	8 (28.6)	8 (28.6)
TEAEs leading to treatment discontinuation‡	1 (3.6)	0
Sponsor-identified irAEs	8 (28.6)	1 (3.6)
TEAEs associated with an outcome of death‡	1 (3.6)	1 (3.6)
Any TEAE occurring in ≥10% patients or Grade ≥3 in ≥5% patients§		
Fatigue	14 (50.0)	0
Diarrhea	10 (35.7)	0
Constipation	7 (25.0)	0
Pruritus	7 (25.0)	0
Pyrexia	6 (21.4)	1 (3.6)
Arthralgia	5 (17.9)	0
Decreased appetite	4 (14.3)	1 (3.6)
Dizziness	4 (14.3)	0
Eczema	4 (14.3)	0
Headache	4 (14.3)	1 (3.6)
Nausea	4 (14.3)	0
Weight decreased	4 (14.3)	0
Asthenia	3 (10.7)	1 (3.6)
Blood creatinine increased	3 (10.7)	0
Dry mouth	3 (10.7)	0
Fall	3 (10.7)	1 (3.6)
Hematuria	3 (10.7)	0
Hyperglycemia	3 (10.7)	1 (3.6)
Hypertension	3 (10.7)	2 (7.1)
Hypokalemia	3 (10.7)	1 (3.6)
Myalgia	3 (10.7)	0
Pneumonitis	3 (10.7)	1 (3.6)
Rash	3 (10.7)	0
Vomiting	3 (10.7)	0
Weight increased	3 (10.7)	0

†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 the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
‡Adverse events leading to death: staphylococcal pneumonia deemed unrelated to treatment.
§The events are listed in descending order of frequency in any grade.

Summary and Conclusions

- This interim analysis demonstrates that cemiplimab is the first agent to provide clinically meaningful anti-tumor activity, including durable responses, in patients with mBCC after progression or intolerance on HHI therapy.
- The safety profile of cemiplimab is consistent with previous reports of cemiplimab in other tumor types.
- Combined with data from the laBCC cohort,[9] these results confirm that cemiplimab has substantial activity in advanced BCC tumors.

References

1. Puig S et al. *Clin Transl Oncol*. 2015;17:497–503.
2. Wu S et al. *Am J Epidemiol*. 2013;178:890–897.
3. Migden MR et al. *Cancer Treat Rev*. 2018;64:1–10.
4. Murphy AJ et al. *Proc Natl Acad Sci USA*. 2014;111:5153–5158.
5. Macdonald LE et al. *Proc Natl Acad Sci USA*. 2014;111:5147–5152.
6. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870.
7. Sezer A et al. Poster presented at European Society of Medical Oncology (ESMO) Virtual Congress 2020. September 19–21, 2020: LBA52.
8. Migden MR et al. *N Engl J Med*. 2018;379:341–351.
9. Stratigos A et al. Poster presented at ESMO Virtual Congress 2020. September 19–21, 2020: LBA47.

Acknowledgments

The authors would like to thank the patients, their families, all other investigators, and all investigational site members involved in this study. The study was funded by Regeneron Pharmaceuticals, Inc. and Sanofi. Medical writing support and typesetting was provided by Kate Carolan, PhD, of Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc. and Sanofi.

Disclosures

Dr Lewis reports personal fees from Regeneron Pharmaceuticals, Inc., and grants, and/or personal fees from Array BioPharma, Merck, Roche, Incyte, Nektar, Iovance Biotherapeutics, and Bristol-Myers Squibb. **Dr Peris** reports advisory board roles with Abbvie, LEO Pharma, Janssen, Almirall, Lilly, Galderma, Novartis, Pierre Fabre, and Sanofi. **Dr Sekulic** reports advisory role with Regeneron Pharmaceuticals, Inc. and Roche. **Dr Stratigos** reports advisory board or steering committee roles with Janssen CILAG, Regeneron Pharmaceuticals, Inc., and Sanofi, and research support from Abbvie, Bristol-Myers Squibb, Genesis Pharma, and Novartis. **Dr Dunn** reports research funding from Eisai, Regeneron Pharmaceuticals, Inc., and CUE Biopharma, and advisory board payments from Regeneron Pharmaceuticals, Inc., CUE Biopharma, and Merck. **Dr Eroglu** reports advisory roles with Array BioPharma, Regeneron Pharmaceuticals, Inc., Novartis, Genetech, and SunPharma, and has received research funding from Novartis. **Dr Chang** reports advisory roles with Regeneron Pharmaceuticals, Inc. and Merck, and research funding from Regeneron Pharmaceuticals, Inc., Merck, Novartis, and Galderma. **Dr Migden** reports advisory roles with and travel fees from Regeneron Pharmaceuticals, Inc. and Sun Pharmaceuticals, advisory role with Rakuten Medical, and research funding from Regeneron Pharmaceuticals, Inc. and Pelle Pharm. **Drs Li**, **Yoo**, **Mohan**, **Coates**, **Okoye**, **Seebach**, **Lowy**, **Bowler,** and **Fury** are shareholders and employees of Regeneron Pharmaceuticals, Inc. **Drs Baurain** and **Bechter** have nothing to disclose. **Dr Hauschild** reports institutional funding and personal fees from Amgen, Bristol-Myers Squibb, MerckSerono, MSD/Merck, Philogen, Pierre Fabre, Provectus, Regeneron Pharmaceuticals, Inc., Roche, Sanofi-Genzyme, and Novartis, and consultancy fees from OncoSec and Sun Pharma. **Dr Butler** reports advisory roles with Sanofi-Genzyme, Novartis, Sun Pharmaceuticals, Pfizer, Merck, Immunocore, Turnstone, Bristol-Myers Squibb, and research funding from Merck and Takara Bio. **Dr Hernandez-Aya** reports an advisory role with Massive Bio, personal fees from Regeneron Pharmaceuticals, Inc., Sanofi, and Bristol-Myers Squibb, and research funding from Immunocore, Merck Sharp & Dohme, Polynoma, Corvus Pharmaceuticals, Roche, Merck Serono, Amgen, MedImmune, and Takeda. **Dr Licitra** reports funding (for institution) for clinical studies and research from AstraZeneca, Boehringer Ingelheim, Eisai, Merck Serono, MSD, Novartis, and Roche, has received compensation for service as a consultant/advisor and/or for lectures from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Debiopharm, Eisai, Merck Serono, MSD, Novartis, Roche, and Sobi, and has received travel coverage for medical meetings from Bayer, Bristol-Myers Squibb, Debiopharm, Merck Serono, MSD, and Sobi. **Dr Neves** reports an advisory role with Novartis, Sanofi-Genzyme, Castle Biosciences and Roche, and research funding from Castle Biosciences and Regeneron Pharmaceuticals, Inc. **Dr Ruiz** reports an advisory role with Pellepharm, Inc.

Presented at the 2021 Winter Clinical Dermatology Conference, January 16–24, Virtual Conference (encore of SITC 2020 poster presentation).