Phase 1 Study of Cemiplimab, a Human Monoclonal Antibody to Programmed Death-1, in Japanese Patients with Advanced Malignancies: Results from the Dose Exploration

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Background

- Cemiplimab is a high-affinity, highly potent, human monoclonal antibody directed against programmed death (PD)-1.[1,2]
- In patients outside of Japan, cemiplimab has demonstrated a safety profile comparable with those of other anti-PD-1 agents and substantial antitumor activity in multiple solid tumors, including cutaneous squamous cell carcinoma (CSCC) and non-small-cell lung cancer (NSCLC).[2-4]
- Cemiplimab-rwlc is approved by the US Food and Drug Administration (FDA) for the treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[5]
- The two-part Phase 1 study (NCT03233139) evaluates safety, tolerability, and pharmacokinetics (PK) of cemiplimab in Japanese patients with advanced malignancies. In Part 1, two monotherapy doses of cemiplimab were evaluated in patients with a variety of tumor types. In Part 2, cemiplimab alone or in combination is being evaluated in patients with NSCLC. Here, we present interim results of Part 1.

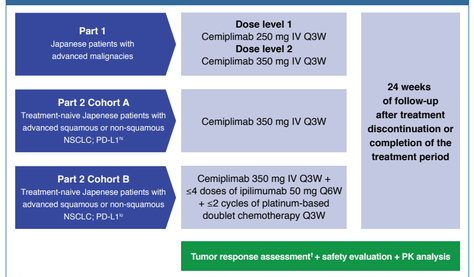
Objectives

- The primary objectives of the study were to assess the safety, tolerability, and PK of cemiplimab in Japanese patients with advanced malignancies.
- The secondary objective was to assess the immunogenicity of cemiplimab in these patients.
- The exploratory objective of Part 1 was to evaluate tumor response to cemiplimab monotherapy in Japanese patients with advanced malignancies.

Methods

- In Part 1 of the study, patients with advanced malignancies with no alternative standard-of-care therapeutic options were enrolled and received cemiplimab 250 mg or 350 mg every 3 weeks (Q3W) intravenously (IV) for up to 108 weeks.
- Key inclusion criteria for Part 1 included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function. In addition, patients must have been born in Japan, and their biological parents and grandparents must be of Japanese origin.
- Patients were excluded from Part 1 of the study if they received prior treatment with agents targeting anti-PD-1/PD-ligand 1 (PD-L1) pathway; had ongoing or recent autoimmune disease that required systemic immunosuppressive treatments; were treated with corticosteroids (>10 mg prednisone daily or equivalent) within first 4 weeks prior to the first dose of cemiplimab; had active brain metastases, among others. Patients with controlled human immunodeficiency virus, hepatitis C virus, or hepatitis B virus infections are allowed.
- Tumor responses were assessed using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1)[6] by investigators in Part 1 every 9 weeks in the first year, every 12 weeks in the second year, and every 8 weeks during the follow-up period.
- 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 was January 20, 2019.

Figure 1. Study design†



†Tumor responses were assessed using RECIST 1.1[6] by investigators in Part 1 and Part 2 Cohort B and by an independent review committee in Part 2 Cohort A every 9 weeks in the first year, every 12 weeks in the second year and every 8 weeks during the follow-up.
PD-L1[b]: PD-L1 expression is ≥50% of the tumor cells; PD-L1[low]: PD-L1 expression is <50% of the tumor cells.
Q6W, every 6 weeks.

Results

Baseline characteristics, disposition, and treatment exposure

- Thirteen patients with advanced malignancies were enrolled. Patient baseline characteristics are summarized in **Table 1**.
- At the time of data cut-off, Part 1 of the study was fully enrolled. Eleven patients (84.6%) discontinued treatment; zero completed, and two (15.4%) remain on treatment.
  - The most common reason for treatment discontinuation was disease progression (n=8, 61.5%).
- The median number of administered doses of cemiplimab was 4 (range: 1–26) and the median duration of exposure was 13.1 weeks (range: 3.0–80.9).
- The median duration of follow-up at the time of data cut-off was 8.11 months (range: 2.0–18.8).
- No dose limiting toxicities were observed.

Table 1. Patient demographics and baseline characteristics

	N=13
Median age, years (range)	62 (33–75)
≥ 65 years, n (%)	5 (38.5)
Male, n (%)	5 (38.5)
ECOG performance status, n (%)	
0	8 (61.5)
1	5 (38.5)
Primary tumor site, n (%)	
Other	3 (23.1)
Bladder/urethra	2 (15.4)
Lung	2 (15.4)
Breast	1 (7.7)
Head/neck	1 (7.7)
Ovary	1 (7.7)
Prostate	1 (7.7)
Pancreas	1 (7.7)
Uterus	1 (7.7)
Prior cancer-related radiotherapy, n (%)	7 (53.8)
Median number of prior cancer-related radiotherapy (range)	1.0 (0–2)
Prior cancer-related systemic therapy, n (%)	12 (92.3)
Median number of prior cancer-related systemic therapy (range)	3 (0–12)
Prior cancer-related surgery, n (%)	9 (69.2)
Median number of prior cancer-related surgeries (range)	1 (0–5)

Treatment-emergent adverse events (TEAEs)

- Twelve (92.3%) patients experienced at least one TEAE of any grade, regardless of attribution.
- TEAEs regardless of attribution are summarized in **Table 2**.
- There were no grade ≥3 TEAEs that occurred in more than one patient.
- The most common treatment-related TEAEs were: rash (n=3, 23.1%), fatigue, hyperthyroidism, and increased aspartate aminotransferase (each n=2, 15.4%).
- Each of the following grade ≥3 TEAEs occurred once: autoimmune colitis, dehydration, hyponatremia, hypophosphatemia, and myositis.

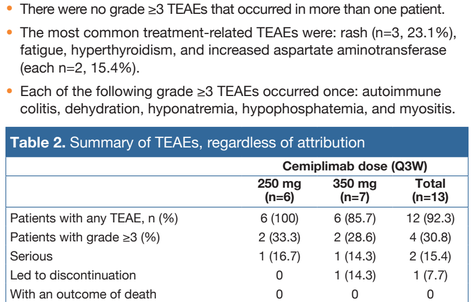
Table 2. Summary of TEAEs, regardless of attribution

	Cemiplimab dose (Q3W)		
	250 mg (n=6)	350 mg (n=7)	Total (n=13)
Patients with any TEAE, n (%)	6 (100)	6 (85.7)	12 (92.3)
Patients with grade ≥3 (%)	2 (33.3)	2 (28.6)	4 (30.8)
Serious	1 (16.7)	1 (14.3)	2 (15.4)
Led to discontinuation	0	1 (14.3)	1 (7.7)
With an outcome of death	0	0	0
Occurred in all patients enrolled			
Dermatitis contact	1 (16.7)	2 (28.6)	3 (23.1)
Rash	2 (33.3)	1 (14.3)	3 (23.1)
Viral upper respiratory tract infection	2 (33.3)	1 (14.3)	3 (23.1)
Aspartate aminotransferase increase	1 (16.7)	1 (14.3)	2 (15.4)
Fatigue	0	2 (28.6)	2 (15.4)
Hyperthyroidism	1 (16.7)	1 (14.3)	2 (15.4)
Hypophosphatemia	2 (33.3)	0	2 (15.4)
Insomnia	1 (16.7)	1 (14.3)	2 (15.4)
Pruritus	2 (33.3)	0	2 (15.4)

Clinical efficacy

- Tumor response per investigator assessment is summarized in **Table 3**.
- At the time of data cut-off, the disease control rate was 53.8% (n=7; 4 partial response + 3 stable disease).
- Clinical tumor response data are shown in **Figures 2–4**.

Figure 2. Clinical activity of tumor response to cemiplimab by investigator assessment



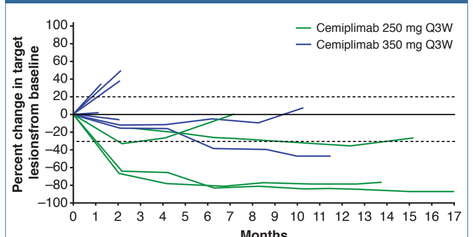
Plot shows the best percentage change in the sum of target lesion diameters from baseline for the 11 patients who had at least one response evaluation. Lesion measurements after progression were excluded. Black horizontal lines indicate criteria for partial response (≥30% decrease in the sum of target lesion diameters) and progressive disease (≥20% increase in the target lesion diameters), respectively. Two patients with non-target lesions are not included; one had best overall response of non-complete response/non-progressive disease, the other had best overall response of progressive disease.

Table 3. Tumor response assessment by investigator assessment

	Cemiplimab dose (Q3W)		
	250 mg (n=6)	350 mg (n=7)	Total (n=13)
Best overall response (%)			
Complete response	0	0	0
Partial response	3 (50.0)	1 (14.3)	4 (30.8)
Stable disease	1 (16.7)	1 (14.3)	2 (15.4)
Non-complete response/ non-progressive disease	1 (16.7)	0	1 (7.7)
Progressive disease	1 (16.7)	5 (71.4)	6 (46.2)
ORR, % (95% CI)	50.0 (11.8–88.2)	14.3 (0.4–57.9)	30.8 (9.1–61.4)
Disease control rate, % (95% CI)	83.3 (35.9–99.6)	28.6 (3.7–71.0)	53.8 (25.1–80.8)

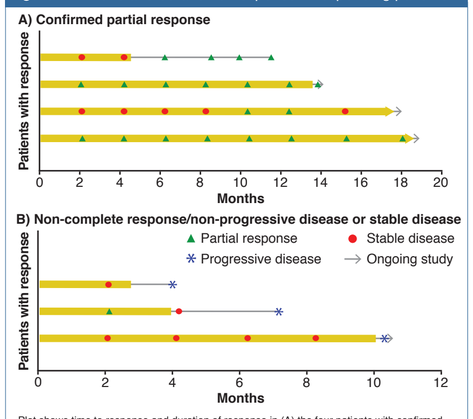
CI, confidence interval; ORR, objective response rate.

Figure 3. Change in target lesion over time



Plot shows the percent change in target lesions from baseline over time. Patients shown on these figures are the same as those on 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 (A) the four patients with confirmed partial response and (B) one patient with non-complete response/non-progressive disease and two patients with stable disease.

Pharmacokinetics

- Cemiplimab serum exposures and PK parameters are comparable between Japanese and non-Japanese patients.

Table 4. Cemiplimab exposure and PK parameters

				Mean (SD) exposure and PK parameters					
				After the first dose				At steady state	
Study	Patient (Median body weight)	Dose	N+	C_{trough} (mg/L)	C_{eoi} (mg/L)	AUC_{tau} (mg/L*d)	$T_{1/2}$ (day)	C_{trough} (mg/L)	C_{eoi} (mg/L)
Pop PK*	Non-Japanese (75 kg)	350 mg Q3W	505	20.4 (7.61)	107 (26.3)	1025 (303)	12.5 (2.79)	58.7 (28.0)	166 (46.1)
Current study	Japanese (59 kg)	250 mg Q3W	6	31.3 (7.10)	110.8 (23.1)	1089 (86.7)	23.9 (26.1)	55.7 (21.8)	178 (13.9)
	Japanese (55 kg)	350 mg Q3W	7	41.0 (6.9)	145.1 (24.8)	1293 (198.3)	16.44 (3.38)	82.6† (1.6)	262† (32.5)

*Population PK (PopPK) predictions are post-hoc estimates for a typical patient (75 kg) based on data from non-Japanese patients (NCT02383212 and NCT03233139);
†Only two patients. N+, number of patients after first dose.

Conclusions

- Cemiplimab monotherapy showed an acceptable safety profile and demonstrated antitumor activity in Japanese patients with advanced malignancies.
  - The safety profile was comparable with those previously reported for cemiplimab and other anti-PD-1 agents.
- Cemiplimab 350 mg Q3W dosing regimen was selected for the expansion cohorts. Part 2 is open and enrolling patients with NSCLC in Japan.

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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 Cindi Hoover, PhD of Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc., and Sanofi.

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Poster presented at the 2019 ASCO-SITC Clinical Immuno-Oncology Symposium, February 28 – March 2, 2019, San Francisco, California.