Phase 1 Study of Cemiplimab, a Human Monoclonal Anti-PD-1, in Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Final Efficacy and Safety Data

Taofeek K. Owonikoko,[1] Kyriakos P. Papadopoulos,[2] Melissa L. Johnson,[3] Marta Gil-Martin,[4] Victor Moreno,[5] April K. Salama,[6] Emiliano Calvo,[7] Nelson S. Yee,[8] Howard Safran,[9] Raid Aljumaily,[10] Daruka Mahadevan,[11] Jiaxin Niu,[12] Kosalai Kal Mohan,[13] Jingjin Li,[14] Elizabeth Stankevich,[14] Melissa Mathias,[13] Israel Lowy,[13] Matthew G. Fury,[14] Hani M. Babiker[15]

[1]*Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA;* [2]*START, San Antonio, TX, USA;* [3]*Sarah Cannon Research Institute, Nashville, TN, USA;* [4]*Institut Català D'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain;* [5]*START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain;* [6]*Duke University, Durham, NC, USA;* [7]*START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain;* [8]*Hematology/Oncology Division and Penn State Cancer Institute, Hershey, PA, USA;* [9]*Brown University, Providence, RI, USA;* [10]*Oklahoma University Medical Center, Oklahoma City, OK, USA;* [11]*The University of Arizona Cancer Center, Tucson, AZ, USA. Formerly of The University of Tennessee Health Science Center and West Cancer Center, Memphis, TN, USA;* [12]*Department of Medical Oncology,Banner MD Anderson Cancer Center, Gilbert, AZ, USA;* [13]*Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA;* [14]*Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA;* [15]*University of Arizona Cancer Center, AZ, USA.*

Background

- Cemiplimab (REGN2810) is a high-affinity, highly potent, human, hinge-stabilized IgG4 monoclonal antibody, generated using VelocImmune® technology,[1,2] directed against programmed death-1 (PD-1) receptor blocking the interactions of PD-1 with PD-ligand 1 (PD-L1) and PD-L2.[3]
- In the dose escalation portion of the Phase 1 study of cemiplimab, an acceptable safety profile with no dose-limiting toxicities was demonstrated in patients with advanced solid tumors.[4]
  - A deep and durable response was observed in a patient with advanced cutaneous squamous cell carcinoma (CSCC).[4]
- CSCC is the second most common cancer in the US after basal cell carcinoma, and represents 20–50% of skin cancers in the US.[5,6]
- Although CSCC has a surgical cure rate of >95%, an estimated 3,932–8,791 patients died from CSCC in 2012 in the US.[7,8]
- There is no approved systemic therapy for patients with advanced CSCC (locally advanced CSCC that is no longer amenable to surgery or radiation therapy, and metastatic CSCC).
- Preliminary analysis suggests a positive risk/benefit profile and antitumor activity with cemiplimab treatment in the Phase 1 CSCC expansion cohorts of the first-in-human study.[9]
- We now report mature final data from the CSCC expansion cohorts of the Phase 1 study (NCT02383212).

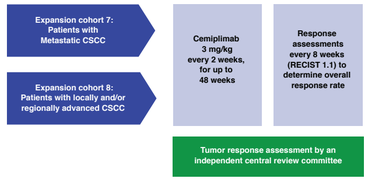
Objectives

- The co-primary objectives of the CSCC expansion cohorts were to:
  - Characterize the safety and tolerability of cemiplimab 3 mg/kg every two weeks (Q2W)
  - Evaluate the efficacy of cemiplimab 3 mg/kg Q2W by measuring overall response rate (ORR).

Methods

- Adult patients with metastatic CSCC or locally and/or regionally advanced CSCC who were not candidates for surgery were enrolled (**Figure 1**).
- Acceptable reasons for surgery to be deemed inappropriate for patients with locally/regionally advanced CSCC were:
  - Recurrence of CSCC after two or more surgical procedures and an expectation that curative resection would be unlikely, and/or;
  - Substantial morbidity or deformity anticipated from surgery.
- Key inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and at least one lesion measurable by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.[10]

Figure 1. Study design: CSCC expansion cohorts



- Patients were excluded if they had any ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression; active brain metastases; or invasive malignancy within 5 years.
- Other selected exclusion criteria were treatment with immunosuppressive doses of steroids (>10 mg prednisone daily or equivalent); systemic antitumor treatment within 4 weeks of initial dose of cemiplimab; history of solid organ transplant; or primary tumors of lip or eyelid.
- Severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).
- The data cut-off date was October 02, 2017.

Results

Baseline characteristics, disposition, and treatment exposure

- Twenty-six patients (median age, 73 years; 10 metastatic and 16 locally/regionally advanced CSCC) were enrolled.
- Patient baseline characteristics are summarized in **Table 1**.
- At the time of data cut-off (October 02, 2017), one patient (3.8%) was on treatment and 25 patients (96.2%) were off treatment.
  - Of the patients off treatment, 11 completed planned treatment and 14 have discontinued treatment (the most common reason for discontinuation was disease progression [n=7]).
- The median number of administered doses of cemiplimab was 16 (range: 2–36) and the median duration of exposure was 36.0 weeks (range: 4.0–71.0).
  - One patient had 71.0 weeks of continued cemiplimab exposure (beyond the planned 48-week treatment duration) as it was considered to be in the best interest of the patient.
- The median duration of follow-up at the time of data cut-off was 11.0 months (range: 1.1–17.0).

Table 1. Patient demographics and baseline characteristics

	Metastatic CSCC (n=10)	Locally / regionally advanced CSCC (n=16)	Total (N=26)
Median age (range), year	71 (55–85)	73 (56–88)	73 (55–88)
≥65 years old, n (%)	7 (70.0)	14 (87.5)	21 (80.8)
Male sex, n (%)	8 (80.0)	13 (81.3)	21 (80.8)
ECOG performance status score, n (%)			
0	4 (40.0)	6 (37.5)	10 (38.5)
1	6 (60.0)	10 (62.5)	16 (61.5)
Primary CSCC site, n (%)			
Head/neck†	5 (50.0)	13 (81.2)	18 (69.2)
Extremity‡	3 (30.0)	2 (12.5)	5 (19.2)
Trunk	1 (10.0)	1 (6.3)	2 (7.7)
Penis	1 (10.0)	0	1 (3.8)
Prior systemic therapy for CSCC, n (%)	9 (90.0)	6 (37.5)	15 (57.7)
Prior radiotherapy for CSCC, n (%)	6 (60.0)	14 (87.5)	20 (76.9)

†Includes ear and temple. ‡Includes arms/hands and legs/feet.

Treatment-emergent adverse events (TEAEs)

- TEAEs of any grade, regardless of attribution, were reported in all patients (**Table 2**).

Table 2. Summary of TEAEs, regardless of attribution, in the combined CSCC expansion cohorts

TEAEs	N=26	
n (%)	Any grade	Grade ≥3
Any	26 (100.0)	12 (46.2)
Serious	7 (26.9)	6 (23.1)
Led to discontinuation	2 (7.7)	0
With an outcome of death†	1 (3.8)	1 (3.8)
Occurred in at least four patients		
Fatigue	7 (26.9)	0
Constipation	4 (15.4)	0
Decreased appetite	4 (15.4)	0
Diarrhea	4 (15.4)	0
Hypercalcemia	4 (15.4)	2 (7.7)
Hypophosphatemia	4 (15.4)	0
Nausea	4 (15.4)	0
Urinary tract infection	4 (15.4)	1 (3.8)

†The fatal TEAE occurred in an 80-year-old man with baseline congestive heart failure and renal insufficiency who later had a TEAE of urinary tract infection and became anuric. The fatal renal failure was considered unrelated to study treatment.

- Investigator-assessed treatment-related TEAEs of any grade occurred in 15 patients (57.7%), with five patients (19.2%) experiencing the following six grade ≥3 treatment-related TEAEs:
  - Adrenal insufficiency, asthenia, increased alanine aminotransferase, increased aspartate aminotransferase, maculo-papular rash, and myalgia.
- Two patients (7.7%) discontinued treatment due to treatment-related TEAEs:
  - An 85-year-old female developed grade 3 rash after three doses of cemiplimab; she completed post-treatment follow-up
  - A 57-year-old male developed grade 2 muscular weakness after four doses of cemiplimab; patient continued treatment for an additional five doses before treatment was permanently discontinued due to this TEAE.
- The most common investigator-assessed treatment-related TEAEs of any grade were fatigue (26.9%), and arthralgia, diarrhea, hypothyroidism, muscle weakness, and maculo-papular rash (each 7.7%).

Clinical efficacy

- ORR by independent central review was 50.0% (13/26 patients: 95% confidence interval [CI]: 29.9–70.1) (**Table 3**).
- Durable disease control rate was 65.4% (95% CI: 44.3–82.8).

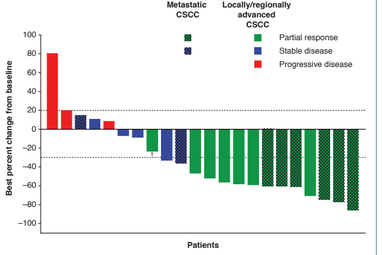
Table 3. Tumor response assessment by central review

	Metastatic CSCC (n=10)	Locally / regionally advanced CSCC (n=16)	Total (N=26)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	6 (60.0)	7 (43.8)	13 (50.0)
Stable disease	2 (20.0)	4 (25.0)	6 (23.1)
Non-complete response/ non-progressive disease†	1 (10.0)	0	1 (3.8)
Progressive disease	0	3 (18.8)	3 (11.5)
Not evaluable‡	1 (10.0)	2 (12.5)	3 (11.5)
Overall response rate, % (95% CI)	60.0 (26.2–87.8)	43.8 (19.8–70.1)	50.0 (29.9–70.1)
Durable disease control rate, % (95% CI)§	80.0 (44.4–97.5)	56.3 (29.9–80.2)	65.4 (44.3–82.8)
Median observed time to response, months (range)¶	2.1 (1.7–3.6)	3.7 (1.7–7.3)	2.3 (1.7–7.3)

†Patients with non-measurable disease on central review of baseline imaging. ‡Include missing and unknown tumor response. §Defined as the proportion of patients without progressive disease for at least 105 days. ¶Data shown are for patients with confirmed partial response as follows: metastatic CSCC, n=6; locally/regionally advanced CSCC, n=7; total, n=13.

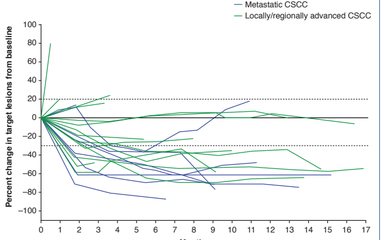
- Rapid, deep, and durable target lesion reductions were observed in most patients who had at least one tumor assessment on treatment (**Figures 2–4**).
- Median duration of response had not been reached at data cut-off.

Figure 2. Clinical activity of tumor response to cemiplimab in patients who underwent radiologic evaluation per independent central review



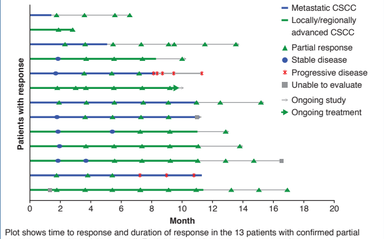
Plot shows the best percentage change in the sum of target lesion diameters from baseline for 22 patients from both CSCC expansion cohorts who underwent radiologic evaluation per independent central review. Lesion measurements after progression were excluded. The horizontal dashed lines indicate criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters). The following four patients do not appear in the figure (but are included in the ORR analysis [Table 3], per intention-to-treat): one metastatic CSCC patient with best response of non-complete response/ non-progressive disease and three patients (one metastatic and two locally/regionally advanced CSCC) with no evaluable post-treatment tumor assessment.
†Considered partial response by independent central review of photographs, although RECIST measurements on radiology scans did not reach –30%.

Figure 3. Change in target lesion over time



Plot shows the percent change in target lesion diameters from baseline over time. Patients shown in this figure are the same as those in Figure 2. The horizontal dashed lines indicate criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters).

Figure 4. Time to and duration of response in responding patients



Plot shows time to response and duration of response in the 13 patients with confirmed partial response at the time of data cut-off. Each horizontal bar represents one patient.

Conclusions

- Final data from the CSCC expansion cohorts of the Phase 1 study show that cemiplimab demonstrated an acceptable risk/benefit profile with substantial antitumor activity as well as durable responses.
- Furthermore, these results showed that CSCC tumors, whether distantly metastatic or locally and/or regionally advanced, are responsive to cemiplimab.
- Primary analysis of the Phase 2 study (NCT02760498) provides further evidence of substantial antitumor activity and durable response with cemiplimab treatment in advanced CSCC.

References

1. Macdonald LE et al. *Proc Natl Acad Sci.* 2014;111:5147–5152.
2. Murphy AJ et al. *Proc Natl Acad Sci.* 2014;111:5153–5158.
3. Burova E et al. *Mol Cancer Ther.* 2017;16:861–870.
4. Papadopoulos KP et al. *J Clin Oncol.* 2016;34(suppl abstr 3024).
5. Rogers HW et al. *JAMA Dermatol.* 2015;151:1081–1086.
6. Que SKT et al. *J Am Acad Dermatol.* 2018;78:237–247.
7. Kauvar AN et al. *Dermatol Surg.* 2015;41:1214–1240.
8. Karia PS et al. *J Am Acad Dermatol.* 2013;68:957–966.
9. Papadopoulos KP et al. *J Clin Oncol.* 2017;35(suppl abstr 9503).
10. Eisenhauer EA et al. *Eur J Cancer.* 2009;45:228–247.

Acknowledgments

We thank the patients, their families, and all investigators involved in this study. The study was funded by Regeneron Pharmaceuticals, Inc., and Sanofi. Medical writing support and typesetting was provided by Emmanuel Ogunnowo of Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc., and Sanofi.

Poster presented at the 2018 Fall Clinical Dermatology Conference, October 18–21, Las Vegas, Nevada (encore of ASCO 2018 poster presentation).