First-In-Human Study of Cemiplimab Alone or In Combination with Radiotherapy and/or Low-dose Cyclophosphamide in Patients with Advanced Malignancies

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ABSTRACT

Purpose: This first-in-human study assessed the safety, tolerability, dose-limiting toxicities (DLT), antitumor activity, and pharmacokinetics of cemiplimab, a monoclonal anti-programmed cell death-1 (PD-1), as monotherapy and in combination with hypofractionated radiotherapy (hfRT) and/or cyclophosphamide (CPA) in patients with advanced solid tumors.

Patients and Methods: Patients were enrolled in 1 of 10 dose escalation cohorts and received cemiplimab 1, 3, or 10 mg/kg every 2 weeks intravenously for up to 48 weeks. Depending on the cohort, patients received hfRT and/or low-dose (200 mg/m^2) CPA. Safety was evaluated. Antitumor activity was assessed by Response Evaluation Criteria in Solid Tumors version 1.1.

Results: Sixty patients were enrolled. The median duration of follow-up was 19.3 weeks (range, 2.3–84.3). There were no DLTs. The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (45.0%), nausea (36.7%), and vomiting (25.0%). The most common immune-related adverse events (irAEs) of any grade were arthralgia (10.0%), hypothyroidism (8.3%), and maculopapular rash (8.3%). Cemiplimab pharmacokinetic parameters increased in a close to dose-proportional manner and were similar regardless of combination therapy regimen. Two patients (one with cutaneous squamous cell carcinoma and one with cervical cancer) experienced a complete response; 7 had a partial response. Observed duration of response was $\geq$12 months in 6 patients.

Conclusions: The safety profile of cemiplimab was comparable with other anti–PD-1 agents. Addition of hfRT and/or CPA did not appear to increase grade $\geq$3 irAEs, suggesting that cemiplimab can be safely administered with hfRT and/or CPA. Cemiplimab exhibited encouraging antitumor activity with 2 complete responses and 7 partial responses observed; responses were also durable.

Introduction

Monotherapy with anti-programmed cell death receptor-1 (PD-1) or anti-programmed cell death-ligand 1 (PD-L1) agents does not achieve responses in all cancers (1, 2). Combination strategies with immune modulators, including radiotherapy and cyclophosphamide (CPA), have been hypothesized to increase the proportion of patients who might benefit from immunotherapy.

Radiotherapy has been shown to enhance tumor antigen release, antigen presentation, and influx of effector T-cells (3, 4). Tumor cells may counterbalance the immune-enhancing effects of radiation by upregulating PD-L1 levels. Importantly, anti–PD-L1 administration has been shown to enhance radiation-induced tumor regression and survival in mouse models, suggesting that PD-1/PD-L1 blockade may overcome immunosuppression mediated by radiation-induced PD-L1 upregulation (5). CPA inhibits regulatory T-cell responses, and combination of CPA with immunotherapy has demonstrated significant regression of tumors compared with either modality alone (6).

Cemiplimab is a high-affinity, highly potent, human, hinge-stabilized IgG4 mAb to the PD-1 receptor (7). Here, we report results from the first-in-human (FIH) dose escalation study of cemiplimab, examined over a dose range of 1 to 10 mg/kg every 2 weeks, alone or in combination with radiotherapy and/or CPA. The primary objective of

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Blockade of the programmed cell death receptor-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway has demonstrated clinical benefit in multiple cancers. However, monotherapy with anti–PD-1 or anti–PD-L1 agents does not achieve responses in all cancers. This report provides results from the first-in-human experience of cemiplimab, a high-affinity, highly potent human mAb directed against PD-1, as monotherapy or in combination with hypofractionated radiotherapy (hfRT) and/or cyclophosphamide (CPA) in patients with advanced solid tumors. There were no dose-limiting toxicities. Early efficacy signals, including two complete responses, were observed. The results provided the basis for further studies of cemiplimab in multiple tumor types, leading to its first approval (as cemiplimab-rwlc) in the United States for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or patients with locally advanced CSCC who are not candidates for curative surgery/radiation. This study also showed that cemiplimab can be safely administered with hfRT and/or CPA.

the dose escalation study was to assess the safety, tolerability, and dose-limiting toxicities (DLTs) of cemiplimab as monotherapy and in combination with hypofractionated radiotherapy (hfRT) and/or CPA. Secondary objectives included determination of a recommended phase II dose, assessment of antitumor activity, and characterization of the pharmacokinetics and dose-proportionality of cemiplimab as monotherapy and in combination with hfRT and/or CPA. Immunogenicity of cemiplimab was also assessed.

Patients and Methods

Patient population

Patients were eligible if they were ≥18 years, had histologically or cytologically confirmed diagnosis of advanced solid tumors, had no alternative standard-of-care therapeutic option, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were required to have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (8), and for those receiving hfRT, at least one measurable nonirradiated lesion. Select exclusion criteria included any prior treatment with an anti–PD-1/anti–PD-L1 agent, prior treatment with other immune-modulating agents within 4 weeks of initiation of cemiplimab, ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression, or active brain metastasis. Additional details of inclusion/exclusion criteria for the dose escalation study are provided in the Supplementary Data. All patients provided written informed consent.

Study design

This was a FIH open-label, multicenter, dose escalation and cohort expansion study of cemiplimab in patients with advanced solid tumors (NCT02383212). The study protocol and all amendments were approved by the institutional review board (or ethics committee) at each participating study site. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. This article reports data from the dose-escalation portion of the study. Patients were enrolled in 1 of 10 possible cohorts in the dose escalation study, comprising either cemiplimab given as a monotherapy or in combination with hfRT and/or CPA (**Table 1**).

Patients received cemiplimab 1, 3, or 10 mg/kg every 2 weeks by intravenous infusion over 30 minutes for up to six 56-day treatment cycles, for a total of up to 48 weeks of treatment or until disease progression, unacceptable toxicity, withdrawal of consent, or when other study withdrawal criteria were met. There was a posttreatment follow-up period of up to 24 weeks (Supplementary Fig. S1).

In hfRT cohorts (**Table 1**), patients received either 30 Gy given as 5 fractions of 6 Gy administered daily (6 Gy × 5) or 27 Gy given as 3 fractions of 9 Gy administered every other day (9 Gy × 3) starting 1 week after the first dose of cemiplimab. The lesions selected for radiation met protocol criteria regarding clinical appropriateness for radiation and were treated with focal irradiation while sparing the index lesion(s) according to technical specifications in the protocol. In CPA cohorts (**Table 1**), low-dose (200 mg/m^2) CPA was administered intravenously 1 day prior to each of the four doses of cemiplimab in cycle 1.

Dose escalation followed a traditional 3 + 3 design and no intrapatient dose escalation was permitted. All cohorts were expanded to 6 patients if not already expanded during the DLT observation period (Supplementary Fig. S2). The DLT monitoring period was 28 days starting with cycle 1 day 1. Prespecified DLT included grade ≥2 uveitis [considered as a potential immune-related adverse event (irAE)], grade 4 neutropenia that lasted for more than 7 days, grade 4 thrombocytopenia, grade 3 thrombocytopenia with bleeding, grade ≥3 febrile neutropenia, grade ≥3 neutropenia with documented infection, or grade ≥3 nonhematologic toxicity. Exceptions of the latter included grade 3 nausea, vomiting, or diarrhea that were not persistent beyond 7 days duration; grade ≥3 laboratory abnormalities that were considered clinically insignificant and did not meet criteria for a treatment-emergent adverse event (TEAE); grade 3 infusion-related reactions that resolved with medical treatment (because these are not strictly dose-related); and grade 3 irAE other than uveitis that improved within 14 days to grade 2 or lower with medical treatment. Maximum tolerated dose (MTD) would be exceeded if any DLT occurred in 2 or more of the 6 patients during the DLT monitoring period for the specific dose escalation cohort.

Table 1. Dose escalation cohorts and treatment assignment.

Cohort no. (n = 6 each)	Assigned treatment
1	Cemiplimab 1 mg/kg Q2W monotherapy
2	Cemiplimab 3 mg/kg Q2W monotherapy
3	Cemiplimab 10 mg/kg Q2W monotherapy
4	Cemiplimab 1 mg/kg Q2W + hfRT (6 Gy × 5)
5	Cemiplimab 1 mg/kg Q2W + hfRT (9 Gy × 3)
6	Cemiplimab 3 mg/kg Q2W (or MTD) + CPA
7	Cemiplimab 3 mg/kg Q2W (or MTD) + hfRT (6 Gy × 5)
8	Cemiplimab 3 mg/kg Q2W (or MTD) + hfRT (9 Gy × 3)
9	Cemiplimab 3 mg/kg Q2W (or MTD) + hfRT (6 Gy × 5) + CPA
10	Cemiplimab 3 mg/kg Q2W (or MTD) + hfRT (9 Gy × 3) + CPA

Abbreviations: CPA, cyclophosphamide; hfRT, hypofractionated radiotherapy; Q2W, every 2 weeks.

Assessments

Severity of TEAEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Extensive safety evaluations were performed during screening and on day 1 of each subsequent treatment cycle throughout the study. Routine safety evaluations were performed at each cemiplimab dosing visit. Immune-relatedness of adverse events was based on investigators' assessment.

Samples for cemiplimab pharmacokinetic assessments were collected at cycle 1 day 1 (prior to dosing, at the end of infusion (EOI), and at 1, 4, 8, 24, 48, and 72 hour(s) following dosing), cycle 1 day 8 (any time), cycle 1 days 15, 29, and 43 (prior to dosing and EOI), and cycles 2–6 (prior to dosing and EOI on days 1, 15, 29, and 43). Cemiplimab concentration in serum was assessed using a validated ELISA with a lower limit of quantification (LLOQ) of cemiplimab of 0.078 mg/L. Immunogenicity of cemiplimab was assessed in all patients who received treatment and had at least one nonbaseline postdose antidrug antibody (ADA) result. Cemiplimab ADA levels were assessed in serum samples using a validated electrochemiluminescence bridging immunoassay. The presence of neutralizing antibodies was evaluated in ADA-positive serum samples using a validated competitive ligand-binding assay.

Tumor assessments were performed by investigators, per RECIST 1.1, at the end of each 8-week treatment cycle. For patients whose treatment included hfRT, response assessments were based on measurements of nonirradiated lesions only. The data cut-off date was September 1, 2017.

Statistical analysis

The sample size for the dose escalation study was determined empirically. Categorical and continuous data were summarized with frequencies and percentages or descriptive statistics, respectively. All patients exposed to cemiplimab were included in the safety and efficacy analyses. Kaplan–Meier analysis was performed for progression-free survival (PFS) and overall survival (OS).

Results

Patient characteristics

Between February 2015 and March 2016, 60 patients were enrolled in the dose-escalation part of the FIH study, with 6 patients enrolled into each of the 10 dose escalation cohorts. Eighteen patients were enrolled in the cemiplimab 1 mg/kg every 2 weeks cohorts, 36 in the cemiplimab 3 mg/kg every 2 weeks cohorts, and 6 in the cemiplimab 10 mg/kg every 2 weeks cohorts. The median age was 58 years (range: 31–79), 34 patients (56.7%) were men, and ECOG performance status was 0 in 29 patients (48.3%). The most common tumor types were colorectal ($n = 7$; 11.7%), head and neck ($n = 6$; 10.0%), and breast, non-melanoma skin cancer, and soft-tissue sarcoma (each $n = 5$;

Table 2. Patient demographics and baseline disease characteristics.

	Cemiplimab 1 mg/kg Q2W ($n = 18$)	Cemiplimab 3 mg/kg Q2W ($n = 36$)	Cemiplimab 10 mg/kg Q2W ($n = 6$)	Total ($N = 60$)
Median age (range), y	59 (31–77)	59 (39–79)	54 (46–79)	58 (31–79)
Sex, *n* (%)				
Male	12 (66.7)	18 (50.0)	4 (66.7)	34 (56.7)
Female	6 (33.3)	18 (50.0)	2 (33.3)	26 (43.3)
Race, *n* (%)				
White	17 (94.4)	32 (88.9)	6 (100)	55 (91.7)
Black or African American	1 (5.6)	2 (5.6)	0	3 (5.0)
Asian	0	2 (5.6)	0	2 (3.3)
Primary site of cancer, *n* (%)				
Colorectal	1 (5.6)	6 (16.7)	0	7 (11.7)
Head and neck	2 (11.1)	2 (5.6)	2 (33.3)	6 (10.0)
Breast	0	5 (13.9)	0	5 (8.3)
Non–melanoma skin cancer[a]	2 (11.1)	2 (5.6)	1 (16.7)	5 (8.3)
Soft tissue sarcoma	1 (5.6)	2 (5.6)	2 (33.3)	5 (8.3)
Cervix	2 (11.1)	1 (2.8)	0	3 (5.0)
Prostate	1 (5.6)	2 (5.6)	0	3 (5.0)
Salivary gland	1 (5.6)	2 (5.6)	0	3 (5.0)
Uterus	1 (5.6)	2 (5.6)	0	3 (5.0)
Esophageal	0	2 (5.6)	0	2 (3.3)
Ovary	1 (5.6)	1 (2.8)	0	2 (3.3)
Pancreas	0	1 (2.8)	1 (16.7)	2 (3.3)
Other[b]	6 (33.3)	8 (22.2)	0	14 (23.3)
ECOG PS, *n* (%)				
0	8 (44.4)	18 (50.0)	3 (50.0)	29 (48.3)
1	10 (55.6)	18 (50.0)	3 (50.0)	31 (51.7)
Prior cancer-related systemic therapy, *n* (%)				
Any regimen	17 (94.4)	36 (100.0)	6 (100.0)	59 (98.3)
≥3 regimens	12 (66.7)	23 (63.9)	5 (83.3)	40 (66.7)
Prior cancer-related radiotherapy, *n* (%)	14 (77.8)	21 (58.3)	6 (100.0)	41 (68.3)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q2W, every 2 weeks; SCC, squamous cell carcinoma.
[a]Includes one cutaneous squamous cell carcinoma, two basal cell carcinomas, and two Merkel cell carcinomas.
[b]Includes one of each for the following sites: anal, appendix, bladder, cholangiocarcinoma, lung, and thyroid for the cemiplimab 1 mg/kg every 2 weeks dose group, and adrenals, endometrial, kidneys, liver, penis SCC, small intestine, vagina SCC, and vulva SCC for the cemiplimab 3 mg/kg dose.

Table 3. TEAEs by therapy and overall.

No. of patients (%)	Cemiplimab monotherapy ($n = 18$)		Cemiplimab + CPA ($n = 6$)		Cemiplimab + hfRT ($n = 24$)		Cemiplimab + CPA + hfRT ($n = 12$)		Total ($N = 60$)	
TEAEs	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	16 (88.9)	5 (27.8)	6 (100)	1 (16.7)	24 (100)	15 (62.5)	12 (100)	9 (75.0)	58 (96.7)	30 (50.0)
Serious	3 (16.7)	3 (16.7)	1 (16.7)	0	7 (29.2)	6 (25.0)	4 (33.3)	4 (33.3)	15 (25.0)	13 (21.7)
Led to treatment discontinuation	1 (5.6)	1 (5.6)	0	0	1 (4.2)	1 (4.2)	0	0	2 (3.3)	2 (3.3)
With an outcome of death	1 (5.6)	1 (5.6)	0	0	0	0	0	0	1 (1.7)	1 (1.7)
Occurred in ≥10% overall patients										
Fatigue	10 (55.6)	0	0	0	10 (41.7)	0	7 (58.3)	0	27 (45.0)	0
Nausea	5 (27.8)	0	1 (16.7)	0	12 (50.0)	1 (4.2)	4 (33.3)	0	22 (36.7)	1 (1.7)
Vomiting	4 (22.2)	0	1 (16.7)	0	8 (33.3)	1 (4.2)	2 (16.7)	0	15 (25.0)	1 (1.7)
Arthralgia	3 (16.7)	0	2 (33.3)	0	7 (29.2)	0	0	0	12 (20.0)	0
Constipation	3 (16.7)	0	1 (16.7)	0	5 (20.8)	0	3 (25.0)	1 (8.3)	12 (20.0)	1 (1.7)
Cough	4 (22.2)	0	2 (33.3)	0	4 (16.7)	1 (4.2)	2 (16.7)	0	12 (20.0)	1 (1.7)
Anemia	1 (5.6)	0	0	0	8 (33.3)	5 (20.8)	2 (16.7)	0	11 (18.3)	5 (8.3)
Dehydration	3 (16.7)	0	0	0	7 (29.2)	1 (4.2)	1 (8.3)	0	11 (18.3)	1 (1.7)
Decreased appetite	3 (16.7)	0	1 (16.7)	0	4 (16.7)	0	2 (16.7)	0	10 (16.7)	0
Headache	2 (11.1)	0	2 (33.3)	0	4 (16.7)	0	2 (16.7)	0	10 (16.7)	0
Pyrexia	0	0	1 (16.7)	0	7 (29.2)	0	2 (16.7)	0	10 (16.7)	0
Insomnia	0	0	0	0	8 (33.3)	0	1 (8.3)	0	9 (15.0)	0
Dyspnea	2 (11.1)	0	0	0	4 (16.7)	1 (4.2)	2 (16.7)	0	8 (13.3)	1 (1.7)
Upper respiratory tract infection	3 (16.7)	0	0	0	4 (16.7)	0	1 (8.3)	0	8 (13.3)	0
Lymphopenia	2 (11.1)	1 (5.6)	0	0	4 (16.7)	4 (16.7)	1 (8.3)	1 (8.3)	7 (11.7)	6 (10.0)
Abdominal pain	1 (5.6)	0	2 (33.3)	1 (16.7)	2 (8.3)	0	1 (8.3)	0	6 (10.0)	1 (1.7)
Back pain	1 (5.6)	0	0	0	5 (20.8)	1 (4.2)	0	0	6 (10.0)	1 (1.7)
Diarrhea	1 (5.6)	0	0	0	4 (16.7)	0	1 (8.3)	0	6 (10.0)	0
Dizziness	2 (11.1)	0	0	0	4 (16.7)	0	0	0	6 (10.0)	0
Maculopapular rash	3 (16.7)	0	0	0	3 (12.5)	0	0	0	6 (10.0)	0

Note: TEAEs were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 20.0. The severity of TEAEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
Abbreviations: CPA, cyclophosphamide; hfRT, hypofractionated radiotherapy; TEAE, treatment-emergent adverse event.

8.3%). All but one patient had received at least one prior line of systemic therapy for their cancer; the median number of prior lines of systemic therapy was 4 (range: 1–13). Forty-one patients (68.3%) had received at least one prior course of radiotherapy (**Table 2**). As of September 1, 2017 (date of data cutoff), all patients were off treatment; 12 patients (20.0%) had completed the planned 6 cycles of treatment and 48 (80.0%) had discontinued treatment prior to completion of the planned 6 cycles, primarily due to disease progression [$n = 38$; 63.3% (Supplementary Table S1)]. The median duration of exposure to cemiplimab was 16 weeks (range: 2–49).

Treatment-emergent adverse events

The median duration of follow-up was 19.3 weeks (range 2.3–84.3). Overall, TEAEs of any grade were reported in 58 patients (96.7%) with 30 patients (50.0%) experiencing grade ≥3 TEAEs. Fifteen patients (25.0%) experienced serious TEAEs of any grade. Two patients (3.3%) discontinued treatment due to grades ≥3 TEAEs: one patient treated with cemiplimab 1 mg/kg every 2 weeks who experienced increased bilirubin and one patient treated with cemiplimab 10 mg/kg every 2 weeks who experienced anti-HuD associated paraneoplastic limbic encephalitis. The latter case is discussed further below. Of the 18 patients treated with cemiplimab monotherapy, 16 (88.9%) experienced at least one TEAE of any grade, with 5 (27.8%) experiencing grade ≥3 TEAEs. TEAEs of any grade were reported in all patients who received cemiplimab in combination with hfRT and/or CPA. Of the patients treated with cemiplimab in combination with CPA ($n = 6$), or hfRT ($n = 24$), or both CPA and hfRT ($n = 12$), 1 (16.7%), 15 (62.5%), and 9 (75.0%), respectively, experienced grade ≥3 TEAEs (**Table 3**). Grade ≥3 TEAEs were experienced by 11 (61.1%), 17 (47.2%), and 2 (33.3%) of the patients treated at 1 mg/kg every 2 weeks, 3 mg/kg every 2 weeks, and 10 mg/kg every 2 weeks, respectively (Supplementary Table S2). There were no DLTs; therefore, MTD was not identified for cemiplimab.

The most common TEAEs of any grade were fatigue (45.0%), nausea (36.7%), and vomiting (25.0%). Grade ≥3 TEAEs that occurred in more than one patient were lymphopenia ($n = 6$, 10.0%), anemia ($n = 5$, 8.3%), increased aspartate aminotransferase ($n = 4$, 6.7%), hyponatremia, and increased blood alkaline phosphatase (each $n = 3$, 5.0%), hyperglycemia, increased alanine aminotransferase, and hyperbilirubinemia (each $n = 2$, 3.3%).

Overall, 32 patients (53.3%) experienced irAEs with four (6.7%) experiencing grade ≥3 irAEs. By regimen, 8 (44.4%), 3 (50.0%), 13 (54.2%), and 8 (66.7%) of patients treated with cemiplimab monotherapy, cemiplimab in combination with CPA, cemiplimab in combination with hfRT, and cemiplimab in combination with hfRT and CPA, respectively, experienced irAEs of any grade. The corresponding incidence of grade ≥3 irAEs were 1 (5.6%), 0, 1 (4.2%), and 2 (16.7%), respectively. The most common irAEs of any grade were arthralgia ($n = 6$, 10.0%), hypothyroidism ($n = 5$, 8.3%), and maculopapular rash ($n = 5$, 8.3%). Grade ≥3 irAEs were increased aspartate aminotransferase (each $n = 1$, 5.6%) at cemiplimab 1 mg/kg every 2 weeks, hyperthyroidism, and pruritic rash (each $n = 1$, 2.8%) at cemiplimab 3 mg/kg every 2 weeks, and paraneoplastic encephalomyelitis ($n = 1$, 16.7%) at cemiplimab 10 mg/kg every 2 weeks. The

latter patient, with extraskeletal myxoid chondrosarcoma, died from anti-HuD associated paraneoplastic limbic encephalomyelitis that was considered as possibly related to cemiplimab treatment, after receiving five doses of cemiplimab (previously published as a case report; ref. 9).

Pharmacokinetics

Cemiplimab concentrations in serum increased in a close to dose-proportional manner, although dose-normalized C_{trough} was numerically lower at the 1 mg/kg every 2 weeks dose compared

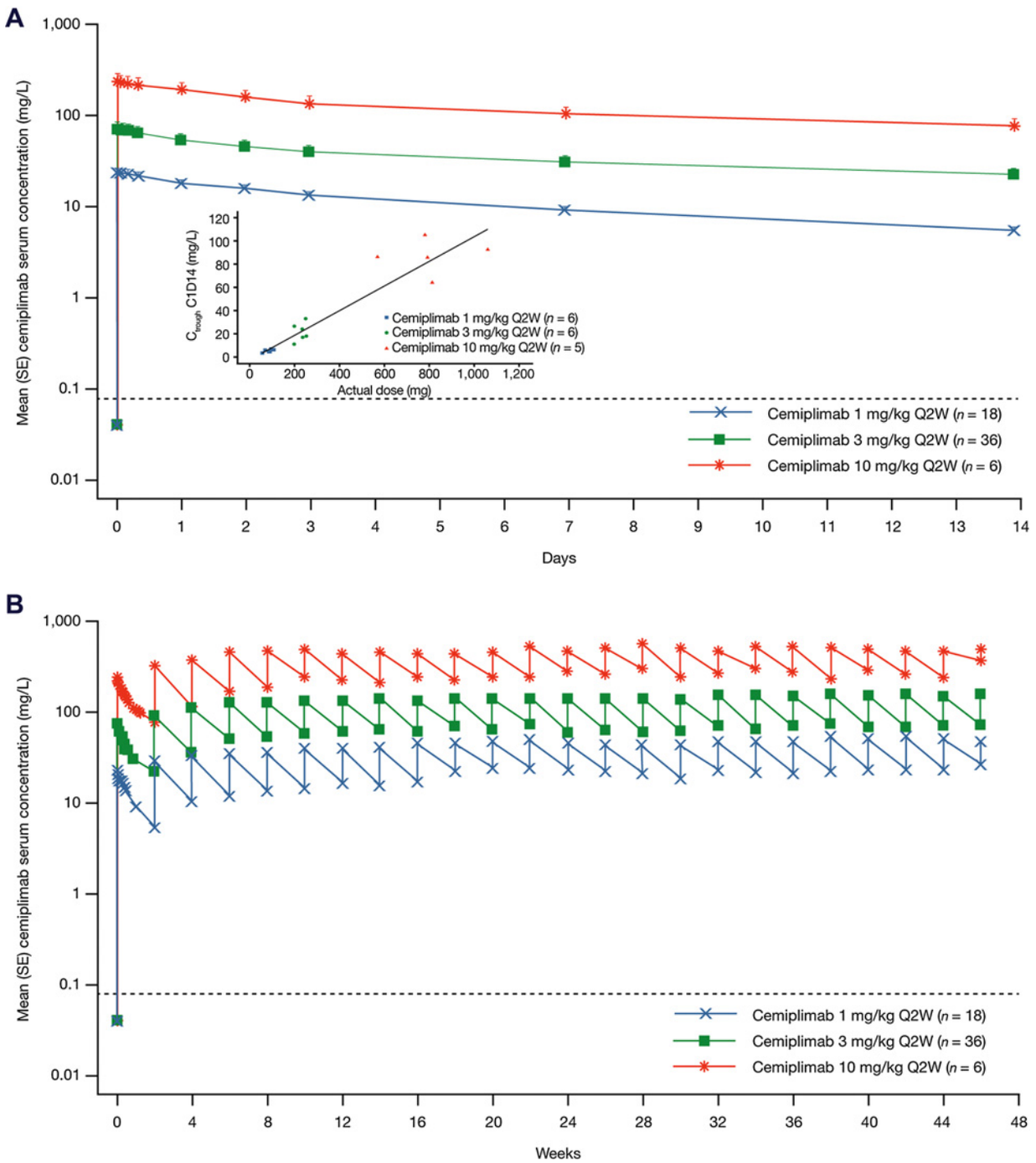

Figure 1.

Concentration–time profile for cemiplimab in the dose escalation study after a single dose (with dose-proportionality curve in-set (**A**) and the full treatment period, in logarithmic scale (**B**). Concentration–time profiles are in semi-logarithmic scale. Inset shows dose-proportionality on linear scale. Horizontal dashed line on the graphs represent the LLOQ/2 of cemiplimab (0.039 mg/L); LLOQ/2 was used in log scale plots. SE, standard error; Q2W, every 2 weeks.

with the higher doses. Cemiplimab half-life after the first dose was approximately 12 days and steady state was reached after 4 months of treatment (end of cycle 2). Pharmacokinetic profiles for cemiplimab as monotherapy or in combination with radiation and/or CPA were similar. Cemiplimab concentration–time profiles in serum after a single intravenous dose of 1, 3, and 10 mg/kg every 2 weeks and full treatment profile are shown in **Fig. 1**. Pharmacokinetic parameters of cemiplimab after the first dose and at steady state (cycle 3 day 1) are summarized in Supplementary Table S3.

Immunogenicity

A total of 49 patients was evaluable for ADA assessments. The ADA incidence rate was low ($n = 1$; 2.0%); the patient with treatment-emergent ADA was on cemiplimab 1 mg/kg every 2 weeks in combination with hfRT (9 Gy × 3). This patient became ADA-positive (low

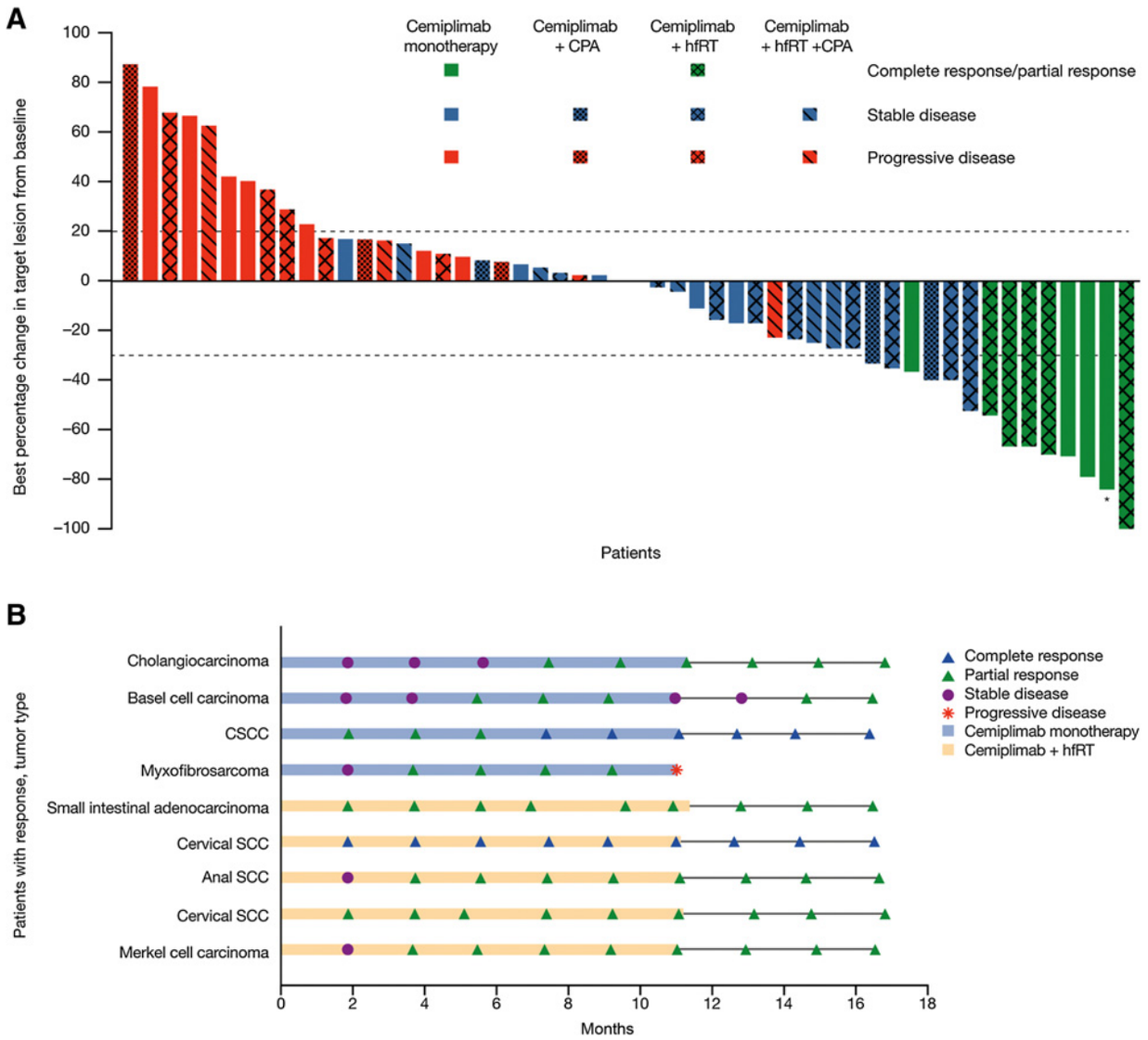

Figure 2.

Clinical characteristics of tumor response to cemiplimab as monotherapy or in combination with hypofractionated radiotherapy and/or CPA. **A,** Best tumor response for the 52 patients in the dose escalation study who underwent radiologic evaluation per investigator assessment. Lesions measurements after progression were excluded. 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). One patient (with asterisk under bar) had a target lesion of lymph node that decreased in size to <10 mm, which is considered a complete response according to RECIST version 1.1. The following 8 patients do not appear in the figure [but are included in the ORR analysis (**Table 4**), per intention-to-treat): 3 patients without any postbaseline tumor assessment and 5 patients for whom at the only postbaseline tumor assessment, their target lesions were either not evaluable or had only new lesions that were measurable. **B,** Time to and duration of response, by cancer type and radiation status, in responding patients. All but two responses were ongoing at the time of completion of 48 weeks on therapy and with 6 months of follow-up. CPA, cyclophosphamide; CSCC, cutaneous squamous cell carcinoma; hfRT, hypofractionated radiotherapy; ORR, objective response rate; SCC, squamous cell carcinoma.

Table 4. Investigator-assessed response by therapy and overall.

	Cemiplimab monotherapy ($n = 18$)	Cemiplimab + CPA ($n = 6$)	Cemiplimab + hfRT ($n = 24$)	Cemiplimab + hfRT + CPA ($n = 12$)	Total ($N = 60$)
Best overall response, *n* (%)					
Complete response	1 (5.6)	0	1 (4.2)	0	2 (3.3)
Partial response	3 (16.7)	0	4 (16.7)	0	7 (11.7)
Stable disease	5 (27.8)	3 (50.0)	10 (41.7)	6 (50.0)	24 (40.0)
Progressive disease	8 (44.4)	3 (50.0)	8 (33.3)	4 (33.3)	23 (38.3)
Not evaluable	1 (5.6)	0	1 (4.2)	2 (16.7)	4 (6.7)
ORR, % (95% CI)	22.2 (6.4–47.6)	0 (0–45.9)	20.8 (7.1–42.2)	0 (0–26.5)	15.0 (7.1–26.6)
Durable disease control rate[a], % (95% CI)	27.8 (9.7–53.5)	50.0 (11.8–88.2)	33.3 (15.6–55.3)	16.7 (2.1–48.4)	30.0 (18.8–43.2)
Median time to response[b], months (range)	4.6 (1.9–7.4)	NA	1.9 (1.8–3.7)	NA	3.6 (1.8–7.4)

Abbreviations: CI, confidence interval; CPA, cyclophosphamide; hfRT, hypofractionated radiotherapy; NA, not applicable; ORR, objective response rate.
[a]Defined as the proportion of patients without progressive disease for at least 105 days.
[b]The data are from patients who had a confirmed complete or partial response.

titer) at cycle 2 day 1; no data were available beyond cycle 2 day 1. No patients tested positive for neutralizing ADAs.

Clinical activity

Two patients experienced a complete response by RECIST 1.1 (**Fig. 2A**; **Table 4**): one had cutaneous squamous cell carcinoma (CSCC) and was treated with cemiplimab 1 mg/kg as monotherapy (previously published as a case report; ref 10); the other had cervical cancer and was treated with cemiplimab 1 mg/kg in combination with hfRT (9 Gy × 3). Seven patients experienced a partial response with cemiplimab monotherapy or in combination with hfRT and 24 had stable disease with cemiplimab monotherapy or in combination with hfRT with or without CPA. Time to and duration of tumor response in patients with complete or partial response by tumor types and summary of responders are shown in **Fig. 2B** and Supplementary Table S4. The objective response rate (ORR) was 15.0% [95% confidence interval (CI): 7.1–26.6). ORR was 22.2% (95% CI: 6.4–47.6) for patients treated with cemiplimab monotherapy and 20.8% (95% CI: 7.1–42.2) for patients treated with cemiplimab in combination with hfRT. No response was observed in patients who received CPA as part of their treatment regimen. The durable disease control rate for all patients was 30.0% (95% CI: 18.8–43.2). Observed duration of response was ≥12 months in 6 of 9 responding patients (66.7%). Changes in target lesions over time for responders are shown in Supplementary Fig. S3. Tumor response over time in patients with best response of stable disease is shown in Supplementary Fig. S4.

In a subanalysis of tumor response (in nonirradiated lesions) by radiation site, a complete response was observed in a cervical cancer patient who received hfRT to abdominal wall lesions. A partial response was observed in two of eight patients with radiation site of lymph node, one of five with radiation site of liver, and one patient with radiation site of small intestine. No response to treatment was observed in the patients who received hfRT to bone ($n = 6$) or lung ($n = 7$). Investigator-assessed response by radiation site for patients treated with hfRT is summarized in Supplementary Table S5.

The median (95% CI) Kaplan–Meier estimation of PFS and OS was 3.6 (1.9–4.0) months and 23.5 (11.0–not evaluable) months, respectively. Kaplan–Meier PFS and OS are shown in Supplementary Fig. S5.

Discussion

In the dose escalation cohorts of this FIH study, cemiplimab demonstrated a safety profile comparable with those of other anti–PD-1 agents in patients with advanced solid tumors (11, 12). MTD was not reached and no DLTs were reported with cemiplimab 1, 3, or 10 mg/kg intravenously every 2 weeks as monotherapy or in combination with hfRT and/or CPA, demonstrating that cemiplimab can be safely combined with either or both therapies. Addition of hfRT (with or without CPA) did not appear to increase incidence of grade ≥3 irAEs.

Overall, cemiplimab pharmacokinetic parameters were similar as monotherapy or in combination with hfRT and/or CPA. Safety and pharmacokinetic data from the dose escalation study supported further evaluation of cemiplimab at the recommended dose of 3 mg/kg every 2 weeks or equivalent, as monotherapy or in combination with hfRT and other antitumor modalities, in expansion cohorts of this phase I study.

In this heavily pretreated population of patients, including several with solid tumors considered resistant to immune checkpoint inhibitors, an ORR of 15.0% indicates that cemiplimab is a clinically active inhibitor of the PD-1 pathway. The efficacy is similar to the phase I experience of other anti–PD-1 agents in advanced solid tumors (11, 12), with responses observed at all doses of cemiplimab tested, and most were durable beyond 6 months.

There was no apparent increase in ORR to cemiplimab by the addition of hfRT, with or without CPA in this small, nonrandomized sample of heterogeneous phase I patient population. Further study is required to investigate whether hfRT can augment the responses to PD-1 blockade, either in selected tumor types or by considering alternative sequencing approaches. In a subanalysis of tumor response by radiation site, responses to nonirradiated lesions were observed in patients who received hfRT to the lymph node, liver, abdominal wall, and small intestine lesions, but not to bone or lung. However, it is inconclusive from this analysis what lesions might be best for hfRT in combination with cemiplimab. The addition of CPA, administered at doses reputed to selectively diminish T regulatory cells, resulted in no objective responses.

The intent of the dose escalation study was to establish the safety of cemiplimab as monotherapy and in combination with hfRT and/or CPA. It was not powered to support comparison of clinical activities between these treatment regimens. Larger expansion cohorts of these regimens are currently being analyzed and may provide insights regarding how the combination regimens modulate immune responses against tumors.

The incidence of overall grade ≥3 TEAEs was higher in cohorts that contained hfRT. Given the small number of patients, it is not possible to determine whether this was due to differences in the patients who enrolled in the hfRT cohorts versus non-hfRT cohorts, the effects of

hfRT, or other factors. However, inclusion criteria for hfRT cohorts specified that these patients should have a symptomatic lesion for which palliative radiotherapy would be appropriate. Patients in the non-hfRT cohorts were not required to have symptomatic lesions, indicating the patient populations in hfRT and non-hfRT cohorts could have differed clinically.

Efficacy signals in tumor types in which the clinical utility of PD-1 blockade had not been established at the time of the study suggested directions for further development. Specifically, clinical efficacy was observed in non–melanoma skin cancers [CSCC, basal cell carcinoma (BCC), and Merkel cell carcinoma) and human papillomavirus–associated tumors (cervical cancer and anal cancer). These observations motivated registrational studies of cemiplimab in CSCC (phase II, NCT02760498), BCC (phase II, NCT03132636), and cervical cancer (phase III, NCT03257267). Data from the advanced CSCC expansion cohorts of this phase I study and the phase II study of advanced CSCC (13) supported the approval of cemiplimab-rwlc in the United States for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation (14). Additional clinical studies are exploring cemiplimab alone or in combination with other therapies in non–small cell lung cancer (phase III, NCT03409614, NCT03088540) and head and neck squamous cell carcinoma (phase II, NCT03565783).

In conclusion, the safety profile of cemiplimab administered at doses up to 10 mg/kg every 2 weeks appeared to be comparable with other anti–PD-1 agents. Combining hfRT and/or CPA with cemiplimab did not appear to increase occurrence of grade $\geq$3 irAEs, and was not associated with any obvious increase in tumor response rates. Cemiplimab demonstrated antitumor activity with durable responses in patients with advanced solid tumors.

Disclosure of Potential Conflicts of Interest

K.P. Papadoulos is an employee/paid consultant for Bayer, reports receiving commercial research grants from ADC Therapeutics, Amgen, ARMO, Bayer, Merck Serono, Incyte, F-Star, Jounce, Medimmune, Regeneron Pharmaceuticals, Inc., MABSpace Biosciences, 3D Medicines. M.L. 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