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Phase I study on neoadjuvant combination immunotherapy with mogamulizumab and nivolumab for solid tumors

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ABSTRACT

Background Effector regulatory T cells expressing C-C chemokine receptor 4 (CCR4) suppress antitumor immune responses. We conducted a phase I clinical trial to evaluate the safety and efficacy of preoperative combination therapy with mogamulizumab (an anti-CCR4 antibody) and nivolumab (an anti-programmed death-1 antibody) in patients with solid tumors.

Methods Patients with operable solid tumors were enrolled in a 3+3 design, with preoperative nivolumab (3.0 mg/kg) administered intravenously every 2 weeks three times and mogamulizumab at 0.1 mg/kg (cohort 1), 0.3 mg/kg (cohort 2), or 1.0 mg/kg (cohort 3) every week four times. The primary endpoints were safety and the effects of depleting Forkhead box $P3^+$ ($FoxP3^+$) T cells in the tumor.

Results 16 patients were enrolled between June 2016 and April 2020, including those with renal (n=7), lung (n=5), esophageal (n=3), and oral (n=1) cancers. Grade 3–4 treatment-related adverse events were observed in 6 of 16 patients, with lymphopenia (25%) and maculopapular rash (13%) being the most frequent. Grade 5 interstitial pneumonia was observed in one patient; however, the cause of death was disease progression. There were three partial responses (PRs) (one lung and two esophageal cancers) among clinical responses and one complete response (one lung cancer) and nine PRs (five kidney, two lung, and two esophageal cancers) among pathological responses. $CCR4^+FoxP3^+$ T cells were depleted in the tumors of all patients and increases in lymphocytes in tumor tissue according to the tumor immune microenvironment classification were observed in 50% of the patients, which correlated with a better prognosis.

Conclusions The preoperative combination of mogamulizumab and nivolumab was safely managed, exerted antitumor effects, and may be an effective option in the preoperative setting.

Trial registration number The present study was registered with ClinicalTrials.gov as NCT02946671 (registration date 2016-10-05).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The control of regulatory T cells (Tregs) may activate antitumor immunity. Mogamulizumab, a humanized IgG1 monoclonal antibody targeting anti-C-C chemokine receptor type 4, has been shown to deplete blood Tregs; however, its effects on tumor-infiltrating Tregs remain unclear.

WHAT THIS STUDY ADDS

⇒ This clinical trial demonstrated that the neoadjuvant combination of mogamulizumab and nivolumab was safely managed and yielded favorable outcomes in patients with operable solid tumors. Treg depletion was observed in both blood and tumors, and increases in lymphocytes in tumor tissue according to the tumor immune microenvironment classification were associated with a better prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Treg depletion by mogamulizumab in combination with nivolumab is a promising treatment strategy that needs to be tested in larger clinical trials in the future.

INTRODUCTION

Immune checkpoint inhibitors (ICIs), such as programmed death-1 (PD-1) blockade, are currently used in clinical practice to treat several cancer types.[1–4] While durable therapeutic effects are achieved in some patients with various cancer types, therapeutic effects associated with the single use of ICIs are limited to approximately 20%.[5 6] The mechanisms underlying the therapeutic effects of PD-1 blockade involve the activation of T cells through the inhibition of the PD-1-programmed death-ligand 1 (PD-L1) axis; however, T cell activation is not always induced. Regulatory T cells (Tregs) function to maintain immune homeostasis by

inhibiting excessive immune responses, and inhibit antitumor immune responses by suppressing cytotoxic T cell activation induced by PD-1 blockade.[7] Therefore, the regulation of Tregs has the potential to activate antitumor immunity; however, no therapeutic agents have been developed for this purpose.

Mogamulizumab is a humanized anti-C-C chemokine receptor type 4 (CCR4) IgG1 monoclonal antibody (mAb) with enhanced antibody-dependent cytotoxic activity and has been approved for the treatment of CCR4-positive relapsed or refractory T cell lymphomas.[8] Previous clinical trials on mogamulizumab for hematological diseases reported a decrease in Tregs in peripheral blood, suggesting the depletion of Tregs by mogamulizumab. Based on these findings, we conducted a clinical trial on the single agent mogamulizumab for the treatment of CCR4-negative solid tumors with Treg depletion as the therapeutic mechanism. We confirmed the tolerability and safety of mogamulizumab as well as Treg depletion in peripheral blood, and long-term therapeutic effects were observed in a few patients.[9–11] As the mechanisms underlying the therapeutic effects of PD-1 blockade involve the activation of T cells, the combination of mogamulizumab and PD-1 blockade may exert synergistic immunological effects.

Preoperative immunotherapy may activate antitumor T cells in the presence of the primary tumor as the antigen source, and these antitumor T cells may exert antitumor effects against residual tumor cells after resection of the primary tumor, thereby preventing recurrence.[12] Based on the benefits of the preoperative use of immunotherapy,[13–15] we conducted a phase I clinical trial on combination therapy with mogamulizumab and nivolumab in the preoperative setting. The objective of the present study was to investigate the safety of preoperative immunotherapy in combination with mogamulizumab and nivolumab in patients with solid tumors and to examine the effects of Treg depletion in peripheral blood and tumors.

MATERIALS AND METHODS

Patients

Operable patients older than 20 years of age and with an Eastern Cooperative Oncology Group performance status of 0–2 were included. Pathologically confirmed malignancies, including cT2N0–2M0 or cT3N0–1M0 gastric adenocarcinoma, cT1bN0M0 or cT2N0M0 esophageal squamous cell carcinoma, cStage IIA, IIB, or IIIA (N2) non-small cell lung cancer (NSCLC), cStage III (excluding T3aN0M0) or cStage IV renal cell carcinoma, and cT2–3N0M0 oral squamous cell carcinoma, were eligible. cStage IV patients with renal cell carcinoma were included because cytoreductive nephrectomy is considered to be the standard treatment, even for Stage IV patients with distant metastases. Clinical stages were assessed according to the Unio Internationalis Contra Cancrum tumor, node, metastases seventh edition. Patients who refused the recommended regimen of neoadjuvant chemotherapy were included. Eligibility criteria for laboratory values were as follows: a neutrophil count≥1.5×10^9/L, hemoglobin≥100 g/L, platelet count≥100×10^9/L, total bilirubin≤1.5 mg/dL, aspartate aminotransferase≤2.5 × the upper limit of the normal range (UNL), alanine aminotransferase≤2.5 × UNL, serum creatinine≤1.2 mg/dL (≤1.5 for renal cancer), and arterial blood oxygen saturation≥95%. All subjects underwent electrocardiography to confirm the absence of abnormalities in heart function requiring treatment. Patients were excluded if they had an active infection, a history of organ transplantation, active concurrent cancer, any autoimmune disease, interstitial pneumonia, uncontrolled hypertension, poorly controlled endocrine disorders, active inflammatory bowel disease, poorly controlled diabetes, type 1 diabetes, unstable angina pectoris, the administration of corticosteroids or immunosuppressive and immunoenhancing agents, central nervous system involvement by tumors, hepatitis B or C virus infection, or HIV infection.

Study design

The present study was designed as a multi-institutional, open-label, investigator-initiated phase I clinical trial on neoadjuvant immunotherapy with mogamulizumab and nivolumab. The investigational drug mogamulizumab was provided by Kyowa Kirin (Tokyo, Japan) and nivolumab by Ono Pharmaceutical (Osaka, Japan). The primary endpoints were the safety of neoadjuvant immunotherapy with mogamulizumab and nivolumab in patients with solid tumors and the effects of depleting Forkhead box $P3^+$ ($FoxP3^+$) cells in tumors with immunohistochemistry (IHC). Secondary endpoints were the effects of Treg depletion in peripheral blood mononuclear cells (PBMCs) with a flow cytometry analysis and the effects of tumor reduction. The effects of tumor reduction (clinical response) were evaluated 7 weeks after the start of treatment or at the time of study discontinuation using CT, MRI, or endoscopy. Clinical responses were assessed by investigators based on the Response Evaluation Criteria in Solid Tumors (V.1.1).[16] In addition, the method outlined in the "Gastric Cancer Treatment Guidelines, 14th Edition" was used to assess the treatment effect on the primary lesion in gastric cancer[17] and the method described in the "Esophageal Cancer Treatment Guidelines, 11th Edition" to evaluate the primary lesion with endoscopy in esophageal cancer.[18] Clinical responses for each subject were confirmed by the efficacy assessment committee with a central evaluation. Patients were enrolled in a 3+3 design, with nivolumab (3.0 mg/kg) given intravenously every 2 weeks three times and mogamulizumab at 0.1 mg/kg (cohort 1), 0.3 mg/kg (cohort 2), or 1.0 mg/kg (cohort 3) every week four times. Oral antihistamines and acetaminophen were administered before each mogamulizumab infusion, and hydrocortisone was simultaneously injected intravenously for the first mogamulizumab dose to prevent infusion reactions.

The study was moved to the next cohort if the incidence of dose-limiting toxicity (DLT) was less than or equal to one of six patients in each cohort. Movement to the next cohort was approved by the Clinical Trial Coordinating Committee based on the recommendation of the Efficacy and Safety Evaluation Committee, considering adverse events (AEs), clinical responses, and the effects of Treg depletion. Patients were considered to be intolerant to mogamulizumab or nivolumab if toxicity was observed in two or more patients in each cohort. Surgery was performed between days 43 and 57. The study continued even if surgery was not conducted during that period.

Evaluation of AEs and definition of DLT

Safety was evaluated by AEs graded with the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0[19] and intraoperative and postoperative complications graded with the Clavien-Dindo classification,[20] during the start of treatment and 30 days after surgery on the primary tumor or 60 days after the last dose of the study drug, whichever was later.

The evaluation period for DLT was during the start of treatment and 7 days after surgery for the primary disease. DLT was defined as any of the following AEs for which a causal relationship to the investigational drugs could not be ruled out: grade 4 neutropenia for longer than 7 days, grade 4 neutropenia with fever≥38.0°C for more than 2 days, grade 4 thrombocytopenia requiring platelet transfusion, ≥grade 3 non-hematological toxicity, and intraoperative and postoperative complications≥grade 3 that may be causally related to the investigational drugs. An independent Data Monitoring Committee evaluated safety data at all dose levels.

Pathological response evaluation

All resected specimens were examined by pathologists, and the degree of tumor regression and scarring was graded by HE staining with the four categories of the American Joint Committee of Cancer and College of American Pathologists tumor regression grading (TRG) system, which were classified as follows: grade 0 (a complete response (CR)), no remaining viable cancer cells; grade 1 (a moderate response), only a small cluster or single cancer cells remaining; grade 2 (a minimal response), residual cancer remaining, but with predominant fibrosis; grade 3 (a poor response), minimal or no tumor cells killed with extensive residual cancer.[21] In the present study, CR was defined as TRG grade 0, a partial response (PR) as TRG grades 1–2, and no response (NR) as TRG grade 3.

Effects of Treg depletion in PBMCs

Treg depletion in PBMCs was assessed as previously described.[9 10] Blood samples were collected at baseline, on days 3, 15, 29, and 43 after the start of treatment, and at the end of the study. PBMCs were isolated from heparinized blood by density gradient centrifugation using Ficoll-Paque Plus (GE Healthcare, Fairfield, Connecticut, USA). Cells were stored in liquid N_2 until used. Treg depletion was assessed by flow cytometry as previously reported.[9–11] In brief, cell surfaces were stained with anti-CD4-PerCP (clone SK3; BD Biosciences, San Jose, California, USA), anti-CD25-APC (clone 2A3; BD Biosciences), and anti-CD45RA-FITC (clone ALB11; Beckman Coulter, Brea, California, USA) mAbs. The intracellular staining of FoxP3 was performed with anti-FoxP3-PE (clone PCH101; eBioscience, San Diego, California, USA) mAb and a FoxP3/Transcription Factor Staining Buffer Set (eBioscience) according to the manufacturer's instructions. $CD45RA^{+}FoxP3^{lo}$ naïve Tregs, $CD45RA^{-}FoxP3^{hi}$ effector Tregs, and $CD45RA^{-}FoxP3^{lo}$ non-Tregs were analyzed as previously described.[22]

Effects of Treg depletion in tumors

Formalin-fixed paraffin-embedded tumor biopsy samples at baseline and surgical specimens were used to evaluate Tregs in tumors. $FoxP3^{+}$ T cells and $CCR4^{+}FoxP3^{+}$ T cells were analyzed by IHC as previously reported[23] (online supplemental figure 1). The number of cells per field of view (0.35 mm^2) was measured using WinROOF2015 image analysis software (MITANI Corporation, Tokyo, Japan). Cells were counted at 3–5 locations with biopsy specimens and at 10–30 locations with surgical specimens. The average of counts was calculated.

Evaluation by the tumor immune microenvironment classification

The tumor immune microenvironment (TIME) classification was used to assess the lymphocyte infiltration pattern around or in the cancer nest based on HE staining[24] (online supplemental figure 2). TIME was characterized into three types: "immune-desert" in which the infiltration of T cells into the tumor is negligible; "immune-excluded" in which T cells infiltrate the stroma, but not the tumor nest; "immune-inflamed" in which T cells infiltrate the tumor nest and stroma. The extent of lymphocyte infiltration was assessed using −, +, and ++for each location. Cases with stroma (−) and tumor nest (−) were classified as "desert", those with stroma (+/++) and tumor nest (−) were classified as "excluded", and those with stroma (+/++) and tumor nest (+/++) were classified as "inflamed". A change in the TIME classification from "immune-desert" to "immune-excluded" or "immune-inflamed", or from "immune-excluded" to "immune-inflamed" was regarded as an increase in the infiltrating lymphocytes within the tumor, indicating an improvement in the immune phenotype.

Statistical analysis

Quantitative data without a normal distribution were analyzed using the two-tailed non-parametric Mann-Whitney U test. The two-tailed Fisher's exact probability test was used for bivariate analyses. Cumulative survival was plotted using the Kaplan-Meier method, and differences were compared using the Log-rank test. Statistical analyses were performed using Statistical Analysis System

(RRID:SCR_008567) V.9.4 (SAS, Cary, North Carolina, USA) and JMP Pro, V.16.0.0 (JMP, Tokyo, Japan). P values<0.05 were considered to be significant.

RESULTS

Patient backgrounds

The present study enrolled 16 patients with operable solid tumors between June 2016 and April 2020, including renal (n=6), lung (n=2), esophageal (n=1), and oral (n=1) cancers in cohort 1 and renal (n=1), lung (n=3), and esophageal (n=2) cancers in cohort 2 (online supplemental figure 3, table 1). Since skin-related disorders were more severe in cohort 2 than in cohort 1, even though they were all manageable, and tumor shrinkage was observed in some patients in cohort 1, along with intratumoral Treg depletion confirmed by IHC, the study did not proceed to cohort 3 with the approval of the Clinical Trial Coordinating Committee based on the recommendation of the Efficacy and Safety Evaluation Committee. Instead, four additional patients were enrolled in cohort 1 after the inclusion of cohort 2. The study treatment was discontinued before surgery in one patient in cohort 1 (#1–08) due to the progression of the primary disease. In cohort 2, one patient (#2–02) did not receive a dose of nivolumab and another (#2–05) did not receive a dose of mogamulizumab due to grade 2 skin-related disorders. Figure 1 shows the treatment course of patients with a median follow-up duration of 872 days (range; 66–1297 days). All patients underwent scheduled surgery, except for one (#1–08) for whom the trial was terminated due to progression of the primary disease.

AEs

All grades of treatment-related AEs (TRAEs) occurred in 10 (100%) of 10 patients in cohort 1 and 6 (100%) of 6 patients in cohort 2 (table 1). Grade 3–5 TRAEs were observed in 4 (40%) of 10 patients in cohort 1 and 3 (50%) of 6 patients in cohort 2. Table 2 lists all TRAEs considered to be related to the study drug, with 36 AEs in cohort 1 and 19 in cohort 2. The most frequently observed categories of TRAEs were skin disorders (n=14 in cohort 1 and 10 in cohort 2). Nine grade 3–5 TRAEs were observed in cohort 1 (Grade 3; n=5, Grade 4; n=3, Grade 5; n=1) and 4 in cohort 2 (Grade 3; n=4). Grade 3 TRAEs were lymphopenia (n=4, 25%), maculopapular rash (n=2, 13%), rash, diarrhea and dehydration (n=1, 6% each). Grade 4 TRAEs were hypopituitarism, adrenal insufficiency, and pneumonia (n=1, 6% each), and the grade 5 TRAE was interstitial pneumonia (n=1, 6%). These AEs had already been identified as AEs of nivolumab and mogamulizumab, and were not considered to be a new risk for the investigational treatment.

Intraoperative and postoperative complications were observed in four (40%) patients in cohort 1 and four (67%) in cohort 2 (table 3). Grade 3 postoperative wound infection and grade 4 incisional hernia were detected in cohort 1 (n=1, 6% each), while grade 3 pleural effusion and grade 3 intestinal fistula infection were noted in cohort 2 (n=1, 6% each). A treatment-related complication potentially related to the study drugs was grade 1 liver dysfunction in cohort 2 (n=1, 6%). Since no serious intraoperative or postoperative complications related to the study drugs were observed, preoperative combination therapy was not considered to preclude surgical treatment.

DLT of grade 5 interstitial pneumonia was observed in one patient in cohort 1 (#1–08). The patient had locally advanced NSCLC and was treated with three doses of mogamulizumab and two doses of nivolumab. However, the study was discontinued on day 19 due to progression of the primary disease, and radiotherapy was started as the next treatment on day 34. On day 41, radiography revealed pneumonia, which was treated with antibiotics; however, pneumonia worsened. Steroids were then administered on day 44 because pneumonia was considered to be interstitial pneumonia. Although pneumonia initially improved, the respiratory status eventually deteriorated and the patient died on day 67. Although the cause of death was progression of the primary disease, the patient's clinical course was considered to be significantly affected by interstitial pneumonia as well as by radiotherapy and bacterial pneumonia. Therefore, we judged interstitial pneumonia to be DLT.

Clinical response

All patients underwent a clinical response evaluation in week 7, except for one patient (#1–08), who underwent a CT evaluation in week 4 after receiving three doses of mogamulizumab, which confirmed the progression of the primary tumor and led to study discontinuation. Clinical responses in cohort 1 were one PR, eight stable disease (SD), and one non-CR/non-progressive disease (PD), while those in cohort 2 were two PR, three SD, and one PD (table 1). Pathological responses in cohort 1 were one CR, five PR, and three NR, and those in cohort 2 were four PR and two NR. Therefore, there were 3 PR (19%) and 11 SD (69%) with a clinical response and 1 CR (6%) and 9 PR (56%) with a pathological response. According to the clinical response based on tumor type, SD and PR were observed in two of three patients with esophageal cancer (66%), zero of seven patients with renal cancer (0%), and one of five patients with lung cancer (20%). Similarly, according to the pathological response, PR and CR were observed in two of three patients with esophageal cancer (66%), five of seven patients with renal cancer (71%), and three of five patients with lung cancer (60%). Regarding prognosis, no significant differences were observed in progression-free survival (PFS) or overall survival (OS) between cohorts 1 and 2 (figure 2a-b). There were three deaths caused by primary disease progression in two patients and aspiration pneumonia in one patient (figure 1). We presented two patients with a good treatment response and long-term disease control (#1–04 and #2–04) (online supplemental figure 4 and 5).

Table 1 Patient characteristics

ID	KW-0761 dose (mg/kg)	Age	Tumor type	Clinical stage	PD-L1 expression	No. of infusions		Clinical response	Pathological response	Treatment-related AEs (All)	Treatment-related AEs (Grades 3–5)	Treg depletion	
						KW-0761	ONO-4538					PBMC	Tumor
1–01	0.1	50s	Kidney	IV		4	3	SD	NR	+	–	+	+
1–02	0.1	60s	Kidney	IV		4	3	SD	NR	+	–	+	+
1–03	0.1	60s	Kidney	IV		4	3	SD	PR	+	+	+	+
1–04	0.1	50s	Lung	IIIA	1–49%	4	3	PR	CR	+	+	+	+
1–05	0.1	60s	Kidney	IV		4	3	SD	PR	+	+	+	+
1–06	0.1	70s	Esophagus	IB		4	3	SD	PR	+	–	+	+
1–07	0.1	50s	Kidney	IV		4	3	SD	PR	+	–	+	+
1–08	0.1	70s	Lung	IIIA	1–49%	3	2	SD	N/A	+	+	+	nt
1–09	0.1	70s	Kidney	IV		4	3	SD	PR	+	–	+	+
1–10	0.1	20s	Oral	II		4	3	Non-CR/non-PD	NR	+	–	+	+
2–01	0.3	70s	Esophagus	IA		4	3	PR	NR	+	+	+	+
2–02	0.3	60s	Kidney	IV		3	3	SD	PR	+	+	+	+
2–03	0.3	60s	Lung	IIA	N/A	4	3	PD	NR	+	–	+	+
2–04	0.3	60s	Esophagus	IA		4	3	PR	PR	+	+	+	+
2–05	0.3	50s	Lung	IIB	N/A	4	2	SD	PR	+	–	+	+
2–06	0.3	60s	Lung	IIA	≥50%	4	3	SD	PR	+	–	+	+

Gray highlighting shows patients with less than the prescribed number of doses in No. of infusions, and PR or CR responses in clinical response and pathological response.
AEs, adverse events; CR, complete response; N/A, not applicable; NR, no response; nt, not tested; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

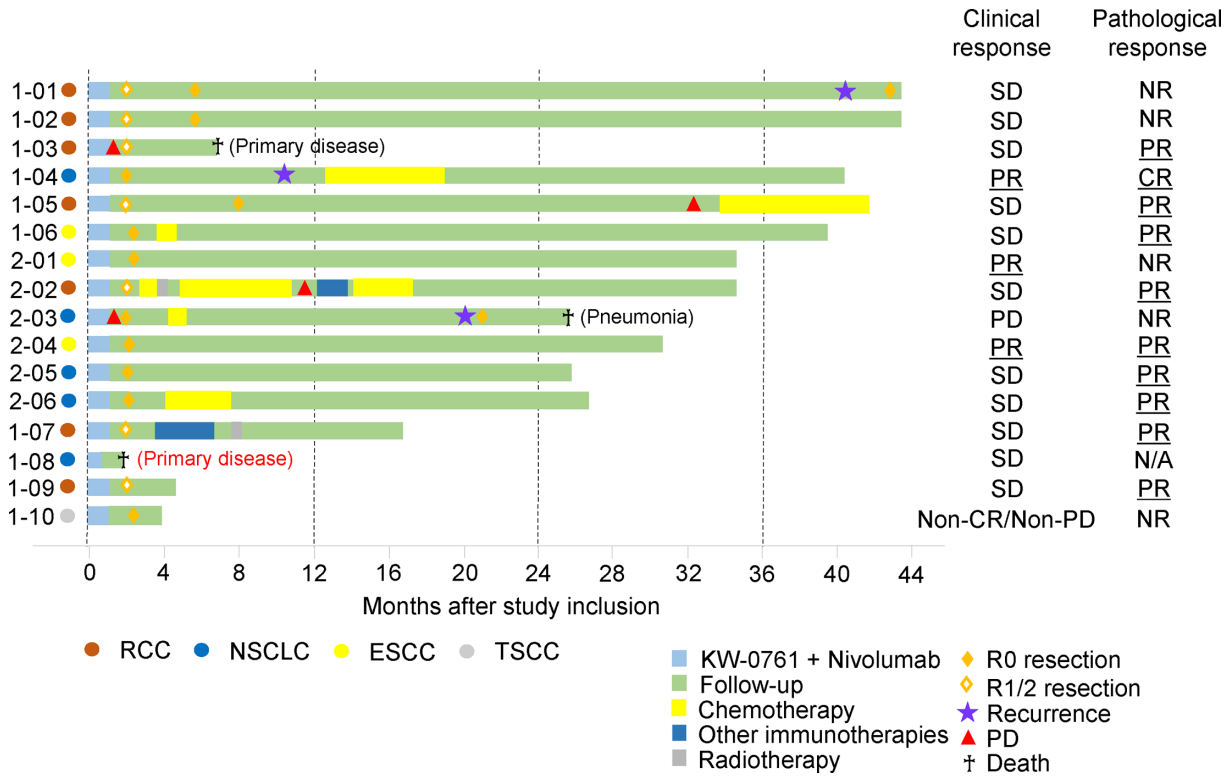

Figure 1 The clinical course of all patients in the trial. Treatment courses are shown for all 16 patients. The tumor type, clinical response, and pathological response are annotated for each patient. Blue represents the study treatment, green for the follow-up, yellow for chemotherapy, dark blue for other immunotherapies, and gray for radiation therapy. Radical resection is a diamond, non-radical resection is a hollow diamond. Red triangles indicate PD, stars indicate recurrence, and cross symbols indicate death. CR, complete response; ESCC, esophageal squamous cell carcinoma; N/A, not applicable; NR, no response; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; TSCC, tongue squamous cell carcinoma.

FoxP3^{high}CD4^{+} Treg depletion in PBMCs

Treg depletion in peripheral blood by mogamulizumab was assessed using flow cytometry at baseline, at 2, 4, and 6 weeks after treatment initiation, and at the end of the study. The percentage of effector Tregs in CD4^{+} T cells was significantly reduced 3 days after treatment initiation, with this depletion being maintained throughout the treatment duration (online supplemental figure 6a-b). However, the percentage of effector Tregs increased after the end of treatment. The median percentages of effector Tregs in CD4^{+} T cells in cohorts 1 and 2 were 2.8% (range: 0.73–6.7%) and 2.1% (range: 0.72–4.9%) at baseline, 0.25% (range: 0.08–0.97%) and 0.18% (range: 0.00–1.2%) on day 43, and 0.43% (range: 0.10–9.6%) and 1.6% (range: 0.13–2.8%) at the end of the trial, respectively.

FoxP3^{+} Treg depletion in tumors

To analyze Treg depletion in tumors, we assessed the infiltration of tumors by FoxP3^{+} T cells and CCR4^{+}FoxP3^{+} T cells in surgically dissected tumor samples using IHC. The number of FoxP3^{+} T cells in tumors decreased in 50% of patients, with a median change of −11.1% (range: −73.2 to 87.8%) (table 4). Furthermore, the count of CCR4^{+} FoxP3^{+} T cells in tumors decreased in all patients, showing a median change of −86.7% (range: −94.8 to −52.7%). In comparisons of Treg levels between responders (PR or CR) and non-responders (SD or PD) with clinical responses, the pretreatment number of FoxP3^{+} T cells was higher in responders than in non-responders, whereas the percentage decrease was slightly higher in responders than in non-responders (online supplemental figure 7). These results suggest that tumors with higher pretreatment Treg infiltration exhibited more efficient Treg removal, leading to improved treatment efficacy.

Increases in lymphocytes in tumor tissue based on the TIME classification

To examine potential improvements in the tumor microenvironment by Treg depletion in tumors, we assessed the TIME classification using surgically dissected tumor samples and IHC. Pretreatment evaluations categorized eight patients as immune-desert (one esophageal, one lung, and six renal cancers), five as immune-excluded (one esophageal, two lung, one renal, and one oral cancer), and two as immune-inflamed (one esophageal and one lung cancer) (table 4, online supplemental figure 2). Post-treatment evaluations categorized two patients as immune-desert, nine as immune-excluded, and three as immune-inflamed. Increases in lymphocytes in tumor tissue were observed in eight patients (two esophageal, four renal, and two lung cancers), while only one patient

Table 2 Treatment-related adverse events

		0.1 mg/kg (n=10)					0.3 mg/kg (n=6)				
	Grade	1	2	3	4	5	1	2	3	4	5
Cases		7	9	3	1	1	5	6	3	0	0
Total events		10	17	5	3	1	6	9	4	0	0
Non-hematological											
General											
	Fever						1				
	Fatigue		1								
	Appetite loss	1									
	Dehydration			1							
Skin and subcutaneous tissue											
	Rash	2	7				1	4	1		
	Maculopapular rash			2			1	2			
	Pruritus						1				
	Purpura		1								
	Hives	1									
	Vitiligo	1									
Gastrointestinal disorders											
	Diarrhea			1							
	Vomiting		1								
	Stomatitis	1									
Infections											
	Pneumonia				1						
Hepatobiliary disorders											
	Liver dysfunction							1			
Endocrine disorders											
	Hypopituitarism				1						
	Hypothyroidism	1									
	Adrenal insufficiency				1						
Musculoskeletal disorders											
	Muscle pain						1				
Thoracic disorders											
	Interstitial pneumonia					1					
Cardiac disorders											
	SVPC	1									
Nervous system disorders											
	Dizziness	1									
Hematological											
	Leukopenia							1			
	Lymphopenia		4	1				1	3		
	Eosinophilia	1									
	Anemia		1								
	ALT increased		2								
	TSH decreased						1				

SVPC, supraventricular premature contraction; ALT, alanine aminotransferase; TSH, thyroid-stimulating hormone.

Table 3 Intraoperative and postoperative complications

	0.1 mg/kg (n=10)					0.3 mg/kg (n=6)				
Grade	1	2	3	4	5	1	2	3	4	5
Cases	2	2	1	1	0	2	2	2	0	0
Total events	2	2	1	1	0	3	2	2	0	0
Thoracic disorders										
Pleural effusion								1		
Pleuritis							1			
Lung fistula						1				
Skin and subcutaneous tissue										
Aerodermectasia	1					1				
Gastrointestinal disorders										
Intestinal obstruction		1								
Infections										
Postoperative wound infection			1							
Intestinal fistula infection								1		
Hepatobiliary disorders										
Liver dysfunction						1				
Procedural complications										
Wound complications		1								
Incisional hernia				1						
Cardiac disorders										
Atrial fibrillation							1			
Hematological disorders										
Lipase increase	1									

exhibited a worsening change from immune-inflamed to immune-excluded (one esophageal). In comparisons of the TIME classification with pathological therapeutic responses, all eight patients showing increases in lymphocytes in tumor tissue had a pathological response of PR (table 4). In addition, patients with increases in lymphocytes in tumor tissue were more likely to have better PFS and OS (online supplemental figure 8a-b).

DISCUSSION

To the best of our knowledge, we are the first to conduct a clinical trial on mogamulizumab combined with nivolumab as a preoperative treatment for solid tumors. The present study evaluated the TRAEs and intraoperative and postoperative complications of combination therapy. In previous studies, severe AEs of grade 3 or

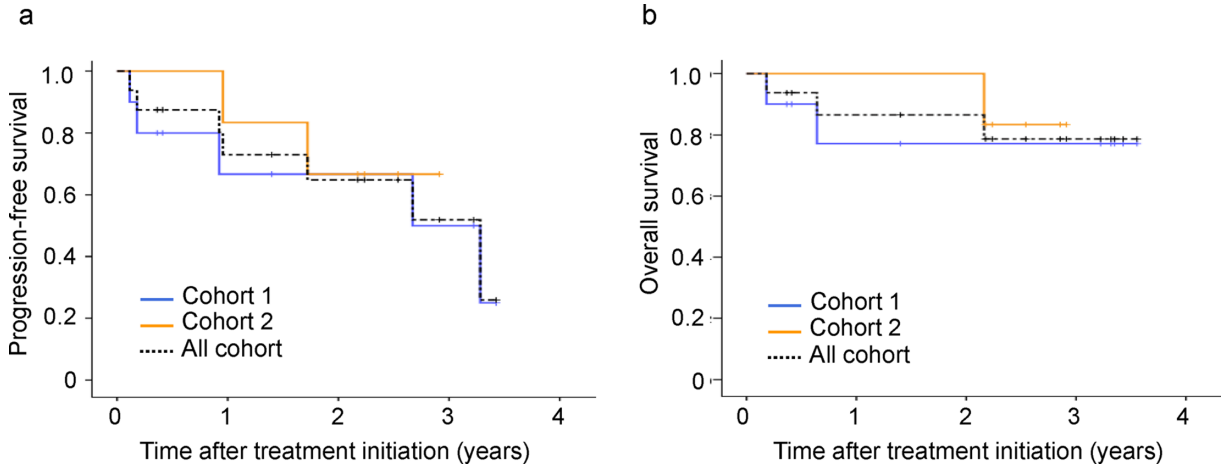

Figure 2 Kaplan-Meier survival curve for 16 patients. Progression-free survival (a) and overall survival (b) are shown according to cohort 1 (blue line, n=10), cohort 2 (orange line, n=6), and all cohorts (black dots, n=16).

Table 4 Number of immune cells by IHC and the TIME classification

		Treg			CCR4⁺ Treg			TIME			Therapeutic effect	
ID	Tumor type	Pre*	Post*	Change (%)	Pre*	Post*	Change (%)	Pre	Post	Change	Clinical response	Pathological response
1–01	RCC	4.3	1.4	−67.7	1.8	0.1	−93.9	De	De	→	SD	NR
1–02	RCC	12.6	11.2	−11.1	3.0	0.3	−90.0	De	De	→	SD	NR
1–03	RCC	49.3	19.7	−60.0	38.7	3.0	−92.3	Ex	Ex	→	SD	PR
1–04	NSCLC	48.9	34.5	−29.3	8.9	1.2	−86.7	In	UD	→	PR	CR
1–05	RCC	8.6	14.9	73.3	5.0	0.7	−86.0	De	In	↑	SD	PR
1–06	ESCC	62.6	64.5	3.1	23.6	3.9	−83.4	De	Ex	↑	SD	PR
1–07	RCC	30.4	17.2	−43.4	16.4	0.9	−94.5	De	Ex	↑	SD	PR
1–08	NSCLC	4.0	nt	nt	4.0	nt	nt	UD	–	–	SD	N/A
1–09	RCC	26.9	45.7	69.9	6.8	1.7	−75.0	De	Ex	↑	SD	PR
1–10	TSCC	21.3	40.0	87.8	13.3	3.4	−74.4	Ex	Ex	→	Non-CR/non-PD	NR
2–01	ESCC	397.8	106.6	−73.2	265.6	21.2	−92.0	In	Ex	↓	PR	NR
2–02	RCC	7.5	7.8	4.0	2.0	0.2	−90.0	De	Ex	↑	SD	PR
2–03	NSCLC	93.7	132.4	41.4	21.7	4.4	−79.7	Ex	Ex	→	PD	NR
2–04	ESCC	145.6	92.6	−36.4	75.4	12.6	−83.3	Ex	In	↑	PR	PR
2–05	NSCLC	104.7	157.6	50.6	17.3	8.2	−52.7	De	Ex	↑	SD	PR
2–06	NSCLC	118	84	−28.8	49.6	2.6	−94.8	Ex	In	↑	SD	PR

Gray highlighting shows patients with less than 0% in change in Tregs, less than −90% in change in CCR4⁺ Tregs, an improved TIME classification in change in TIME, and PR or CR responses in clinical response and pathological response.
*Number of cells per field of view (0.35 mm^2).
CCR4⁺, C-C chemokine receptor 4⁺ ; CR, complete response; De, immune-desert; ESCC, esophageal squamous cell carcinoma; Ex, immune-excluded; IHC, immunohistochemistry; In, immune-inflamed; N/A, not applicable; NR, no response; NSCLC, non-small cell lung cancer; nt, not tested; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; TIME, tumor immune microenvironment; Treg, regulatory T cell; TSCC, tongue squamous cell carcinoma; UD, undecidable.

higher with PD-1 blockade were rash in 0.4–6.7% of cases, endocrine disturbances in 0–0.6%, diarrhea in 1–3.9%, and interstitial pneumonia in 0–4.3%.[25–29] Severe AEs of grade 3 or higher with mogamulizumab were rash in 6.3–18.5% of patients in previous clinical trials on hematological diseases and lymphopenia in 29%, rash in 2.6%, endocrine disruption in 0%, and diarrhea in 0% with no serious AEs in previous clinical trials on solid tumors.[9 30 31] In this clinical trial, there were 13 serious TRAEs, and the most frequently observed TRAEs were skin-related (n=3, 18%) and lymphopenia (n=4, 25%). Although the percentage of TRAEs was consistent with that reported with single-agent nivolumab or mogamulizumab therapy, all are known AEs for nivolumab or mogamulizumab, and are manageable. DLT occurred in one patient with interstitial pneumonia in cohort 1, which was considered to be a predictable AE by nivolumab. This patient died and the cause of death was progression of the primary disease. Intraoperative and postoperative complications were within acceptable limits. Therefore, the combination of mogamulizumab and nivolumab was manageable and did not affect short-term surgical outcomes.

Regarding efficacy, effector Tregs were depleted in the peripheral blood and tumors of all patients. Clinical responses were PR in 3 patients and SD in 11, and increases in lymphocytes in tumor tissue according to the TIME classification were observed in 8 patients, which were associated with a better pathological response and prognosis. Clinical trials with single-agent mogamulizumab showed Treg depletion in peripheral blood and Treg depletion in tumors in a few cases; however, clinical efficacy has been limited.[9 32–34] Consequently, clinical trials on combination therapy of mogamulizumab with checkpoint inhibitors, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, demonstrated that although all studies reported Treg depletion in peripheral blood and Treg depletion in tumor biopsy specimens, along with an increase in $CD8^+$ T cells in one study, no additional therapeutic effect was noted. The lack of enhanced therapeutic efficacy was attributed to the additional depletion of CCR4-expressing antitumor effector cells, such as central memory $CD8^+$ T cells, on which the expression of CCR4 was up-regulated by antigen stimulation,[35 36] and also to the induction of other suppressive immune cells, including bone marrow-derived suppressor cells and tumor-associated macrophages.[32] In the present study, a favorable clinical response was observed in patients with reduced Tregs and increases in lymphocytes in tumor tissue, indicating the utility of preoperative combination immunotherapy. In contrast to previous clinical trials on advanced or recurrent solid tumors with large tumor volumes, preoperative combination immunotherapy has the potential to reduce postoperative recurrence with minimal residual disease. Since this study had a small sample size and had a short follow-up, the results obtained need to be confirmed in a larger cohort with a longer follow-up in the future.

There are some advantages to using immunotherapy in a neoadjuvant setting.[37] Neoadjuvant immunotherapy may efficiently induce antitumor T cells in the presence of the primary tumor with abundant tumor antigens.[12] In the preoperative setting, immunotherapy in the presence of abundant tumor antigens may induce more efficient effector T cells. In addition, preoperatively activated antitumor T cells are expected to be preserved in the bloodstream during the postoperative period, leading to the elimination of residual cancer cells and the prevention of recurrence. Furthermore, dissected specimens allowed us to investigate intratumoral immune responses caused by immunotherapy in detail. Some clinical trials using mogamulizumab combined with other immunotherapy drugs against recurrent or advanced solid tumors demonstrated effector Treg depletion in tumors and peripheral blood; however, these analyses showed effector Treg depletion with biopsy samples before and after the treatment in only some of the cohort.[9 32–34] In the present study, a detailed analysis of intratumoral immune responses showed the depletion of 80–90% of $CCR4^+Foxp3^+$ cells from the tumor as well as the complete depletion of blood effector Tregs and increases in lymphocytes in the tumor tissue of 50% of patients. Therefore, these results imply that combination therapy with mogamulizumab and nivolumab improved the tumor immune environment through Treg removal, even within the tumor.

In this study, cohort 1 was administered mogamulizumab at a low dose of 0.1 mg/kg, which was sufficient to deplete $CCR4^+$ Treg in both peripheral blood and tumors. This result is consistent with previous findings showing efficient Treg depletion in blood with a lower dose (0.003–0.3 mg/kg).[38] Therefore, 0.1 mg/kg of mogamulizumab is a sufficient dose to deplete Tregs in blood and tumors. In addition, effector Tregs decreased immediately in blood after the start of treatment, and were maintained at a low level throughout the treatment period; however, effector Tregs increased a few months later after the last dose. Therefore, it may be necessary to continue administering mogamulizumab every 2 weeks to maintain the effects of Treg depletion in tumors.

In conclusion, although it is necessary to monitor the AEs associated with combined immunotherapy, preoperative combination therapy with mogamulizumab and nivolumab was safely managed for operable solid tumors and did not preclude surgical treatment. Treg depletion was observed in tumors and blood, and increases in lymphocytes in tumor tissue were observed in 50% of patients, which was associated with a favorable prognosis. Preoperative combination therapy with mogamulizumab and nivolumab has potential as a novel immunotherapy option with the regulation of the PD-1–PD-L1 pathway and the depletion of Tregs as therapeutic mechanisms.

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Correction notice This article has been corrected since it was first published online. Hisashi Wada's affiliation has been updated to 'Department of Clinical Research in Tumor Immunology, Osaka University Graduate School of Medicine, Osaka, Japan'.

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Contributors HW and RU are the principal investigators and the guarantors. HW and RU designed the study protocol. KKu, TK, TT, TM, TO, SI, JN, YD, and HW recruited study participants and aided in data collection. KJ, TS, SS, TT, HN, KKa, MO, RU, and HW analyzed the data. KJ and TS wrote the original draft. All authors contributed to the writing and approved the final version of the manuscript.

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REFERENCES

1 Doki Y, Ajani JA, Kato K, *et al*. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med* 2022;386:449–62.
2 Motzer RJ, Rini BI, McDermott DF, *et al*. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol* 2019;20:1370–85.
3 Ready N, Hellmann MD, Awad MM, *et al*. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. *J Clin Oncol* 2019;37:992–1000.
4 Ozawa S, Uchi Y, Ando T, *et al*. Essential updates 2020/2021: Recent topics in surgery and perioperative therapy for esophageal cancer. *Ann Gastroenterol Surg* 2023;7:346–57.
5 Topalian SL, Hodi FS, Brahmer JR, *et al*. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. *N Engl J Med* 2012;366:2443–54.
6 Robert C, Schachter J, Long GV, *et al*. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015;372:2521–32.

7 Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? *Cancer Sci* 2019;110:2080–9.
8 Sato T, Nagai M, Watanabe O, *et al*. Multicenter, randomized, double-blind, placebo-controlled phase 3 study of mogamulizumab with open-label extension study in a minimum number of patients with human T-cell leukemia virus type-1-associated myelopathy. *J Neurol* 2024;271:3471–85.
9 Saito T, Kurose K, Kojima T, *et al*. Phase Ib study on the humanized anti-CCR4 antibody, KW-0761, in advanced solid tumors. *Nagoya J Med Sci* 2021;83:827–40.
10 Kurose K, Ohue Y, Sato E, *et al*. Increase in activated Treg in TIL in lung cancer and in vitro depletion of Treg by ADCC using an antihuman CCR4 mAb (KM2760). *J Thorac Oncol* 2015;10:74–83.
11 Fujikawa K, Saito T, Kurose K, *et al*. Integrated analysis of phase 1a and 1b randomized controlled trials; Treg-targeted cancer immunotherapy with the humanized anti-CCR4 antibody, KW-0761, for advanced solid tumors. *PLoS One* 2023;18:e0291772.
12 Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science* 2020;367:eaax0182.
13 André T, Tougeron D, Piessen G, *et al*. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. *J Clin Oncol* 2023;41:255–65.
14 Provencio M, Nadal E, González-Larriba JL, *et al*. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* 2023;389:504–13.
15 Morito A, Eto K, Iwatsuki M, *et al*. Clinical impact of very early recurrence after conversion surgery for stage IV gastric cancer. *Ann Gastroenterol Surg* 2024;8:214–20.
16 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
17 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. *Gastric Cancer* 2011;14:101–12.
18 Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus 2017;14:1–36.
19 U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Published May 28, 2009. Revised Version 4.03, June 14, 2010.,
20 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
21 Amin MB, Greene FL, Edge SB, *et al*. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more 'personalized' approach to cancer staging. *CA Cancer J Clin* 2017;67:93–9.
22 Miyara M, Yoshioka Y, Kitoh A, *et al*. Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor. *Immunity* 2009;30:899–911.
23 Watanabe M, Kanao K, Suzuki S, *et al*. Increased infiltration of CCR4-positive regulatory T cells in prostate cancer tissue is associated with a poor prognosis. *Prostate* 2019;79:1658–65.
24 Suzuki S, Ogawa T, Sano R, *et al*. Immune-checkpoint molecules on regulatory T-cells as a potential therapeutic target in head and neck squamous cell cancers. *Cancer Sci* 2020;111:1943–57.
25 Sznol M, Postow MA, Davies MJ, *et al*. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. *Cancer Treat Rev* 2017;58:70–6.
26 Nishino M, Giobbie-Hurder A, Hatabu H, *et al*. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2016;2:1607–16.
27 Topalian SL, Sznol M, McDermott DF, *et al*. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol* 2014;32:1020–30.
28 Belum VR, Benhuri B, Postow MA, *et al*. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer* 2016;60:12–25.
29 Dougan M. Checkpoint Blockade Toxicity and Immune Homeostasis in the Gastrointestinal Tract. *Front Immunol* 2017;8:1547.
30 Ishida T, Joh T, Uike N, *et al*. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol* 2012;30:837–42.
31 Yamamoto K, Utsunomiya A, Tobinai K, *et al*. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. *J Clin Oncol* 2010;28:1591–8.
32 Doi T, Muro K, Ishii H, *et al*. 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. *Clin Cancer Res* 2019;25:6614–22.
33 Zamarin D, Hamid O, Nayak-Kapoor A, *et al*. Mogamulizumab in Combination with Durvalumab or Tremelimumab in Patients with Advanced Solid Tumors: A Phase I Study. *Clin Cancer Res* 2020;26:4531–41.
34 Hong DS, Rixe O, Chiu VK, *et al*. Mogamulizumab in Combination with Nivolumab in a Phase I/II Study of Patients with Locally Advanced or Metastatic Solid Tumors. *Clin Cancer Res* 2022;28:479–88.
35 Maeda Y, Wada H, Sugiyama D, *et al*. Depletion of central memory $CD8^+$ T cells might impede the antitumor therapeutic effect of Mogamulizumab. *Nat Commun* 2021;12:7280.
36 Ono S, Suzuki S, Kondo Y, *et al*. Trametinib improves Treg selectivity of anti-CCR4 antibody by regulating CCR4 expression in CTLs in oral squamous cell carcinoma. *Sci Rep* 2022;12:21678.
37 Topalian SL, Forde PM, Emens LA, *et al*. Neoadjuvant immune checkpoint blockade: A window of opportunity to advance cancer immunotherapy. *Cancer Cell* 2023;41:1551–66.
38 Sato T, Coler-Reilly ALG, Yagishita N, *et al*. Mogamulizumab (Anti-CCR4) in HTLV-1-Associated Myelopathy. *N Engl J Med* 2018;378:529–38.