Clinical Cancer Research

A Phase I Study of the Anti-CC Chemokine Receptor 4 Antibody, Mogamulizumab, in Combination with Nivolumab in Patients with Advanced or Metastatic Solid Tumors

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Abstract

Purpose: Regulatory T cells (Tregs) expressing CC chemokine receptor 4 (CCR4) can suppress antitumor immune responses and are associated with poor prognoses in several cancers. We assessed the safety and efficacy of combined mogamulizumab (anti-CCR4 antibody) and nivolumab [anti-programmed death-1 (PD-1) antibody] in immunotherapy-naïve patients with advanced/metastatic solid tumors.

Patients and Methods: This study (NCT02476123) comprised dose-escalation (3+3 design) and expansion parts. Patients received nivolumab (3.0 mg/kg) every 2 weeks, with mogamulizumab (0.3 or 1.0 mg/kg in dose escalation, 1.0 mg/kg in expansion) once weekly for 4 weeks, then every 2 weeks, until progression or unacceptable toxicity. Primary objective was safety; secondary objectives were antitumor effects, pharmacokinetics, and immunogenicity. Exploratory biomarker analyses were conducted.

Results: Ninety-six patients were enrolled (July 2015–November 2016): six patients in the dose-escalation part and 90 in the expansion part. No dose-limiting toxicities were observed in the dose-escalation part. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 29% of patients in the expansion part (no grade 5 TRAEs). The most frequent TRAEs were rash (39%), rash maculopapular (20%), diarrhea (13%), stomatitis (12%), and pruritus (11%). There were four (27%) confirmed tumor responses among 15 patients with hepatocellular carcinoma, and one confirmed and two unconfirmed responses among 15 patients with pancreatic adenocarcinoma. During treatment, populations of effector Tregs ($CD4^+CD45RA^-FoxP3^{high}$) decreased and $CD8^+$ T cells in tumor-infiltrating lymphocytes increased.

Conclusions: Combining an anti–PD-1 antibody, nivolumab, with a Treg-depleting anti-CCR4 antibody, mogamulizumab, provides an acceptable safety profile, antitumor activity, and a potentially effective option in cancer immunotherapy.

Introduction

The immune checkpoint programmed death-1 (PD-1) receptor and its ligand PD-L1 suppress antitumor immunity. Nivolumab, a human IgG4 anti–PD-1 mAb, has been shown in randomized controlled studies to provide clinical benefits in patients with various tumors, and is associated with health-related quality-of-life improvement in patients with advanced melanoma and advanced renal cell carcinoma (1–3). However, it has recently been reported that primary, adaptive, or acquired resistance to anti–PD-1/PD-L1 therapy may be partially mediated by regulatory T cells (Tregs; ref. 4), and that these Tregs inhibit immune responses against tumors (5).

Mogamulizumab is a humanized IgG1 mAb targeting the CC chemokine receptor 4 (CCR4) that has a defucosylated Fc region, which enhances the antibody-dependent cellular cytotoxicity (ADCC; ref. 6), and has been approved for T-cell lymphomas by the Pharmaceuticals and Medical Devices Agency, Food and Drug Administration, and European Medicines Agency. The tolerability, safety, and antitumor activity of mogamulizumab against CCR4-expressing T-cell lymphomas accompanied by the rapid and long-lasting depletion of peripheral Tregs have been confirmed in multiple clinical trials (7–9). In anticipation of this

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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

It was widely known that PD-1/PD-L1 inhibitors have encouraging clinical activity in several cancers and that Tregs are key cells that affect the immunosuppressive tumor microenvironment. Before this study, there was no clinical evidence regarding the combination of Treg depletion and an anti–PD-1/PD-L1 antibody in patients with solid tumors. To our knowledge, this is the first clinical report to provide evidence for the mechanism of tumor immunity activation by Treg depletion in the tumor microenvironment. Combination therapy with mogamulizumab and nivolumab resulted in a clear depletion of effector Tregs and the expansion of $CD8^+$ T cells in tumor-infiltrating lymphocytes. In addition, a manageable safety profile and several tumor responses were observed in patients with solid tumors. These results provide clinical evidence for the safety and potential efficacy of mogamulizumab and nivolumab combination therapy, as well as the potential role of biomarkers in mediating the antitumor effects.

antitumor activity by the depletion of Tregs, a phase I study of mogamulizumab monotherapy in patients with solid cancers was performed and a reduction in peripheral Tregs was clearly observed (10).

High levels of tumor-infiltrating effector Tregs are associated with poor clinical prognoses in some solid tumors (11). Moreover, effector Tregs, which are defined by $CD4^+CD45RA^-$ Forkhead box protein P3 $(FoxP3)^{high}$ that highly expresses CCR4, have the highest suppressive effects on antitumor immune responses in peripheral blood and the tumor microenvironment (TME; ref. 12). According to a previous clinical study, patients with melanoma who progressed after treatment with nivolumab and a multipeptide vaccine had increased Tregs in peripheral blood compared with those who did not have progressive disease (13). Interestingly, a recent preclinical study suggested that Treg depletion synergized with the anti–PD-1 antibody to eradicate established anti–PD-1–resistant tumors (14). These results imply that Tregs may suppress the antitumor immune responses induced by nivolumab.

We hypothesized that Treg depletion by mogamulizumab may synergize with PD-1 blockade to target tumors by alleviating the suppression of antitumor immunity. Using this hypothesis, we conducted the first phase I study to investigate the safety, tolerability, efficacy, and biomarker status of combined therapy with mogamulizumab and nivolumab in patients with advanced or metastatic solid tumors. Interim results of this study have been previously reported in part as an oral presentation (15).

Patients and Methods

Study design and participants

This was a multicenter, open-label, multi-cohort, phase I study conducted in Japan that included a dose-escalation part and an expansion part. The expansion part comprised six cohorts with non–small cell lung cancer (NSCLC), small-cell lung cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma (HCC), and pancreatic adenocarcinoma. Patients were eligible if they met the following criteria: had histologically or cytologically confirmed solid tumors; had progressed, been intolerant to any standard treatment regimen, or had refused standard therapy; were at least 20 years old; had measurable disease based on the revised Response Evaluation Criteria In Solid Tumors (RECIST) guidelines version 1.1; had Eastern Cooperative Oncology Group performance status score of 0 or 1; had adequate hematologic, renal, hepatic, and respiratory functions; and had a life expectancy of at least 3 months. Key exclusion criteria were previous treatment with antibodies or drugs that target T-cell costimulation or checkpoint pathways, or with mogamulizumab. Patients who were pregnant or lactating, or who had uncontrolled central nervous system metastases or known carcinomatous meningitis, were not eligible. Patients with HCC were required to have Child-Pugh scores of 5 or 6 (Child-Pugh A). Patients infected with hepatitis B virus (HBV) (HBs antigen positive) were excluded because of a potential risk of HBV reactivation by mogamulizumab (16).

This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines (GCP) and is registered at ClinicalTrials.gov (identifier NCT02476123). The study protocol and amendments were approved by the institutional review board of each participating institute, and written informed consent was obtained from all patients before conducting any study-related procedures.

Procedures

Patients were enrolled in a 3+3 design and received nivolumab (3.0 mg/kg) intravenously every 2 weeks and mogamulizumab at 0.3 mg/kg (cohort 1) or 1.0 mg/kg (cohort 2) in the dose-escalation part and 1.0 mg/kg in the expansion part weekly during cycle 1 and subsequently every 2 weeks until disease progression or unacceptable toxicity. Each cycle lasted 28 days, and the duration of a cycle was extended in the case of dose delays (the criteria for dose delays are provided in the Supplementary Data). Oral antihistamine and acetaminophen were administered as premedication before each dose, and a systemic corticosteroid was administered intravenously prior to the first dose of mogamulizumab to prevent infusion-related reactions. Patients were observed during cycle 1 treatment for possible dose-limiting toxicity (DLT; defined in the Supplementary Data) in the dose-escalation part. Safety was assessed by the investigators throughout the treatment period and up to 90 days after the end of treatment. Adverse events were defined using the Medical Dictionary for Regulatory Activities, version 18.0. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Tumor responses were assessed by the investigators according to the RECIST guidelines (version 1.1) at 4, 8, 16, 24, 32, 40, 48, and 56 weeks, and every 12 weeks thereafter until death or disease progression. Even if disease progression was observed, administration of the investigational drug could be continued if the patient consented. The best overall response (BOR) was defined as the best response across all time points during the study. A complete response or partial response (PR) was confirmed only if the criteria for each were maintained at the subsequent time point, and at least 4 weeks following initial response. Stable disease (SD) was assigned only if the criteria for SD were met at least 8 weeks after the first assessment.

Plasma concentrations of mogamulizumab were analyzed by an ELISA before treatment and at days 1, 2, 4, and 8 of cycle 1, day 1 of cycles 2 to 7, and day 1 of cycle 13. Pharmacokinetic parameters were area under the plasma concentration time curve

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from time 0 to 168 hours (AUC_{0-168}), calculated using the linear trapezoidal method, and maximum plasma mogamulizumab concentration (C_{max}), recorded as observed. Serum concentrations of nivolumab were analyzed by an electrochemiluminescence (ECL) method before treatment, and at days 1 and 15 of cycle 1, day 1 of cycles 2 to 7, and day 1 of cycle 13. The immunogenicity of mogamulizumab and nivolumab was analyzed using an ECL-based ligand-binding assay before treatment, and at day 1 of cycles 4, 7, and 13, the end of treatment, and 60 days after the end of treatment.

PD-L1 expression levels on tumor tissue at baseline were evaluated by immunohistochemical staining of formalin-fixed, paraffin-embedded slides with a validated assay (Dako) using an anti-PD-L1 rabbit mAb (Clone 28-8, Epitomics). The level of PD-L1 staining on tumor tissues was defined as the percentage of viable tumor cells that exhibited PD-L1 membranous staining. Serum samples for chemokine measurements were collected twice: once before treatment and once at day 1 of cycle 2 or at the end of treatment. Serum chemokine concentrations were measured by V-PLEX Human Cytokine 30-Plex Kit for interferon-gamma (IFN-γ) inducible protein-10 (IP-10; Meso Scale Diagnostics, LLC) and Bio-Plex Pro Human Cytokine Assays Group II for monokine induced by gamma interferon (MIG; Bio-Rad Laboratories). For the flow-cytometry (FCM) analysis of immune cell subsets, peripheral blood was collected before treatment, at day 1 of cycle 2 or the end of treatment, and at day 1 of cycle 3, and tumor-infiltrating lymphocytes (TIL) were dissociated from fresh tumor biopsy samples before and after treatment (day 15 of cycle 2 to day 1 of cycle 3 or the end of treatment). TIL samples that showed sufficient live-cell numbers were analyzed by FCM. Effector Tregs were analyzed according to a previous report (17). The acquired data were analyzed using FlowJo version 7.6.5. The percentage of each immune cell population in peripheral blood was corrected by the number of lymphocytes.

Outcomes

The primary endpoint was safety and tolerability, based on the frequency and severity of adverse events as evaluated by the investigators. The secondary endpoints were efficacy, pharmacokinetics, and immunogenicity. Efficacy was assessed by BOR, time-to-response (TTR), duration-of-response (DOR), progression-free survival (PFS), and overall survival (OS), as specified in the protocol. The exploratory endpoints included PD-L1 expression and immune cell subset analyses.

Statistical analysis

For the dose-escalation part, a sample size of 6 to 18 patients was planned using the 3+3 design. For the expansion part, enrollment of 90 patients in total (15 patients in each cohort) was considered sufficient to evaluate the safety and efficacy for each tumor type, but the sample size was not statistically calculated. Safety was assessed in patients who received at least one dose each of mogamulizumab and nivolumab. BOR and objective response rate (ORR) and its associated Clopper–Pearson 95% confidence intervals (CIs) were calculated. TTR was summarized by descriptive statistics, and DOR, PFS, and OS were analyzed using the Kaplan–Meier method to estimate values for medians and 95% CI. Biomarker analyses were not statistically designed in advance, and *P* values were calculated by two-sided Student *t* test. Data were analyzed using SAS version 9.4 and JMP version 13.2 (SAS Institute).

Results

Between July 1, 2015 and November 29, 2016, 96 Asian patients were enrolled: six patients in the dose-escalation part and 90 in the expansion part.

In the dose-escalation part, one patient each with ovarian cancer, breast cancer, and NSCLC were enrolled in cohort 1, and one patient with NSCLC and two patients with gastric cancer were enrolled in cohort 2; no patients were enrolled in the optional cohort. At the time of data cutoff (August 31, 2017), patients in the dose-escalation part had undergone at least 23 months of follow-up and were discontinued owing to disease progression (Supplementary Table S1). Patients' baseline characteristics and prior cancer therapies are shown in Table 1. No DLTs were observed in the dose-escalation part, but one patient in cohort 2 experienced three grade 3 or 4 treatment-related adverse events (lymphopenia, amylase increased, and lipase increased) after the DLT observation period (Supplementary Table S2). The maximum tolerated dose of mogamulizumab was not determined in the dose-escalation part; therefore, mogamulizumab 1.0 mg/kg, which is the maximum dose, was selected for the expansion part. Fifteen patients were enrolled in each expansion cohort of six tumor types. Median follow-up time was 17.4 months [interquartile range (IQR), 14.5–19.8], and two patients were continuing treatment in the expansion part at the time of data cutoff (Supplementary Table S1). Of the 90 patients in the expansion part, 66 (73%) had received at least two prior systemic cancer therapies (Table 1). The most frequently observed treatment-related adverse events were rash (39%), maculopapular rash (20%), diarrhea (13%), stomatitis (12%), and pruritus (11%; Supplementary Table S3). There were no grade 5 treatment-related adverse events. Grade 3 or 4 treatment-related adverse events occurred in 29% of patients, and these included grade 4 Stevens–Johnson syndrome ($n = 1$) and grade 3 type I diabetes mellitus ($n = 3$; Supplementary Table S3). These events were not unexpected given that Stevens–Johnson syndrome has previously been reported with each monotherapy (16, 18), type I diabetes mellitus has been reported with nivolumab monotherapy (19), and both were managed by appropriate treatment. Mild gastrointestinal disorders such as diarrhea and nausea occurred, but severe adverse events such as colitis did not. Grade 3 or 4 skin disorders were observed in 10% of patients, most of which were managed by dose delays, topical and systemic corticosteroid treatment, or both. Systemic corticosteroid treatment was required to manage adverse events in 37 (41%) patients. No HBV reactivation occurred in this study, which included 18 patients positive for anti-HBs or HBc antibody, and HBV-DNA <2.1 log copies/mL.

Regarding treatment adherence, 74 (77%) patients received ≥90% of the relative dose intensity of mogamulizumab, and 74 (77%) received ≥90% of the relative dose intensity of nivolumab. Six (6%) patients discontinued study treatment owing to unacceptable toxicities (skin disorders, $n = 4$; fulminant type I diabetes mellitus, $n = 1$; aptyalism, $n = 1$), and 33 (34%) patients experienced dose delays.

The concentrations of plasma mogamulizumab and serum nivolumab were analyzed in 78 and 79 patients, respectively (Supplementary Table S4; Supplementary Figs. S1–S3). In one patient with pancreatic adenocarcinoma who had positive anti-mogamulizumab antibodies, the plasma mogamulizumab concentration decreased at day 1 of cycle 13. The C_{max} and AUC_{0-168} of mogamulizumab, which were analyzed in all six patients in the

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Table 1. Patient baseline characteristics

	Dose-escalation part		Expansion part						
Characteristics	**Cohort 1 (*n* = 3)**	**Cohort 2 (*n* = 3)**	**NSCLC (*n* = 15)**	**SCLC (*n* = 15)**	**GC (*n* = 15)**	**EC (*n* = 15)**	**HCC (*n* = 15)**	**PA (*n* = 15)**	**Total (*N* = 96)**
Median age, y	50 (49–52)	64 (62–71)	59 (56–68)	64 (58–66)	63 (60–67)	62 (58–65)	68 (60–74)	63 (54–69)	63 (56–68)
Age ≥65 y	0	1 (33%)	6 (40%)	7 (47%)	6 (40%)	5 (33%)	9 (60%)	7 (47%)	41 (43%)
Sex									
Female	3 (100%)	3 (100%)	4 (27%)	3 (20%)	4 (27%)	2 (13%)	1 (7%)	4 (27%)	24 (25%)
Male	0	0	11 (73%)	12 (80%)	11 (73%)	13 (87%)	14 (93%)	11 (73%)	72 (75%)
Race									
Asian	3 (100%)	3 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	96 (100%)
ECOG performance status									
0	1 (33%)	3 (100%)	7 (47%)	6 (40%)	13 (87%)	9 (60%)	11 (73%)	5 (33%)	55 (57%)
1	2 (67%)	0	8 (53%)	9 (60%)	2 (13%)	6 (40%)	4 (27%)	10 (67%)	41 (43%)
Disease stage at enrollment									
II, III	0	0	0	0	0	0	2 (13%)	0	2 (2%)
IV, IVa, IVb[a]	3 (100%)	3 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	13 (87%)	15 (100%)	94 (98%)
Smoking history									
Current	0	0	0	0	3 (20%)	3 (20%)	1 (7%)	2 (13%)	9 (9%)
Former	1 (33%)	1 (33%)	15 (100%)	15 (100%)	6 (40%)	11 (73%)	12 (80%)	8 (53%)	69 (72%)
Never	2 (67%)	2 (67%)	0	0	6 (40%)	1 (7%)	2 (13%)	5 (33%)	18 (19%)
Systemic prior cancer therapy[b]									
1	0	0	2 (13%)	2 (13%)	4 (27%)	3 (20%)	10 (67%)	1 (7%)	22 (23%)
2	1 (33%)	0	2 (13%)	6 (40%)	5 (33%)	6 (40%)	3 (20%)	4 (27%)	27 (28%)
3 or more	2 (67%)	3 (100%)	11 (73%)	7 (47%)	6 (40%)	6 (40%)	0	10 (67%)	45 (47%)
None	0	0	0	0	0	0	2 (13%)	0	2 (2%)
Topical prior cancer therapy									
Surgical operation	3 (100%)	1 (33%)	4 (27%)	1 (7%)	3 (20%)	7 (47%)	8 (53%)	5 (33%)	32 (33%)
Radiotherapy	1 (33%)	0	5 (33%)	12 (80%)	0	10 (67%)	5 (33%)	1 (7%)	34 (35%)
Other	0	0	2 (13%)	1 (7%)	0	0	9 (60%)	3 (20%)	15 (16%)
None	0	2 (67%)	8 (53%)	3 (20%)	12 (80%)	2 (13%)	3 (20%)	10 (67%)	40 (42%)
Histological type									
Adenocarcinoma	—	—	10 (67%)	—	15 (100%)	0	—	15 (100%)	—
Squamous cell carcinoma	—	—	5 (33%)	—	0	15 (100%)	—	0	—
EGFR mutation status									
Wild type	—	—	6 (40%)	—	—	—	—	—	—
Mutant	—	—	4 (27%)	—	—	—	—	—	—
Unknown	—	—	5 (33%)	—	—	—	—	—	—
ALK translocation status									
Negative	—	—	8 (53%)	—	—	—	—	—	—
Positive	—	—	0	—	—	—	—	—	—
Unknown	—	—	7 (47%)	—	—	—	—	—	—

NOTE: Data are median (IQR) or *n* (%). Cohort 1: ovarian cancer, breast cancer, and NSCLC; cohort 2: NSCLC and 2 GC.
Abbreviations: *ALK*, anaplastic lymphoma kinase; EC, esophageal cancer; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; GC, gastric cancer; PA, pancreatic adenocarcinoma; SCLC, small-cell lung cancer.
[a]Includes relapse.
[b]Includes adjuvant therapy, neoadjuvant therapy, and maintenance therapy.

dose-escalation part and in 36 patients (six patients in six cohorts) with sufficient sampling in the expansion part, increased in a dose-dependent manner (Supplementary Table S4). There was no significant difference in the concentrations of plasma mogamulizumab and serum nivolumab between the six cancer types. Antidrug antibodies against mogamulizumab and nivolumab

Table 2. Clinical activity in the expansion part

	Expansion part					
Response	**NSCLC (*n* = 15)**	**SCLC (*n* = 15)**	**GC (*n* = 15)**	**EC (*n* = 15)**	**HCC (*n* = 15)**	**PA (*n* = 15)**
Confirmed objective response[a]	3 (20% [4–48])	1 (7% [0–32])	0 (0% [0–22])	2 (13% [2–41])	4 (27% [8–55])	1 (7% [0–32])
Confirmed disease control[a]	6 (40% [16–68])	3 (20% [4–48])	4 (27% [8–55])	5 (33% [12–62])	10 (67% [38–88])	6 (40% [16–68])
Best overall responses[a]						
Complete response	0	0	0	0	0	0
Partial response	3 (20%)	1 (7%)	0	2 (13%)	4 (27%)	1 (7%)
Stable disease	3 (20%)	2 (13%)	4 (27%)	3 (20%)	6 (40%)	5 (33%)
Progressive disease	9 (60%)	10 (67%)	10 (67%)	10 (67%)	4 (27%)	9 (60%)
Not evaluable	0	2 (13%)	1 (7%)	0	1 (7%)	0
Median progression-free survival, months[a]	1.1 (0.9–7.3)	1.0 (0.9–2.0)	1.8 (1.0–3.6)	1.0 (0.9–2.8)	3.8 (0.9–7.3)	1.8 (1.0–3.8)
Median overall survival, months	19.0 (4.1–NE)	6.9 (1.5–8.8)	6.9 (2.3–16.7)	6.1 (1.8–10.3)	11.3 (4.0–NE)	6.5 (3.5–10.8)

NOTE: Data are *n* (% [95% CI]), *n* (%), or months (95% CI).
Abbreviations: EC, esophageal cancer; GC, gastric cancer; NE, not estimable; PA, pancreatic adenocarcinoma; SCLC, small-cell lung cancer.
[a]Determined by investigator assessment using RECIST version 1.1.

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Table 3. PD-L1 expression and clinical activity

PD-L1 Expression	NSCLC ($n = 15$)	SCLC ($n = 15$)	GC ($n = 15$)	EC ($n = 15$)	HCC ($n = 15$)	PA ($n = 15$)
PD-L1 $\geq$1%[a]	9 (60%)	2 (13%)	5 (33%)	8 (53%)	2 (13%)	3 (20%)
Objective response	1/9 (11%)	0	0	1/8 (13%)	1/2 (50%)	0
Disease control	3/9 (33%)	0	1/5 (20%)	2/8 (25%)	1/2 (50%)	3/3 (100%)
PD-L1 <1%[a]	5 (33%)	11 (73%)	10 (67%)	5 (33%)	7 (47%)	7 (47%)
Objective response	2/5 (40%)	1/11 (9%)	0	1/5 (20%)	3/7 (43%)	0
Disease control	2/5 (40%)	3/11 (27%)	3/10 (30%)	2/5 (40%)	5/7 (71%)	0
Not evaluable	1 (7%)	2 (13%)	0	2 (13%)	6 (40%)	5 (33%)

NOTE: Data are *n* (%) or *n/N* (%).
Abbreviations: EC, esophageal cancer; GC, gastric cancer; PA, pancreatic adenocarcinoma; SCLC, small-cell lung cancer.
[a]PD-L1 positivity on plasma membranes of tumor cells.

were detected after treatment in some patients (Supplementary Table S5). No neutralizing antibody against mogamulizumab was detected.

Confirmed objective responses were observed in patients with several tumor types (Supplementary Figs. S5 and S6), with the highest ORRs seen in the HCC (27%; 95% CI, 8–55) and NSCLC (20%; 95% CI, 4–48) cohorts (Table 2). Furthermore, in the pancreatic adenocarcinoma cohort, we observed one confirmed and two unconfirmed PRs. Median TTR was 1.9 months (IQR, 1.8–3.7) and median DOR was 5.4 months (95% CI, 3.0–7.7) in all confirmed responders (Supplementary Fig. S4). The median PFS was 3.8 months (95% CI, 0.9–7.3) and 1.8 months (95% CI, 1.0–3.8) and the median OS was 11.3 months (95% CI, 4.0–not estimable) and 6.5 months (95% CI, 3.5–10.8) for the HCC and pancreatic adenocarcinoma cohorts, respectively (Table 2).

Baseline PD-L1, CCR4, and CD8 expression levels, and tumor mutational burden, were retrospectively assessed. Objective responses occurred regardless of PD-L1 expression levels on tumor cells (Table 3), CCR4 expression levels on tumor cells, CD8 expression levels on TILs, and tumor mutational burden (Supplementary Table S6).

According to the FCM analysis, effector Tregs in peripheral blood were clearly depleted at day 1 of cycle 2 and day 1 of cycle 3, irrespective of the BOR (Fig. 1). The concentrations of IFNγ-inducible chemokines in peripheral blood after treatment were also analyzed. Both IP-10 and MIG generally increased during the course of treatment, irrespective of the BOR (Fig. 2A and B), which is similar to observations in a previous nivolumab study (20).

To explore the impact of treatment on the depletion of effector Tregs and the expansion of $CD8^+$ T-cells in the TME, 12 paired TIL samples, dissociated from fresh tumor biopsy samples before and after treatment, were analyzed by FCM. The proportion of effector Tregs tended to decrease, and the proportion of $CD8^+$ T cells tended to increase (Fig. 3A and B). These trends in the TME were observed regardless of the clinical response to treatment.

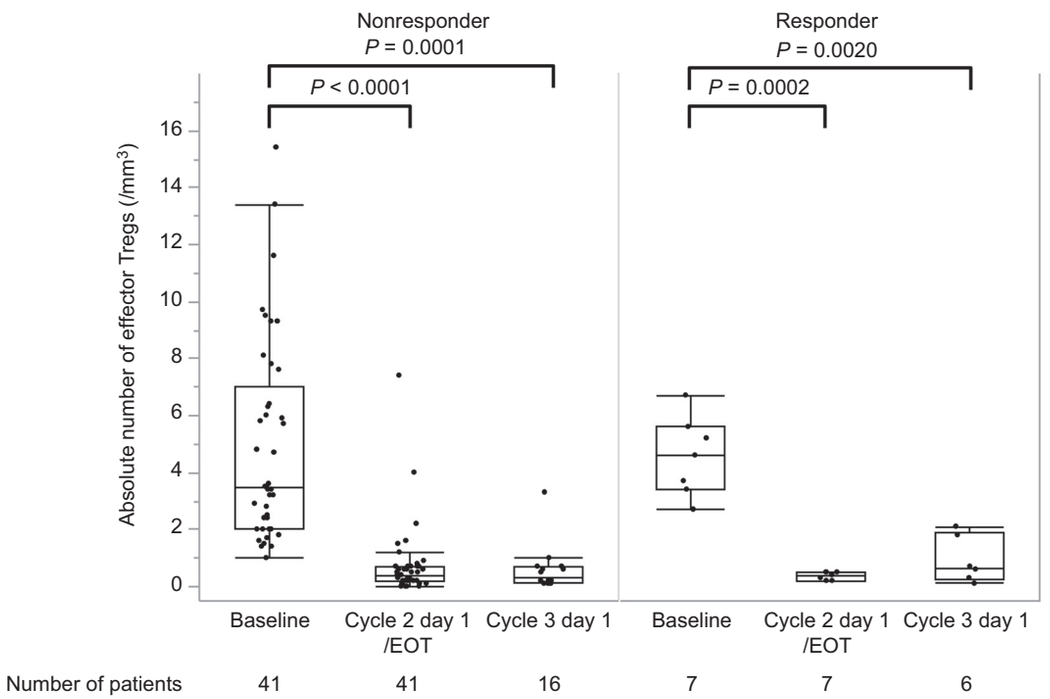

Figure 1.
Frequency of effector Tregs in peripheral blood. Nonresponder, progressive disease or stable disease; responder, partial response or complete response. Abbreviation: EOT, end of treatment. Absolute number of effector Tregs ($CD3^+CD4^+CD45RA^-FoxP3^{high}$) in peripheral blood. Two-sided paired Student *t* test.

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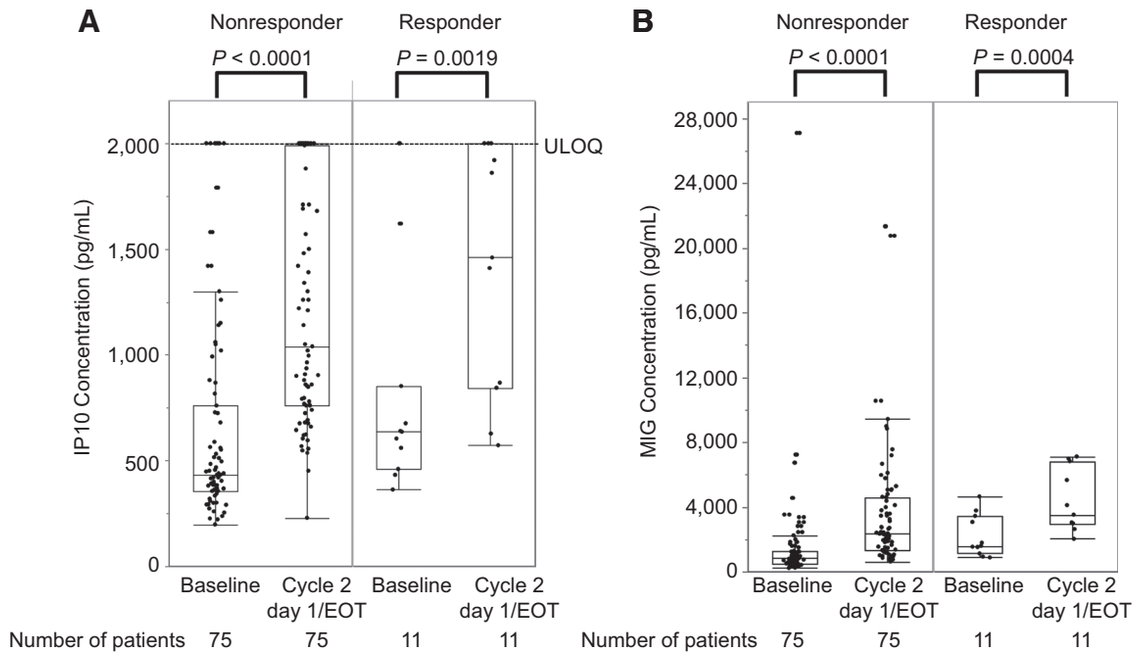

Figure 2.
Serum CXCR3 ligand chemokines. Nonresponder, progressive disease or stable disease; responder, partial response or complete response. **A,** IP-10 concentration. ULOQ was 2,000 pg/mL. Two-sided paired Student *t* test. **B,** MIG concentration. Two-sided paired Student *t* test. Abbreviations: EOT, end of treatment; ULOQ, upper limit of quantitation.

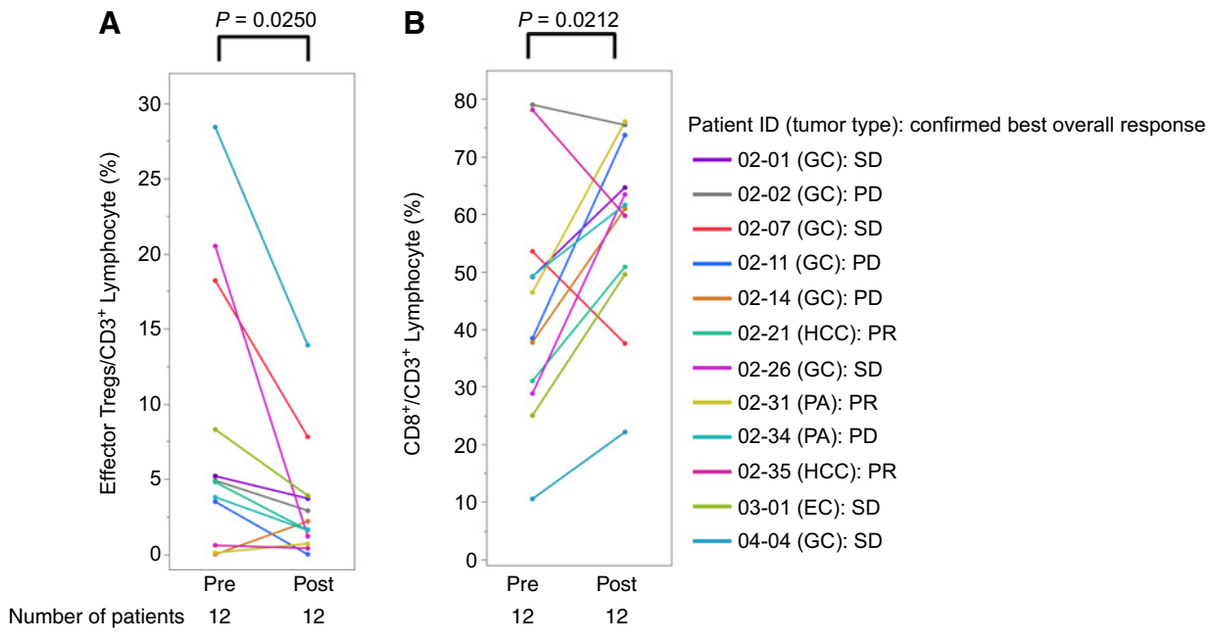

Figure 3.
Frequency of effector Tregs and $CD8^+$ T cells in tumor microenvironment. **A,** Effector Tregs ($CD3^+CD4^+CD45RA^-FoxP3^{high}$) in $CD3^+$ T cells of tumor-infiltrating lymphocytes. Two-sided paired Student *t* test. **B,** $CD8^+$ T cells in $CD3^+$ T cells of tumor-infiltrating lymphocytes. Two-sided paired Student *t* test. Abbreviations: EC, esophageal cancer; GC, gastric cancer; PA, pancreatic adenocarcinoma; PD, progressive disease; SD, stable disease.

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Discussion

In this phase I study, combination therapy with mogamulizumab and nivolumab demonstrated tolerable safety profiles and sufficient exposure at the doses used in these specific Asian patients with advanced or metastatic solid tumors. Plasma mogamulizumab and serum nivolumab concentrations were not notably different from those obtained with administration of the individual drugs (Supplementary Figs. S1–S3; refs. 7, 21). The profile of treatment-related adverse events in each cohort was not substantially different from that seen with mogamulizumab or nivolumab monotherapy, as well as with nivolumab and ipilimumab [anti-cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) antibody] combination therapy, which has been approved in several countries (1, 8, 9, 22, 23). In the expansion part, the total ORR was 12% in the six tumor types and 27% in the HCC cohort, albeit in a limited Asian population of immune checkpoint inhibitor–naïve patients and a small sample size. There are conflicting reports in which high levels of tumor-infiltrating Tregs are associated with good or poor prognosis by tumor type (11). In some studies, tumor-infiltrating Tregs in HCC are associated with poor prognosis (11). This suggests that Treg depletion by mogamulizumab might enhance the clinical effects of nivolumab in advanced HCC. In patients with pancreatic adenocarcinoma, we observed one confirmed PR and two unconfirmed PRs, which is notable because pancreatic cancer restricts the access of immune cells to the tumor parenchyma (24) and is poorly responsive to anti–PD-1/PD-L1 antibodies (25, 26). Recent clinical trials have shown that pembrolizumab is effective in patients with microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) advanced solid tumors, including pancreatic cancer (27). Approximately 13% of pancreatic adenocarcinoma in Japanese patients are MSI-H (28). However, as MSI-H and dMMR status were not assessed in this study, further clinical investigations are needed to confirm the value of this combination therapy for patients with pancreatic adenocarcinoma.

The detection of Tregs is crucial to the investigation of the effect of Treg-targeting drugs. However, the complex nature of defining Tregs makes such detection challenging. FoxP3, a master regulator of Tregs, is the most extensively studied Treg marker, but it is often expressed on nonsuppressive Tregs (17). It is therefore important to confirm that truly immune-suppressive Tregs can be detected by using multiple markers such as effector Treg-associated markers, including not only $FoxP3^{high}$ but also $CD45RA^{-}$ and/or $CTLA\text{-}4^{high}$, in FCM analysis.

To the best of our knowledge, this is the first report to demonstrate the depletion of effector Tregs, strictly defined as $CD3^{+}CD4^{+}CD45RA^{-}FoxP3^{high}$, in peripheral blood and in the TME (Figs. 1 and 3A). The tendency for more effective depletion of $CCR4^{+}$ effector Tregs than $CCR4^{-}$ effector Tregs in the TME suggests that the ADCC of 1.0 mg/kg mogamulizumab was evident not only in peripheral blood but also in the TME (Supplementary Fig. S7). In addition, increases in IFNγ-inducible chemokines were also observed in responders (Fig. 2A and B). Nevertheless, in FCM analyses, there was no clear relationship between the depletion of effector Tregs in peripheral blood and the TME and objective tumor responses, or between effector Tregs and cancer types. Potential hypotheses regarding the lack of Treg effect include a role for other suppressive immune cells, such as myeloid-derived suppressor cells and tumor-associated macrophages, in countering the effect of effector Treg depletion. Also, mogamulizumab may attenuate antitumor immunity by partially depleting $CCR4^{+}$ T-cell subsets (e.g., Th2, Th17, Th22, and a minor population of memory $CD8^{+}$ T-cell subset; refs. 29, 30). Although the proportion of CCR4 expression on lymphocytes was not high (10), most patients experienced depletion of approximately half of their total lymphocytes compared with baseline (Supplementary Fig. S8). This lymphodepletion has been observed in patients with $CCR4^{+}$ T-cell lymphoma or $CCR4^{-}$ solid tumors treated with 0.1–1.0 mg/kg mogamulizumab weekly (8–10). Moreover, effector Tregs have greater CCR4 expression compared with other mogamulizumab-targeted cells such as $CD4^{+}$ $FoxP3^{-}$ cells (i.e., helper T cells; ref. 12). Interestingly, a recent clinical trial of patients with human T-cell leukemia virus type 1–associated myelopathy showed that the lower dose intensity (0.003–0.3 mg/kg at single dosing) of mogamulizumab almost depleted the conventional Tregs (i.e., $CD4^{+}$ $CD25^{+}$ $FoxP3^{+}$) over 4 weeks with minimal lymphopenia (31). The evidence as a whole suggests that administration of 1.0 mg/kg mogamulizumab to patients with solid tumors may modulate immune-related functions of other CCR4-expressing cells despite the expected Treg depletion.

In summary, treatment with mogamulizumab in combination with nivolumab was associated with tolerable safety profiles and several tumor responses, even though the study involved a limited number of Asian participants who were immune checkpoint inhibitor naïve. This study also supports the mechanism of tumor immunity activation by Treg depletion. Although further refinement of the regimen is required—and translational research to understand the complexity of the TME is warranted—combination therapy with mogamulizumab and nivolumab suggests that targeting both PD-1 and Treg depletion may represent an effective option in cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

T. Doi reports receiving other commercial research support from Eli Lilly, Novartis, MSD, Chugai Pharm, Kyowa Hakka Kirin, Nippon Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Tahio Pharm, Merck Serono, Janssen Pharm, Takeda Pharm, Sumitomo Dainippon, Celgene, Astellas, and Bayer, and is a consultant/advisory board member for Eli Lilly, Novartis, MSD, Chugai Pharm, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Daiichi Sankyo, and Amgen. K. Muro reports receiving other commercial research support from Kyowa Hakko Kirin, and reports receiving speakers bureau honoraria from Eli Lilly, Chugai, Takeda, Taiho, Bayer, Ono, and Bristol-Myers Squibb. T. Kato reports receiving other commercial research support from Chugai Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Eli Lilly Japan, Merck Sharp & Dohme, Ono Pharmaceutical, Taiho Pharmaceutical, AbbVie, Pfizer Japan, Bristol-Myers Squibb, Kyowa Hakko Kirin, and Merck Serono, and reports receiving speakers bureau honoraria from Chugai Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Eli Lilly Japan, Merck Sharp & Dohme, and Ono Pharmaceutical. M. Takenoyama reports receiving commercial research grants from Chugai Pharmaceutical, Eli Lilly Japan, Kaketsuken, Kyowa Hakko Kirin, MSD, Ono Pharmaceutical, AstraZeneca, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Novartis, and Taiho, and reports receiving speakers bureau honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Covidien Japan, Eli Lilly Japan, Kyowa Hakko Kirin, MSD, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, Pfizer Japan, and Taiho. S. Oizumi reports receiving commercial research grants from Bristol-Myers Squibb, Kyowa Hakko Kirin, Merck Serono, Ono Pharmaceutical, and Pfizer, and reports receiving speakers bureau honoraria from AstraZeneca and Eli Lilly. H. Suna is an employee of Ono Pharmaceutical. K. Enokitani is an employee of Kyowa Kirin. H. Nishikawa reports receiving commercial research grants from Kyowa Hakko Kirin, Ono Pharmaceutical, Bristol-Myers Squibb, Taiho

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Disclaimer

The sponsors worked with the authors on the design of the study and the data collection and interpretation. The sponsors were responsible for the data analysis. All drafts of the manuscript were written by the sponsors and authors. All authors had access to the data and were responsible for the decision to publish.

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Study supervision: T. Doi, T. Kawakami, N. Yamamoto

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