Tolerability and Antitumor Activity of Cemiplimab, a Human Monoclonal Anti-PD-1, in Patients with Non-small-cell Lung Cancer (NSCLC): Interim Data from Phase 1 Dose Escalation and NSCLC Expansion Cohort

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Background

- Non-small-cell lung cancer (NSCLC) is the most common histological subtype of all lung cancers, accounting for more than 80%.[1–3] Most patients with NSCLC are at an advanced stage at the time of diagnosis.
- Until recently, platinum-based doublet chemotherapy was the standard first-line treatment for all patients with advanced NSCLC without mutations in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), or a C-ROS oncogene receptor tyrosine kinase (*ROS1*).[4]
- Platinum-based doublet chemotherapy has demonstrated an overall response rate (ORR) of 19–32% in patients with advanced NSCLC, but patients often progress after initial response to treatment.[4–7]
- Recently, pembrolizumab in combination with pemetrexed and platinum chemotherapy received approval for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no *EGFR* or *ALK* mutations.[8]
- Cemiplimab-rwlc (REGN2810) is a high-affinity, highly potent, human monoclonal antibody directed against programmed cell death-1 (PD-1) that recently received approval from the Food and Drug Administration for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or radiation.[9–11]
- Cemiplimab has exhibited antitumor activity with a safety profile comparable with that of other anti-PD-1 agents in patients with advanced tumors, including those with NSCLC.[10,12–13]
- Here, we report interim results from the study of cemiplimab monotherapy in patients with advanced NSCLC from the Phase 1 dose escalation and expansion cohort 1 (NCT02383212).

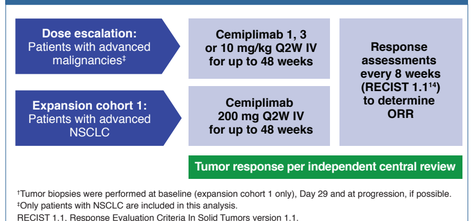
Objectives

- The co-primary objectives of the dose escalation and expansion cohort 1 were to:
  - Characterize the safety and tolerability of cemiplimab
  - Evaluate the efficacy of cemiplimab.

Methods

- In the dose escalation phase, patients with advanced malignancies with no alternative standard-of-care therapeutic option were enrolled and received cemiplimab 1, 3, or 10 mg/kg every 2 weeks (Q2W) intravenously (IV) for up to 48 weeks.
- In expansion cohort 1, patients with advanced NSCLC who had relapsed after, or were refractory to at least first-line therapy were enrolled and received cemiplimab 200 mg Q2W IV for up to 48 weeks (**Figure 1**).

Figure 1. Study design†



†Tumor biopsies were performed at baseline (expansion cohort 1 only), Day 29 and at progression, if possible.
‡Only patients with NSCLC are included in this analysis.
RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

- 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 RECIST 1.1.[14]
- Patients were excluded if they had prior exposure to anti-PD-1 or anti-programmed cell death-ligand 1 (PD-L1) agents; 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; or history of solid organ transplant.
- 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 September 1, 2017.

Results

Baseline characteristics, disposition, and treatment exposure

- Twenty-one patients with NSCLC (one from dose escalation treated at cemiplimab 1 mg/kg and 20 from expansion cohort 1) were enrolled. Patient baseline characteristics are summarized in **Table 1**.
- At the time of data cut-off (September 1, 2017), all 21 patients were off treatment; eight (38.1%) completed treatment and 13 (61.9%) discontinued treatment.
  - The most common reason for treatment discontinuation was disease progression (n=12, 57.1%).
- The median number of administered doses of cemiplimab was 16 (range: 2–24) and the median duration of exposure was 31.9 weeks (range: 4.0–55.0).
- The median duration of follow-up at the time of data cut-off was 8.11 months (range: 1.0–18.2).

Table 1. Patient demographics and baseline characteristics

	N=21
Median age, years (range)	65 (50–82)
≥ 65 years, n (%)	11 (52.4)
Male, n (%)	14 (66.7)
ECOG performance status, n (%)	
0	4 (19.0)
1	17 (81.0)
Prior cancer-related radiotherapy, n (%)	16 (76.2)
Prior cancer-related systemic therapy, n (%)	21 (100.0)
Tumor histology, n (%)	
Adenocarcinoma	13 (61.9)
Squamous cell carcinoma	4 (19.0)
Neuroendocrine	3 (14.3)
Adeno/squamous cell carcinoma	1 (4.8)

Treatment-emergent adverse events (TEAEs)

- All patients experienced at least one TEAE of any grade, regardless of attribution.
- TEAEs regardless of attribution are summarized in **Table 2**.
- One patient treated at cemiplimab 200 mg Q2W discontinued treatment due to TEAE of grade 3 pneumonitis that was considered related to study treatment.
- Grade ≥3 TEAEs that occurred in more than one patient were lymphopenia and pneumonia (each n=2, 9.5%).

Table 2. Summary of TEAEs, regardless of attribution

TEAEs, n (%)	N=21	
	All grades	Grade ≥3
Any	21 (100.0)	13 (61.9)
Serious	9 (42.9)	9 (42.9)
Led to discontinuation	1 (4.8)	1 (4.8)
With an outcome of death	0	0
Occurred in at least three patients		
Cough	5 (23.8)	0
Arthralgia	4 (19.0)	0
Asthenia	4 (19.0)	1 (4.8)
Dyspnea	4 (19.0)	1 (4.8)
Fatigue	4 (19.0)	0
Abdominal pain	3 (14.3)	0
Constipation	3 (14.3)	0
Decreased appetite	3 (14.3)	0
Diarrhea	3 (14.3)	1 (4.8)
Dizziness	3 (14.3)	0
Hypothyroidism	3 (14.3)	0
Maculo-papular rash	3 (14.3)	0
Myalgia	3 (14.3)	0
Neck pain	3 (14.3)	0
Pneumonitis	3 (14.3)	1 (4.8)
Upper respiratory tract infection	3 (14.3)	0

- The most common treatment-related TEAEs were asthenia, pneumonitis, and rash (each n=3, 14.3%).
- Each of the following grade ≥3 treatment-related TEAEs occurred once: pneumonitis, diabetic ketoacidosis, and nephritis.

Clinical efficacy

- Tumor response by independent central review is summarized in **Table 3**.

Table 3. Tumor response assessment by independent central review

	N=21
Best overall response, n (%)	
Complete response	0
Partial response	6 (28.6)
Stable disease	4 (19.0)
Progressive disease	9 (42.9)
Non-complete response/non-progressive disease	2 (9.5)
ORR, % (95% CI)	28.6 (11.3–52.2)
Disease control rate, % (95% CI)	57.1 (34.0–78.2)
Durable disease control rate, % (95% CI)†	52.4 (29.8–74.3)
Median observed time to response, months (range)‡	3.0 (1.4–5.6)

†Defined as the proportion of patients without progressive disease for at least 105 days. ‡Data shown are for patients with confirmed partial response.
CI, confidence interval.

- Duration of response exceeded 8 months in five of the six responders.
- Disease control has been maintained for seven patients after planned discontinuation of therapy at 48 weeks.
- Clinical tumor response data are shown in **Figures 2–4**.

Immunohistochemistry

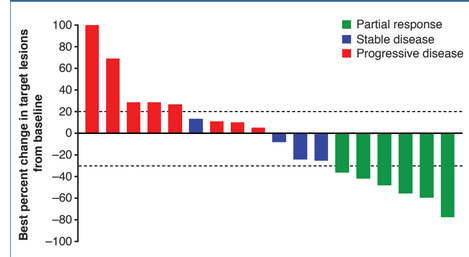
- Of the 17 patients who had tissue available for PD-L1 expression evaluation, 11 (64.7%) had a tumor proportion score (TPS) of <1%, and 3 (17.6) had a TPS of > 50% (**Table 4**).
- Of the four patients whose tumors were not evaluable by immunohistochemistry, best responses were partial response (n=1), non-complete response/non-progressive disease (n=1), and progressive disease (n=2).
- Cemiplimab appears to be active regardless of tumor PD-L1 expression level.

Table 4. Tumor PD-L1 expression by immunohistochemistry

	Total	Complete response	Partial response	Stable disease	Progressive disease	ORR
Tumor PD-L1	Number of patients					
≥50%	3	0	2	0	1	66.7% (2/3)
≥1–49%	3	0	0	1	2	0
<1%	11†	0	3	3	4	27.3% (3/11)

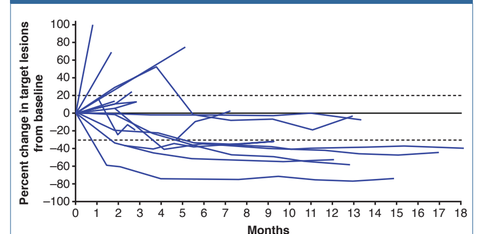
†One dose escalation patient had non-complete response/non-progressive disease.

Figure 2. Clinical activity of tumor response to cemiplimab by independent central review



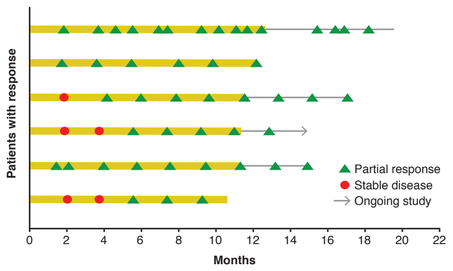
Plot shows the best percentage change in the sum of target lesion diameters from baseline for the 18 patients who had at least one response evaluation per central review. Lesion measurements after progression were excluded. The horizontal lines indicate criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters), respectively. The following three patients who did not have target lesion do not appear in the figure (but included in the overall response analysis [Table 3], per intention-to-treat): one patient (from the dose escalation cohort) who had best overall response of non-complete response/non-progressive disease, and two patients (from expansion cohort) with best overall response of non-complete response/non-progressive disease for one and progressive disease due to a new lesion at the Cycle 1 visit for the other.

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 six patients with partial response at the time of data cut-off. Each horizontal bar represents one patient.

Conclusions

- Cemiplimab showed an acceptable safety profile and demonstrated antitumor activity in pretreated patients with NSCLC.
- Trials of cemiplimab as monotherapy or in combination with other treatments, in patients with advanced NSCLC are currently enrolling patients (NCT03088540; NCT03409614).

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