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ORIGINAL ARTICLE

CCR7 alterations associated with inferior outcome of adult T-cell leukemia/lymphoma under mogamulizumab treatment

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Abstract

Adult T-cell leukemia/lymphoma (ATL) patients have a very poor prognosis. The humanized anti-CCR4 therapeutic monoclonal antibody, mogamulizumab, is a key agent for ATL treatment. Our previous integrated molecular analysis demonstrated that among all the driver genes in ATL, *CCR7* gene alterations were significantly associated with clinical response to mogamulizumab. Accordingly, here we investigated the detailed clinical impact of *CCR7* alterations in a larger cohort of ATL patients. These *CCR7* alterations, most of which lead to C-terminus truncations, were observed in 27 of 223 patients (12%). For patients receiving mogamulizumab but not allogeneic hematopoietic stem cell transplantation (HSCT), *CCR7* alterations were significantly associated with worse survival (median survival from the first dose of mogamulizumab of 0.7 years for 12 patients with *CCR7* alterations vs. 1.6 years for 72 patients without, $p = 0.020$). On the other hand, the presence or absence of *CCR7* alterations had no significant impact on survival in the entire cohort (median overall survival of 1.4 and 1.8 years, respectively, $p = 0.901$), or on the survival of patients receiving

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allogeneic HSCT (median survival from the day of transplantation of 0.9 years for 6 patients with *CCR7* alterations and 1.4 years for 48 without, $p = 0.543$). Multivariate analysis indicated that patients with *CCR4* alterations but lacking *CCR7* alterations ($n = 20$) had significantly better survival after receiving mogamulizumab-containing treatments (hazard ratio for survival, 0.437, 95% confidence interval, 0.192–0.994). This study contributes to the establishment of precision medicine for ATL.

KEYWORDS
adult T-cell leukemia/lymphoma, CCR4, CCR7, mogamulizumab

1 | INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type-1. It has a very poor prognosis.[1,2] Allogeneic hematopoietic stem cell transplantation (HSCT) is generally considered to be the only curative treatment for ATL. Therefore, younger patients (≤70 years of age) and those with relatively well-controlled ATL are recommended to receive this treatment, aiming for long-term survival.[3–6] However, treatment-related adverse events associated with allogeneic HSCT are generally severe compared to other treatments. In addition, many Japanese ATL patients are older (median age at diagnosis, 68 years).[7] Accordingly, the proportion of ATL patients who are candidates for allogeneic HSCT due to their age is decreasing year by year.

The humanized anti-CCR4 monoclonal antibody mogamulizumab has a defucosylated Fc region, which enhances antibody-dependent cellular cytotoxicity (ADCC).[8–10] It is approved in Japan for patients with newly diagnosed or relapsed/refractory ATL,[11,12] and offers clinical benefit for patients with this disease.[13] With respect to the relationship with allogeneic HSCT, pre-transplantation treatment with mogamulizumab within approximately 2 months should be avoided, because it presumably result in increased severity and refractoriness of graft-versus-host disease after transplantation.[14,15] On the other hand, currently, most patients deemed unsuitable for allogeneic HSCT receive mogamulizumab-containing treatment as first-line therapy.[15–17] Accordingly, it is currently a key agent for ATL treatment. In this context, an integrated molecular analysis of ATL was conducted to identify genomic biomarkers of this antibody therapy. Among all the driver genes in ATL, only 2 alterations in the *CCR4* and *CCR7* genes were significantly associated with clinical response to mogamulizumab. Thus, the complete response rate of patients with *CCR7* alterations was 29% (2/7) compared to 72% (40/56) of those without ($p = 0.036$).[18] This prompted us to focus on the clinical significance of *CCR7* alterations, and here we report an investigation on a larger cohort of ATL patients.

2 | METHODS

2.1 | ATL patients

The present study included 223 ATL patients. The diagnosis and assignment of clinical subtypes of ATL was conducted according to the criteria recommended by the Japan Lymphoma Study Group.[2] The present study was approved by the Institutional Ethics Committees of Nagoya City University Graduate School of Medical Sciences (Nagoya, Japan), Imamura General Hospital (Kagoshima, Japan), Oita Prefectural Hospital (Oita, Japan), Fukuoka University (Fukuoka, Japan), National Hospital Organization Kyushu Medical Center (Fukuoka, Japan), and Nagoya University Graduate School of Medicine (Nagoya, Japan).

2.2 | Nucleic acid extraction

We used AllPrep DNA/RNA from formalin-fixed paraffin-embedded (FFPE) Kits (80234, QIAGEN Inc., Germantown, MD) to extract genomic DNA and total RNA FFPE tissues in the 202 patients diagnosed with ATL by histopathology. In the remaining 21 ATL patients, AllPrep DNA/RNA Mini Kits (80204, QIAGEN Inc.) were used to extract genomic DNA and total RNA from peripheral blood mononuclear cells (PBMC) containing >30% abnormal lymphocytes.

2.3 | Detection of *CCR7* single nucleotide variants/insertion-deletions by targeted next-generation sequencing

DNA fragments encompassing codons 338–364 of *CCR7* were amplified from genomic DNA using the primers CCR7-F (5'-GGCGTCAAGTTCCGCAAC-3') and CCR7-R (5'-GGCCTCCACACTCATGGA-3'). The amplicons were then purified using Agencourt AMPure XP (Beckman Coulter Inc., Brea, CA) and barcoded using a Nextera XT Index Kit (Illumina Inc.). Subsequently, the library was re-purified, quantified, and checked for purity using the 2100

Bioanalyzer (Agilent Technologies, Santa Clara, CA). An iSeq instrument (Illumina Inc.) was used for sequencing. All of these procedures were carried out according to Illumina's recommended methods (http://jp.support.illumina.com).

2.4 | Detection of *TP53*, *CD28*, and *CCR4* alterations

TP53 alterations including single nucleotide variants (SNVs)/Indels and copy number variations (CNVs) were analyzed, as previously described.[19] *CD28* alterations including *CD28*-related fusions, SNVs/Indels, and CNVs were also analyzed as previously described.[20] *CCR4* SNVs/indels were analyzed by targeted next-generation sequencing in samples from 46 patients. DNA fragments encompassing codons 322–348 of *CCR4* were amplified from genomic DNA using primers CCR4-F (5'-CAAGTACATCCTACAGCTCTTC-3') and CCR4-R (5'-CATGATCCATGGTGGACTG-3'). The subsequent procedures were the same as used for *CCR7*, as described above. For the remaining samples from 177 patients, *CCR4* SNVs/indels in codons 322–348 were detected, as previously described.[21]

2.5 | Statistical analysis

Differences between two groups were examined with the Mann–Whitney *U*-test or Fisher's exact test. Univariate and multivariate Cox proportional hazards regression models were used to identify prognostically relevant variables. The probability of survival was estimated by the Kaplan–Meier method, and survival times were compared using the log-rank test. Overall survival (OS) was measured from the day when the tumor sample was obtained to death resulting from any cause. To evaluate the impact of allogeneic HSCT, survival was measured from the day of transplantation. When evaluating the impact of mogamulizumab-containing treatment, survival was measured from the day of the first dose of antibody. All analyses were performed with SPSS Statistics 25 (IBM Corporation, Armonk, NY). In this study, $p < 0.050$ (two-sided) was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of the ATL patients

The ATL patients enrolled in this study included 115 men and 108 women (age range, 36–90 years; median, 66 years) (Table 1). Tumor samples were obtained from each patient at the time of initial presentation at the participating hospital, and the clinical characteristics including clinical subtypes were recorded at that time. Treatments administered to these ATL patients varied because they were determined at the discretion of each clinical investigator.

TABLE 1 Characteristics of Adult T-cell leukemia/lymphoma (ATL) patients according to *CCR7* alterations

Characteristics	*CCR7* alterations		*p* value
	Absent	Present	
Number (%)	196 (88)	27 (12)	
Sex			0.063
Female	90 (46)	18 (67)	
Male	106 (54)	9 (33)	
Clinical subtype			1.000
Chronic, smoldering	24 (12)	3 (11)	
Acute, lymphoma	172 (88)	24 (89)	
ECOG PS*			0.816
0, 1	144 (74)	19 (70)	
2, 3, 4	51 (26)	8 (30)	
Serum sIL-2R (U/ml)**			1.000
<20,000	111 (59)	16 (62)	
>20,000	77 (41)	10 (38)	
Serum Ca (mg/dl)***$			0.528
<11.0	168 (88)	21 (84)	
>11.0	23 (12)	4 (16)	
Serum Albmin (g/dl)****			0.823
>3.5	131 (69)	17 (65)	
<3.5	60 (31)	9 (35)	
Age (years)			0.582
Mean	65	68	
Median	64	67	
Range	41–90	41–85	
WBC (/ul)*****			0.712
Mean	13,916	18,260	
Median	8185	7760	
Range	2500-165,800	2800-232,100	
Hb (g/dl)*****			0.412
Mean	12.9	12.6	
Median	13.2	13.1	
Range	6.0–17.1	2.9–15.0	
Plt (×103/μl)*****			0.445
Mean	228	221	
Median	222	190	
Range	4–622	111–444	
CCR4 alterations			0.660
Absent	134 (68)	20 (74)	
Present	62 (32)	7 (26)	

TABLE 1 (Continued)

Characteristics	*CCR7* alterations		*p* value
	Absent	Present	
CD28 alterations			0.832
Absent	122 (62)	18 (67)	
Present	74 (38)	9 (33)	
TP53 alterations			0.059
Absent	120 (61)	11 (41)	
Present	76 (39)	16 (59)	

Abbreviations: ATL, adult T-cell leukemia/lymphoma; Alb, albumin; Ca, calcium; CCR4, CC chemokine receptor 4; ECOG, Eastern Cooperative oncology Group; Hb, hemoglobin; PS, performance status; Plt, platelet count; sIL-2R, soluble interleukin-2 receptor; WBC, white blood cell count; $When serum Alb level was less than 4.0 g/dl, serum Ca was adjusted by the concentration of serum Alb as follows: adjusted Ca level (mg/dl) = measured Ca level (mg/dl) + [4-Alb level (g/dl)]; *A patient's data was unknown; **Nine patients' data were unknown; ***Seven patients' data were unknown; ****Six patients' data were unknown; *****Five patients' data were unknown.

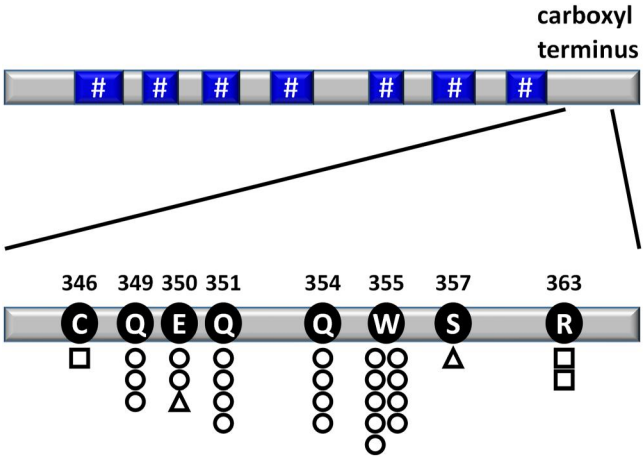

FIGURE 1 Positions, types, and frequencies of somatic alterations of *CCR7* in Adult T-cell leukemia/lymphoma (ATL) patients. DNA fragments encompassing codons 338–364 of *CCR7* were amplified from genomic DNA. Circles, squares, and triangles indicate nonsense, missense, and frameshift single nucleotide variants (SNVs)/indels, respectively. The number of circles, squares, or triangles indicates the number of patients with alterations among the 223 ATL cases. A hash-tag indicates a transmembrane domain of *CCR7*. CCR7 amino acid alterations were determined by reference to the NCBI protein sequence NP_001829.1

3.2 | *CCR7* gene alterations in ATL patients

CCR7 alterations, comprising one C346Y, three Q349*, two E350*, one E350 fs, four Q351*, four Q354*, nine W355*, one S357fs, and two R363 C *CCR7* SNVs/indels, were detected in 27 of 223 patients (12%) (Figure 1).

3.3 | *TP53, CD28 and CCR4* alterations in ATL patients

Sixty SNVs/indels of *TP53* were identified in 49 ATL patients (22%), and six patients were found to harbor more than one of these. *TP53* CNVs, such as homozygous and heterozygous deletions, were observed in 17 and 39 patients (8% and 17%), respectively, and thirteen patients harbored both *TP53* SNVs/indels and CNVs. Collectively, *TP53* alterations were observed in 92 patients (41%) (data not shown).

CD28 alterations were found in 83 patients (37%), including 35 *CD28*-related fusions (5 *CTLA4-CD28* and 30 *ICOS-CD28*), three activating SNVs (F51I, D124V, and D124E), and 53 CNVs (34 gains and 19 amplifications). Five patients simultaneously had a *CD28*-related fusion and CNVs, two harbored two different types of *CD28*-related fusions, and one had a *CD28*-related fusion and SNV (data not shown).

CCR4 alterations were detected in 69 patients (31%), including one T321fs, four R323fs, two F326fs, 17 C329*, one C329fs, five Q330*, one Q330fs, 22 Y331*, four Y331fs, 8 Q336*, one I337fs, and three S345fs *CCR4* SNVs/indels (data not shown).

3.4 | Characteristics of ATL patients stratified by *CCR7* alterations

Female patients tended to be more likely to harbor *CCR7* alterations (18/108 [17%] vs. male, 9/115 [8%], $p = 0.063$). There were no significant differences between patients with or without *CCR7* alterations in the other clinical characteristics recorded, such as clinical subtype (chronic, smoldering or acute, lymphoma), Eastern Cooperative Oncology Group (ECOG) performance status (PS), (0,1 vs. 2,3,4), serum soluble interleukin-2 receptor (sIL-2R) (≤20,000 U/ml vs. > 20,000 U/ml), serum adjusted calcium (Ca) (≤11.0 vs. > 11.0 mg/dl), serum albumin (≥3.5 vs. < 3.5 g/dl), age (years), white blood cell count (/uL), hemoglobin level (g/dl), or platelet count (x 103/ul). Patients with *CCR7* alterations tended to be more likely to harbor *TP53* alterations (16/27 [59%] vs. 76/196 [39%], respectively, $p = 0.059$). However, there were no significant differences between patients with or without *CCR7* alterations in terms of the presence of *CCR4* alterations (7/27 [26%] vs. 62/196 [32%], respectively, $p = 0.660$) *or CD28* alterations (9/27 [33%] vs. 74/196 [38%], respectively, $p = 0.832$) (Table 1).

3.5 | OS of ATL patients stratified by *CCR7* alterations

The median OS of all patients enrolled in the present study was 1.7 years (Figure 2A). Patients aged >70 years had a significantly shorter OS than those aged ≤70 years (median OS, 1.2 vs. 1.9 years, respectively, $p = 0.036$) (data not shown). The OS of patients with an acute or lymphoma subtype was significantly shorter than of those

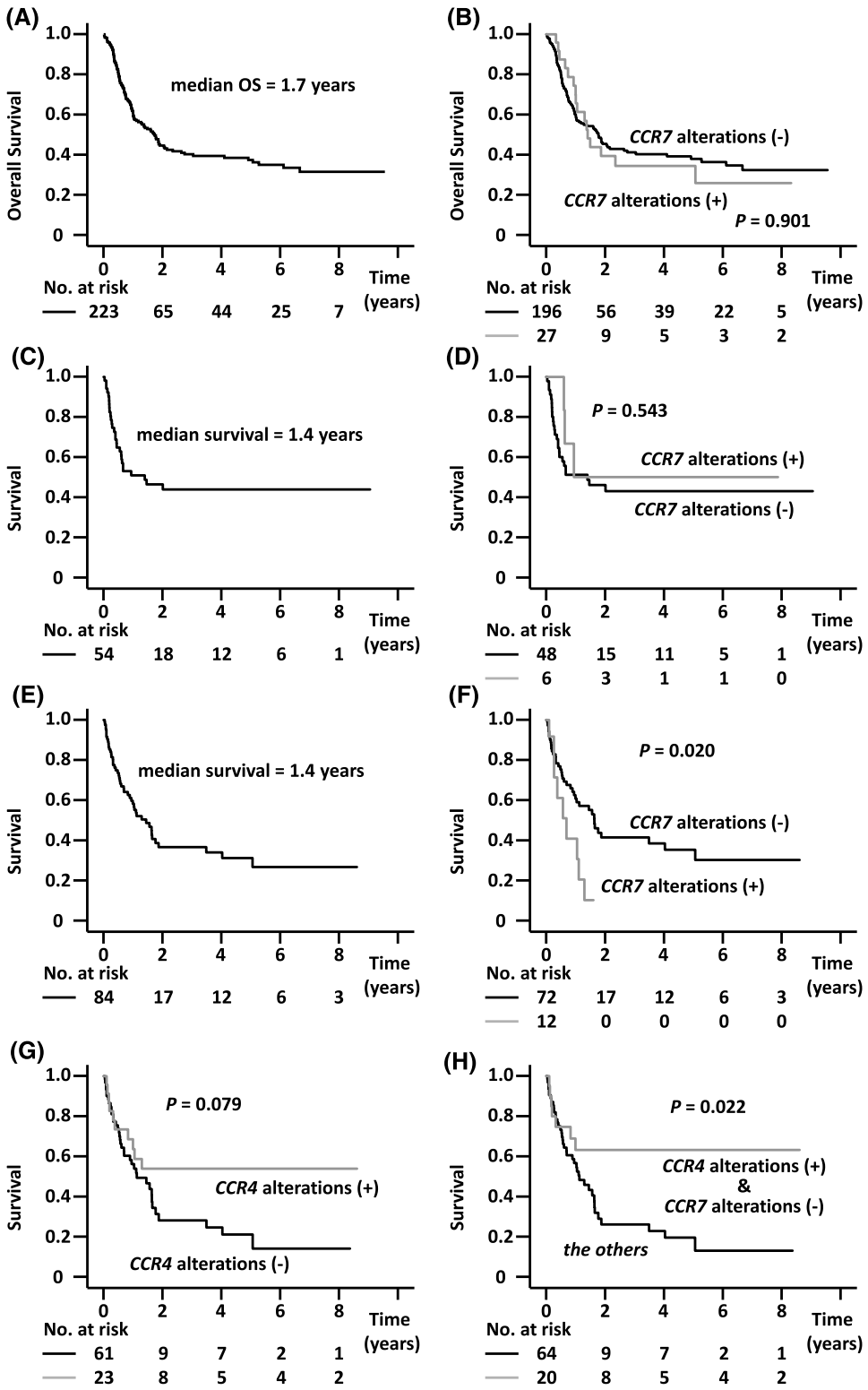

FIGURE 2 Survival of Adult T-cell leukemia/lymphoma (ATL) patients stratified according to *CCR7* gene alterations. (A) Overall survival (OS) of all ATL patients enrolled in the study (n = 223). The median OS was 1.8 years (95% confidence interval [CI], 1.3–2.1 years). (B) OS according to *CCR7* alterations (with *CCR7* alterations [+] compared with no alterations [–]; hazard ratio [HR], 1.034, 95% CI, 0.610–1.752). (C) Survival of ATL patients from the day of allogeneic hematopoietic stem cell transplantation (HSCT) (n = 54). The median survival was 1.4 years (95% CI, 0.0–2.9 years). (D) Survival from the day of allogeneic HSCT according to *CCR7* alterations (with *CCR7* alterations [+] compared to those without [–]; HR, 0.691, 95% CI, 0.208–2.293). (E) Survival of ATL patients receiving mogamulizumab but not allogeneic HSCT (n = 84). The median survival from the first dose of mogamulizumab was 1.4 years (95% CI, 0.8–2.1 years). (F) Survival from the first dose of mogamulizumab according to *CCR7* alterations (with *CCR7* alterations [+] vs. without [-]; HR, 2.372, 95% CI, 1.119–5.027). (G) Survival from the first dose of mogamulizumab according to *CCR4* alterations (with *CCR4* alterations [+] compared to without [–]; HR, 0.538, 95% CI, 0.266–1.087). (H) Survival from the first dose of mogamulizumab according to *CCR4* and *CCR7* alterations (with *CCR4* alterations [+] but without *CCR7* alterations [–] compared with the others; HR, 0.400, 95% CI, 0.178–0.901)

with a chronic or smoldering subtype (median OS, 1.4 years vs. not reached [NR], respectively, $p < 0.001$) (data not shown). The OS of patients with *TP53* alterations was significantly shorter than of those without (median OS, 0.9 years vs. Not reached, respectively, $p < 0.001$). The OS of patients with *CD28* alterations was significantly shorter than of those without (median OS, 1.0 vs. 2.2 years, respectively, $p = 0.010$) (data not shown). Finally, there were no significant differences in OS between patients with and without *CCR4* alterations (median OS, 1.4 vs. 1.8 years, respectively, $p = 0.878$) (data not shown), or *CCR7* alterations (median OS, 1.4 vs. 1.8 years, respectively, $p = 0.901$) (Figure 2B).

3.6 | Survival of ATL patients receiving allogeneic HSCT stratified by *CCR7* alterations

The median survival from the day of allogeneic HSCT of all 54 transplanted patients was 1.4 years (Figure 2C). The median survival from the day of transplantation of patients with or without *TP53* alterations was 0.4 years or NR, respectively ($p = 0.002$) (data not shown). In contrast, there were no significant differences in survival between patients with or without alterations of *CD28* (median survival, 0.6 vs. 2.0 years, respectively, $p = 0.447$), *CCR4* (median survival, respectively, 0.6 vs. 1.5 years, $p = 0.952$) (data not shown), or *CCR7* alterations (median survival, 0.9 vs. 1.4 years, respectively, $p = 0.543$) (Figure 2D).

3.7 | Survival of ATL patients receiving mogamulizumab but not allogeneic HSCT, stratified by *CCR7* alterations

The median survival from the day of the first dose of mogamulizumab of 84 patients who did not receive allogeneic HSCT was 1.4 years (Figure 2E). There was a trend toward worse survival in patients with a higher age (>70 years vs. ≤ 70 years) at the first dose of mogamulizumab (median survival, 0.8 vs. 1.6 years, respectively, $p = 0.095$) (data not shown). There was no significant difference in survival between patients with an acute or lymphoma subtype and those with a chronic or smoldering subtype (median survival, 1.1 vs. 3.5 years, respectively, $p = 0.179$) (data not shown). In contrast, the difference in median survival from the first dose of antibody of patients with or without *TP53* alterations was highly significant, at 0.7 versus 5.1 years, respectively ($p < 0.001$). The presence of *CD28* alterations also had a significant negative impact, at 0.6 versus 1.6 years, respectively ($p = 0.019$) (data not shown). Survival from the first dose of antibody of patients with *CCR7* alterations was also significantly worse than of those without (median survival, 0.7 vs. 1.6 years, respectively, $p = 0.020$) (Figure 2F). On the other hand, there was a trend toward better survival from the first dose of antibody in patients with *CCR4* alterations relative to those without (median survival, NR vs. 1.1 years, respectively, $p = 0.079$) (Figure 2G). Finally, survival from the first dose of mogamulizumab was analyzed in patients stratified by both *CCR4* and *CCR7* alterations together. Thus, median survival in patients with *CCR4* alterations but lacking *CCR7* alterations was NR, which was significantly better than in the other patients (median survival, 1.1 years, $p = 0.022$) (Figure 2H).

3.8 | Multivariate analysis of survival from the first dose of mogamulizumab

Multivariate analysis was performed using the following 5 variables: age at the first dose of mogamulizumab, clinical subtype, *TP53* alterations, *CD28* alterations, and a combination of *CCR4* and *CCR7* alterations. Of these, two variables including *TP53* alterations, and presence of *CCR4* alterations in the absence of *CCR7* alterations, were significantly associated with survival (hazard ratio [HR], 2.685; 95% confidence interval [CI], 1.427–5.050, and HR, 0.437; 95% CI, 0.192–0.994, respectively) (Table 2).

4 | DISCUSSION

CCR7, a 7 transmembrane G-protein-coupled receptor similar to CCR4, is commonly expressed on ATL cells, and interactions with its ligands including CCL19 or CCL21 are important for tumor cell infiltration into or for residence in the lymphoid tissues.[22,23] *CCR7* alterations, most of which were SNVs/indels leading to C-terminus truncations, were observed in these patients. Such *CCR7* alterations had gain-of-function effects leading to enhanced downstream signaling,[24,25] and have also been observed in other mature T-cell neoplasms.[26]

Analyzing the entire cohort of ATL patients examined here, those with *CCR7* alterations did not appear to possess any specific clinical characteristics differentiating them from those without any alterations. However, there was a trend for patients with *CCR7* alterations to be more likely to harbor *TP53* alterations as well, which might be associated with the contribution of *TP53* to genomic stability.[27–29] Regarding clinical outcomes, *CCR7* alterations did not have a significant impact on OS, in contrast to *TP53* or *CD28* alterations, but similar to *CCR4* alterations.

In general, because prognostic factors vary according to the treatment strategy, even in the same disease, we investigated the prognostic significance of *CCR7* alterations in ATL patients stratified according to their treatment modality. *CCR7* alterations, in the cohort of patients receiving allogeneic HSCT, did not have a significant impact on survival from the date of transplantation, in contrast to *TP53* alterations, but similar to *CD28* or *CCR4* alterations. Next, we evaluated the impact of *CCR7* alterations in patients receiving mogamulizumab but not allogeneic HSCT. The analysis focusing on this population is clinically important, in the context of the relationship between mogamulizumab and allogeneic HSCT, as mentioned in the Introduction and elsewhere.[3,4,14,15] In the present study, univariate analysis indicated that *CCR7* alterations were significantly associated with a worse outcome in patients receiving

TABLE 2 Multivariate analysis for survival from the first dose of mogamulizumab

Variables	Number	Hazard ratio	(95% CI)	*p* value
Age[a], years				
<70	54	1.000	-	Reference
>70	30	1.837	(0.979–3.447)	0.058
Clinical subtype				
Chronic, smoldering	8	1.000	-	Reference
Acute, lymphoma	76	2.457	(0.742–8.133)	0.141
TP53 alterations				
Absent	49	1.000	-	Reference
Present	35	2.685	(1.427–5.050)	0.002
CD28 alterations				
Absent	51	1.000	-	Reference
Present	33	1.820	(0.959–3.456)	0.067
Both *CCR4* alterations (+) and *CCR7* alterations (–)				
No	64	1.000	-	Reference
Yes	20	0.437	(0.192–0.994)	0.048

Abbreviation: CI, confidence interval.

[a]age at the first dose of mogamulizumab.

mogamulizumab-containing treatments. This finding is consistent with our earlier study identifying the relationship between *CCR7* alterations and the clinical response to mogamulizumab.[18] We previously reported that the efficacy of mogamulizumab was lower in nodal ATL lesions compared to blood or skin ATL disease.[11] In this context, the enhanced capacity of ATL cells to remain resident in lymphoid tissues as a result of *CCR7* alterations might contribute to refractoriness to mogamulizumab. However, mechanisms related to this phenomenon have not yet been clarified and further investigations are warranted. Regarding *CCR4* alterations, findings in the present study were similar to those of previous reports indicating that they were associated with better survival in patients receiving mogamulizumab-containing treatments.[18,21] When *CCR4* and *CCR7* alterations were assessed together, multivariate analysis indicated that the presence of *CCR4* alterations combined with a lack *CCR7* alterations was an independent predictor of significantly better survival.

In conclusion, the present study documents that the presence or absence of *CCR7* alterations, especially in combination with *CCR4* alterations, is a valuable biomarker to predict the clinical outcome of mogamulizumab-containing treatments in ATL. The present study contributes to the establishment of precision medicine for patients with ATL.

AUTHOR CONTRIBUTIONS

Yuma Sakamoto, Takashi Ishida and Hiroshi Inagaki designed the research. Yuma Sakamoto, Takashi Ishida, Ayako Masaki, Takayuki Murase, Eiichi Ohtsuka, Morishige Takeshita, Reiji Muto, Hiromi Iwasaki, Asahi Ito, Shigeru Kusumoto, Nobuaki Nakano, Masahito Tokunaga, Kentaro Yonekura, Yukie Tashiro, Shinsuke Iida, Atae Utsunomiya, Ryuzo Ueda, and Hiroshi Inagaki performed the experiments. Takashi Ishida, Ryuzo Ueda, and Hiroshi Inagaki analyzed and interpreted data. All authors wrote and approved the manuscript.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support these findings are available from the corresponding author upon reasonable request.

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