Primary Analysis of Phase 2 Results for Cemiplimab, a Human Monoclonal Anti-PD-1, in Patients with Metastatic Cutaneous Squamous Cell Carcinoma

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Background

- Cutaneous squamous cell carcinoma (CSCC) is rivalled in incidence only by basal cell carcinoma as the most common cancer in the US.[1]
- Risk factors for CSCC include chronic sun exposure, advanced age, ultraviolet radiation-sensitive skin, and immunosuppression.[2]
- More than 95% of CSCC patients are cured with surgery; however, due to the very high incidence of the disease, an estimated 3,932–8,791 patients died from CSCC in 2012 in the US.[3,4]
- 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).
- Cemiplimab (REGN2810) is a high-affinity, highly potent, human, hinge-stabilized IgG4 monoclonal antibody, generated using VelocImmune® technology,[5,6] directed against programmed death-1 (PD-1) receptor blocking the interactions of PD-1 with PD-ligand 1 (PD-L1) and PD-L2.[7]
- Cemiplimab treatment demonstrated encouraging preliminary activity in the CSCC expansion cohorts of the first-in-human study.[8]
- Here we present the primary analysis of the metastatic CSCC cohort from the Phase 2 study of cemiplimab in patients with advanced CSCC (NCT02760498).

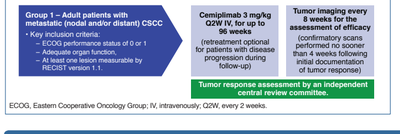
Objectives

- The primary objective was to evaluate overall response rate (ORR; complete response + partial response) according to independent central review per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1[9] (for scans) and modified World Health Organization criteria (for photos).
- Secondary objectives include:
  - Estimation of duration of response, durable disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)
  - Assessment of safety and tolerability of cemiplimab.

Methods

- Patients with metastatic CSCC from Group 1 of the Phase 2, non-randomized, global, pivotal trial of cemiplimab in patients with advanced CSCC are included in this analysis (**Figure 1**).

Figure 1. Phase 2 (Group 1) study design



ECOG, Eastern Cooperative Oncology Group; IV, intravenously; Q2W, every 2 weeks.

- Key exclusion criteria:
  - Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
  - Prior treatments with anti-PD-1 or anti-PD-L1 therapy
  - History of solid organ transplant, concurrent malignancies (unless indolent or not considered life threatening; for example, basal cell carcinoma), or hematologic malignancies.
- Severity of treatment-emergent adverse events (TEAEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).
- The data cut-off date for this analysis was October 27, 2017.

Results

Baseline characteristics, disposition, and treatment exposure

- Of the 59 patients enrolled, 35 (59.3%) remained on treatment at the time of data cut-off, 24 (40.7%) have discontinued treatment mainly due to disease progression (n=14; 23.7%) and adverse events (AEs) (n=4; 6.8%).
- The median duration of exposure to cemiplimab was 32.7 weeks (range: 2.0–69.3) and the median number of doses administered was 17 (range: 1–35).
- The median duration of follow-up at the time of data cut-off was 7.9 months (range: 1.1–15.6).

Clinical efficacy

- Rapid, deep, and durable target lesion reductions were observed in most patients who had at least one tumor assessment on treatment (**Figures 2–4**).

Table 1. Patient demographics and baseline characteristics

	Metastatic CSCC (N = 59)
Median age, years (range)	71 (38–93)
≥ 65 years, n (%)	43 (72.9)
Male sex, n (%)	54 (91.5)
ECOG performance status, n (%)	
0	23 (39.0)
1	36 (61.0)
Primary CSCC site, n (%)	
Head/neck†	38 (64.4)
Extremity‡	12 (20.3)
Trunk	9 (15.3)
Prior systemic therapy for CSCC, n (%)	33 (55.9)
Prior radiotherapy for CSCC, n (%)	50 (84.7)

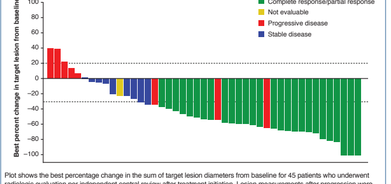
†Includes ear and temple. ‡Includes arms/hands and legs/feet.

Table 2. Tumor response assessment by independent central review

	Metastatic CSCC (N = 59)
Best overall response, n (%)	
Complete response	4 (6.8)
Partial response	24 (40.7)
Stable disease	9 (15.3)
Non-complete response/ non-progressive disease†	4 (6.8)
Progressive disease	11 (18.6)
Not evaluable‡	7 (11.9)
Overall response rate, % (95% CI)	47.5 (34.3–60.9)
Durable disease control rate, % (95% CI)§	61.0 (47.4–73.5)
Median observed time to response, months (range)¶	1.9 (1.7–6.0)

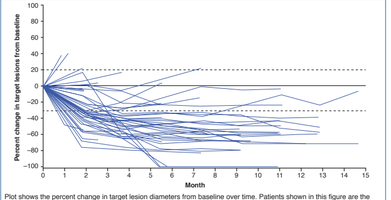
†Patients with non-measurable disease on central review of baseline imaging. ‡Includes missing and unknown tumor response. §Defined as the proportion of patients without progressive disease for at least 105 days. ¶Data shown are from patients with confirmed complete or partial response; n = 28.
CI, confidence interval.

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



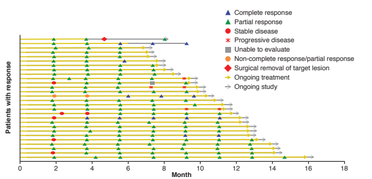
Plot shows the best percentage change in the sum of target lesion diameters from baseline for 45 patients who underwent radiologic evaluation per independent central review after treatment initiation. Lesion measurements after progression were excluded. Horizontal dotted lines indicate criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters). Three patients with target lesion reductions ≥30% were classified as progressive disease (red bars) due to new lesion or progression of non-target lesion. The following patients do not appear in the figure (but are included in the ORR analysis [Table 2], per intention-to-treat): three patients with progression of non-target lesions or new lesion (but no evaluable target lesion), one patient with complete response who had only non-target lesions at baseline, four patients with best response of non-complete response/non-progressive disease, and six patients with no evaluable post-treatment tumor assessments. One patient had stable disease per RECIST 1.1 but was not evaluable (yellow bar) due to externally visible disease that was not evaluable on photographic assessments.

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. Horizontal dotted 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).

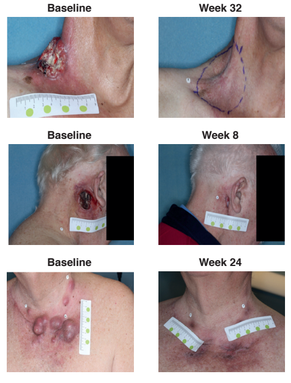
Figure 4. Time to and duration of response in responding patients



Plot shows time to response and duration of response in the 28 responding patients. Each horizontal line represents one patient. Twenty-three of the 28 patients remain in response and on study at time of data cut-off. Three patients had disease progression (red asterisks); one patient was censored after surgical resection of responding target lesion (top line); and one was lost to follow-up after experiencing complete response (second-from-top line).

- Median duration of response had not been reached at data cut-off.
- Neither median PFS nor median OS had been reached at data cut-off.
  - The estimated progression-free probability at 12 months was 52.5% (95% CI: 37.0–65.8).
  - The estimated probability of survival at 12 months was 80.6% (95% CI: 67.7–88.8).

Figure 5. Examples of reductions in visible CSCC lesions following treatment with cemiplimab



The patient in panel A is an 85-year-old man with supraclavicular lesion who had received prior radiotherapy. The patient in panel B is an 83-year-old man with multiple prior surgeries for CSCC. The patient in panel C is a 66-year-old man with anterior chest wall CSCC lesions who had received prior cisplatin.

- Responses to cemiplimab were observed irrespective of prior systemic therapy.
  - ORR in patients without prior systemic anticancer therapy was 57.7% (15/26 patients; 95% CI: 36.9–76.6; three CRs and 12 PRs); durable DCR was 69.2% (95% CI: 48.2–85.7).
  - ORR in patients who had received prior systemic anticancer therapy was 39.4% (13/33 patients; 95% CI: 22.9–57.9; one CR and 12 PRs); durable DCR was 54.5% (95% CI: 36.4–71.9).

Treatment-emergent adverse events

- TEAEs regardless of attribution are summarized in **Table 3**.

Table 3. TEAEs regardless of attribution

TEAEs	Metastatic CSCC (N = 59)	
n (%)	Any grade	Grade ≥3
Any	59 (100.0)	25 (42.4)
Serious	21 (35.6)	17 (28.8)
Led to discontinuation	4 (6.8)	3 (5.1)
With an outcome of death	3 (5.1)	3 (5.1)
Occurred in at least five patients†		
Diarrhea	16 (27.1)	1 (1.7)
Fatigue	14 (23.7)	1 (1.7)
Nausea	10 (16.9)	0
Constipation	9 (15.3)	1 (1.7)
Rash	9 (15.3)	0
Cough	8 (13.6)	0
Decreased appetite	8 (13.6)	0
Pruritus	8 (13.6)	0
Headache	8 (13.6)	0
Dry skin	6 (10.2)	0
Maculo-papular rash	6 (10.2)	0
Vomiting	6 (10.2)	0
Anemia	5 (8.5)	1 (1.7)
Hypothyroidism	5 (8.5)	0
Increased alanine aminotransferase	5 (8.5)	0
Pneumonitis	5 (8.5)	2 (3.4)

†Events are listed as indicated on the case report form. Adverse events were coded according to Preferred Terms (MedDRA version 20.0). Although rash and maculopapular rash may reflect the same condition, they were listed as two distinct events in the safety report. Included in this table are TEAEs of any grade that occurred in ≥5 patients. Events are listed in decreasing order of frequency by any grade.

- Grade ≥3 TEAEs that occurred in more than one patient were cellulitis, pneumonitis, hypercalcemia, death, and pleural effusion.
- Investigator-assessed treatment-related TEAEs of any grade occurred in 44 patients (74.6%), with seven patients (11.9%) experiencing grade ≥3 treatment-related TEAEs.
- A total of nine grade ≥3 immune-related TEAEs (per investigator assessment) occurred in six patients (10.2%) as follows:
  - Pneumonitis (3.4%), and arthritis, aseptic meningitis, colitis with diarrhea, confusional state, hypophysitis, neck pain, and polyarthritis (each 1.7%).
- Four patients (6.8%) discontinued treatment due to treatment-related TEAEs, with three patients (5.1%) discontinuing due to grade ≥3 treatment-related TEAEs.
- The most common treatment-related TEAEs were fatigue (13.6%), diarrhea (11.9%), and pruritus, rash, and maculopapular rash (each 10.2%).
- Pneumonitis was the only grade ≥3 treatment-related TEAE to occur in more than one patient.
- Three patients (5.1%) had TEAEs with outcome of death; however, none were considered related to treatment.
  - A 93-year-old man presented with fever and cough with purulent sputum, and died of complications of pneumonia.
  - A 72-year-old man died in his sleep.
  - A 90-year-old man who had disease progression (per independent review) developed duodenal ulcer and esophagitis that later resolved. The patient subsequently experienced hypercalcemia and deep vein thrombosis and died.

Conclusions

- In the largest prospective study reported in patients with metastatic CSCC, cemiplimab 3 mg/kg Q2W showed substantial activity and durable responses with an acceptable safety profile.
- Cemiplimab showed an acceptable risk/benefit profile in this metastatic CSCC population, which tends to be elderly and associated with medical co-morbidities.
- Combined with the updated CSCC expansion cohorts of the Phase 1 results, these results indicate that advanced CSCC tumors, whether metastatic or locally advanced, are responsive to cemiplimab.
- Evaluation of cemiplimab 3 mg/kg Q2W in patients with locally advanced CSCC in the Phase 2 study of cemiplimab is ongoing.

These results in combination with the Phase 1 results are now published and available at http://NEJM.org (Migden MR and Rischin D et al. *N Engl J Med.* 2018;379:341–351).

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