Mogamulizumab for relapsed adult T-cell leukemia–lymphoma: Updated follow-up analysis of phase I and II studies

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Key words
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The present study sought to elucidate the prognosis of adult T-cell leukemia–lymphoma (ATL) patients receiving mogamulizumab, a defucosylated anti-CCR4 monoclonal antibody. Progression-free survival (PFS) and overall survival (OS) of ATL patients enrolled in two studies are herein updated, namely NCT00355472 (phase I study of mogamulizumab in relapsed patients with ATL and peripheral T-cell lymphoma) and NCT00920790 (phase II study for relapsed ATL). Of 13 patients with relapsed aggressive ATL in the phase I study, four (31%) survived >3 years. For 26 relapsed patients with aggressive ATL in the phase II study, median PFS was 5.2 months and 1-year PFS was 26%, whereas median OS was 14.4 months, and 3-year OS was 23%. For patients without a rash or who developed a grade 1 rash only, median PFS was 0.8 months, and 1-year PFS was zero, with a median OS of 6.0 months, and 3-year OS of 8%. In contrast, for patients who developed a rash grade 2, median PFS was 11.7 months, and 1-year PFS was 50%, with a median OS of 25.6 months, and 3-year OS of 36%. Thus, we conclude that mogamulizumab monotherapy may improve PFS and OS in some patients with relapsed aggressive ATL, especially those who develop a skin rash as a moderate immune-related adverse event. Therefore, further investigation is warranted to validate the present observations and to clarify the mechanisms involved in the activity of mogamulizumab.

Mature T-cell/natural killer cell neoplasms comprise approximately 20 subclassified heterogeneous groups of non-Hodgkin lymphomas and, in general, they have a worse prognosis compared to mature B-cell neoplasms.1,2 Of these, ATL, caused by human T-cell lymphotropic virus type I, has a poor prognosis.3–6 With respect to PTCL-NOS, this also has a miserable prognosis.1,2

CCR4 is expressed on tumor cells derived from most ATL patients,7–8 as well as on tumor cells from a subgroup of PTCL-NOS, which has an unfavorable prognosis.9–15 Therefore, we postulated that CCR4 may represent a novel molecular target for immunotherapy in ATL and other types of PTCL. Accordingly, mogamulizumab (KW-0761), a humanized, anti-CCR4 mAb with a defucosylated Fc region, which markedly enhanced ADCC, was developed,12,13 and a phase I study of mogamulizumab in relapsed patients with CCR4-positive ATL and PTCL was conducted (NCT00355472).14 A phase II study of mogamulizumab in patients with CCR4-positive relapsed, aggressive ATL (acute, lymphoma, or unfavorable chronic types)15 was subsequently carried out (NCT00920790).15 In addition, a phase II study of mogamulizumab in patients with relapsed PTCL and CTCL was conducted (NCT01192984).16

Based on the results of these studies, in 2012, mogamulizumab was approved for the treatment of relapsed/refractory ATL, and in 2014 for PTCL/CTCL in Japan. As a result, mogamulizumab is currently being used in clinical practice for the treatment of patients with CCR4-positive ATL, and those with CCR4-positive relapsed/refractory PTCL and CTCL in Japan. However, long-term, follow-up information on the OS and the PFS of patients who received mogamulizumab remains unclear. In addition, useful biomarkers predicting the therapeutic efficacies of mogamulizumab remain unidentified, whereas fatal AE caused by mogamulizumab have been reported in some patients.17–18 Herein, we report an up-to-date, follow-up analysis of our prior two prospective clinical trials of mogamulizumab.
Materials and Methods

Patients and study design. This study describes the results of a follow-up analysis of patients with relapsed ATL enrolled in two studies, namely a phase I study of mogamulizumab in relapsed patients with ATL and PTCL (NCT00355472),(14) and a phase II study of mogamulizumab for relapsed ATL (NCT00920790).1(5)

Details of patient eligibilities have been previously described.(14,15) In summary, for the phase I study, patients were eligible if aged between 20 and 69 years with aggressive ATL or PTCL with CCR4 expression, and with relapse occurring after at least one prior chemotherapy regimen. For the phase II study, patients were eligible if they were aged 20 years or older with aggressive CCR4-positive ATL who had relapsed after at least one prior chemotherapy regimen.

The former study was conducted from February 2007 to December 2008, and the latter study was conducted from June 2009 to February 2011. Among the 16 patients enrolled in the phase I study, 10 were still alive at data cut-off (December 2008). Among the 26 patients enrolled in the phase II study and who could be evaluated for efficacy, 12 were still alive at data cut-off (February 2011). Subsequent clinical data for 10 and 12 patients in the former and latter studies, respectively, including disease status (progression date or progression-free date at last follow up) and survival (date alive at last follow up, or date of death), were updated in October 2014.

Statistical analysis. Probability of PFS and OS was estimated by the Kaplan–Meier method. PFS and OS were compared using the log–rank test. PFS was defined as the time from first mogamulizumab dose to progression, relapse, or death from any cause, whichever occurred first. OS was measured from the day of first mogamulizumab dose to death from any cause.

For PFS and OS analyses, ATL patients were divided into two groups according to several factors, including ECOG PS, age, and serum Alb level, which were unfavorable prognostic factors for patients with newly diagnosed acute and lymphoma ATL subtypes.(19) In addition, ATL patients were divided into two or four groups according to the presence of an AE in the form of a skin rash, graded according to the National Cancer Institute Common Terminology Criteria for AE, version 3.0, and which was determined as mogamulizumab-related in the previous study.(15)

Differences between the two groups were examined by Mann–Whitney U-test or Fisher’s exact test. Analyses were conducted at the Innovative Clinical Research Center, Kanazawa University, and carried out using SAS version 9.2 or higher (SAS, Cary, NC, USA). Two-sided P < 0.05 was considered statistically significant.

Study overview. The study was compliant with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and was conducted in accordance with the Declaration of Helsinki. This study provided clinical data, which were obtained from two completed studies (NCT00355472 and NCT00920790). The academic investigators and the company were jointly responsible for the study design. The protocol was approved by the institutional review board at each participating site. All of the applicable patients provided written, informed consent.

Results

Long-term follow up in the phase I study. Patients who survived in the phase I study were followed up for 5 years and 10 months after the study data cut-off (December 2008).(14) Among 13 patients with relapsed ATL, three (patient numbers 102, 204, 412) showed longer PFS at the data cut-off.(14) of these, a patient with acute type ATL (number 102) was progression free until October 2014. PFS of this patient was over 2830 days (Table 1). In the present study, two patients (numbers 102 and 412) showed continued OS, and that of the latter

Table 1. Summary of the long-term follow up of patients enrolled in the phase I study

| Patient no. | Sex | Age (years) | Disease | Overall response to mogamulizumab | PFS (days) | OS (days) | Rash (grade) |
|-------------|-----|-------------|---------|----------------------------------|------------|-----------|-------------|
| 1           | M   | 46          | MF tumor stage | PD                  | 29         | 1166†     | 2           |
| 102         | M   | 60          | ATL acute    | SD→CR†              | 2830†      | 2830†     | None        |
| 103         | F   | 68          | ATL acute    | PR                  | 85         | 732       | None        |
| 2           | M   | 55          | ATL acute    | SD                  | 50†        | 230       | None        |
| 202         | F   | 66          | ATL acute    | SD                  | 36         | 201       | None        |
| 203         | M   | 66          | ATL acute    | PD                  | 8†         | 61        | None        |
| 204         | F   | 57          | ATL acute    | CR                  | 1268       | 2447      | None        |
| 3           | M   | 60          | ATL acute    | PD                  | 36         | 298       | None        |
| 302         | M   | 64          | ATL acute    | PD                  | 29         | 270       | None        |
| 303         | F   | 69          | ATL lymphoma | PD                  | 29         | 260       | None        |
| 4           | F   | 64          | PTCL-NOS     | PR                  | 2507†      | 2507†     | 2           |
| 402         | F   | 62          | ATL acute    | PR                  | 64         | 207       | None        |
| 403         | F   | 64          | ATL lymphoma | SD                  | 43         | 1103      | None        |
| Expanded    | M   | 55          | ATL acute    | PD                  | 28         | 506       | None        |
| 412         | M   | 62          | ATL acute    | CR                  | 506        | 2048†     | 3           |
| 413         | F   | 58          | PTCL-NOS     | SD                  | 1272       | 2230†     | 2           |

†Disease had disappeared by 1 year after treatment; patient 102 was categorized as showing a CR. ATL, adult T-cell leukemia-lymphoma; CR, complete response; MF, mycosis fungoides; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; SD, stable disease.
patient with acute type ATL was over 2048 days. Among 13 patients with relapsed ATL, 10 (numbers 102 and 412 survived until October 2014; number 204 died of post-allogeneic HCT complications) died of ATL progression. Thus, in the phase I study, a total of four patients (102, 204, 403, and 412, 31% [4/13]) survived for more than 3 years (Table 1).

**PFS and OS of relapsed ATL patients enrolled in the phase II study.** Patients who survived in the phase II study were followed up for 3 years and 8 months after the study data cut-off (February 2011)\(^{(15)}\). For 26 patients with relapsed aggressive ATL, median PFS was 5.2 months (95% CI, 0.9–10.3 months). Six (patient numbers 301, 306, 321, 616, 1114, 1323) of these patients showed a longer PFS, giving a PFS rate at 1 year of 26% (95% CI, 11%–45%; Table 2; Fig. 1a). Three patients were of an unfavorable chronic ATL subtype, and the remaining three were acute ATL subtypes. Thus, the PFS rate at 1 year was 21% (3/14 patients) for those with the acute subtype, and 50% (3/6 patients) for those with the unfavorable chronic subtype (Table 2).

For the same patients, median OS was 14.4 months (95% CI, 7.4–24.3 months), with six (patient numbers 306, 312, 321, 1114, 1503, 1513) of these patients showing longer OS, yielding an OS rate at 3 years of 23% (95% CI, 9%–40%; Table 2; Fig. 1b). Four such patients were of an unfavorable chronic subtype and the remaining patients consisted of one acute and one lymphoma subtype. Thus, the OS rate at 3 years was 7% (1/14 patients) for acute, 17% (1/6 patients) for lymphoma, and 67% (4/6 patients) for unfavorable chronic subtypes (Table 2).

**PFS and OS according to unfavorable prognostic factors in relapsed ATL patients.** Among ATL patients, of the unfavorable prognostic factors, PS (0–1 vs 2–4; Fig. S1a, b), age (≤70 vs ≥71 years; Fig. S1c, d), and serum Alb (<3.5 vs ≥3.5 g/dL; Fig. S1e, f), none was significantly associated with PFS and OS.

**PFS and OS according to the presence of rashes.** PFS and OS of patients who did not develop a rash were significantly shorter than those of patients who developed a rash (median PFS: 0.8 months vs 10.3 months, \(P = 0.001\); Fig. 2a, and median OS: 5.4 months vs 23.7 months, \(P = 0.005\); Fig. 2b, respectively). According to a breakdown by severity of skin rash, PFS of patients who did not develop a rash or who developed a grade 1 rash was significantly shorter than that of patients who developed a grade 2 or higher rash (median PFS: 0.8 months vs 11.1 months, \(P = 0.001\); Fig. 2c). OS of patients who did not develop a rash or who developed a grade 1 rash was significantly shorter than that of patients who developed a grade 2 or higher rash (median OS: 6.0 months vs 25.6 months, \(P < 0.001\); Fig. 2d). However, there were no significant differences between both PFS and OS in patients who did not develop a rash or who developed grade 1–2 rashes, and those who developed a grade 3 or higher rash (median PFS: 1.6 months vs 7.0 months; Fig. S2a, and median OS: 10.6 months vs 27.0 months, Fig. S2b, respectively).

We then analyzed PFS and OS according to each grade of rash (no rash, rash grades 1, 2 vs 3). PFS of patients who did not develop a rash was significantly shorter than those of patients who developed a grade 1 (median PFS of 0.9 months, \(P = 0.001\), 2 (median PFS of 14.3 months, \(P < 0.001\), or 3 (median PFS of 7.0 months, \(P = 0.004\)) rash. PFS of patients who developed a grade 1 rash was also significantly shorter than that of patients who developed a grade 2 rash (\(P = 0.004\)). However, there was no significant difference in the PFS between patients who developed a grade 1 or 3, or a

**Table 2. Summary of the follow up of patients enrolled in the phase II study**

| Patient number | Sex | Age (years) | Disease subtype | Overall response to mogamulizumab | PFS (days) | OS (days) |
|----------------|-----|-------------|-----------------|-----------------------------------|------------|----------|
| 202            | F   | 61          | Acute           | PD                                | 28         | 269      |
| 217            | F   | 75          | Lymphoma        | CR                                | 339        | 621      |
| 301            | F   | 71          | Acute           | SD                                | 555        | 602      |
| 306            | M   | 55          | Acute           | PR                                | 497        | 1857+    |
| 312            | F   | 66          | Unfavorable Chronic | PR                          | 158        | 1740+    |
| 321            | M   | 56          | Unfavorable Chronic | CR                          | 701        | 1687+    |
| 322            | F   | 63          | Acute           | PD                                | 36         | 330      |
| 427            | M   | 64          | Acute           | PD                                | 17         | 134      |
| 505            | F   | 71          | Lymphoma        | PD                                | 25         | 178      |
| 509            | M   | 64          | Acute           | PD                                | 12         | 101      |
| 519            | M   | 73          | Lymphoma        | SD                                | 31+        | 185      |
| 616            | F   | 64          | Unfavorable Chronic | PR                          | 968        | 992      |
| 710            | M   | 65          | Unfavorable Chronic | CR                          | 313        | 416      |
| 715            | F   | 60          | Acute           | CR                                | 167        | 323      |
| 824            | F   | 76          | Acute           | PD                                | 15         | 116      |
| 904            | F   | 58          | Lymphoma        | PD                                | 23         | 106      |
| 907            | M   | 60          | Acute           | CR                                | 213        | 820      |
| 918            | F   | 65          | Acute           | CR                                | 203        | 722      |
| 1108           | M   | 68          | Acute           | PD                                | 25         | 225      |
| 1114           | M   | 66          | Unfavorable Chronic | PR                          | 1757+      | 1757+    |
| 1226           | M   | 49          | Acute           | PD                                | 17         | 164      |
| 1320           | M   | 61          | Acute           | PD                                | 26         | 234      |
| 1323           | F   | 75          | Acute           | CR                                | 372        | 739      |
| 1411           | F   | 83          | Lymphoma        | SD                                | 55+        | 463      |
| 1503           | F   | 62          | Unfavorable Chronic | PR                          | 50         | 1958+    |
| 1513           | F   | 69          | Lymphoma        | PR                                | 139        | 1779+    |

CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
grade 2 and 3 rash (Fig. 2c). In terms of OS, that of patients who did not develop a rash was significantly shorter than that of patients who developed a grade 2 (median OS of 24.3 months, \( P = 0.01 \)), or 3 (median OS of 27.0 months, \( P = 0.01 \)) rash. OS of patients who developed a grade 1 rash (median OS of 6.1 months) was also significantly shorter than that of patients who developed a grade 2 ( \( P = 0.03 \) ) or 3 ( \( P = 0.04 \) ) rash. In contrast, there was no significant difference in the OS between patients who did not develop a rash or who developed a grade 1 rash ( \( P = 0.19 \) ), or a grade 2 and 3 rash ( \( P = 0.79 \); Fig. 2f).

**Clinical characteristics of ATL patients according to the presence of a rash.** Clinical characteristics, before mogamulizumab treatment, of patients who subsequently developed a grade 2 or higher rash were analyzed. WBC of ATL patients who developed a grade 2 or higher rash was higher compared to that of patients who did not develop a rash or who developed a grade 1 rash ( \( P = 0.05 \), Table 3). An abnormal lymphocyte count was also significantly higher in patients who developed a grade 2 or higher rash ( \( P = 0.04 \) ). In contrast, blood hemoglobin levels and platelet counts were not significantly associated with the presence or absence of a grade 2 or higher rash. Age ( \( \geq 71 \) yrs vs \( \leq 70 \) yrs), sex (male vs female), PS (0–1 vs 2–4), presence or absence of ATL skin lesions, serum Alb ( \( \geq 3.5 \) g/dL vs \( < 3.5 \) g/dL), serum LDH ( \( \geq 2N \) vs \( \leq 2N \); LDH = 2N signifies an LDH level twice the upper limit of normal according to hospital laboratory guidelines) and an eosinophil count ( \( \leq 500/\muL \) vs \( > 500/\muL \) \( )^{20} \) were also not significantly associated with the presence or absence of a grade 2 or higher rash (Table 3).

**Discussion**

The present long-term follow up of a phase I study of mogamulizumab, four (31%) patients survived for more than 3 years, of whom three (23%) survived for at least 5 years. As for 26 patients with relapsed aggressive ATL enrolled in the phase II study, a median PFS of 5.2 months, a PFS rate at 1 year of 26%, a median OS of 14.4 months, and an OS rate at 3 years of 23% were achieved. To date, there have been no prescribed standards of care for patients with relapsed or refractory aggressive ATL, although several studies have been conducted to improve their prognosis. In a phase II study of bortezomib in relapsed or refractory aggressive ATL, a median PFS of 38 days was reported (\( n = 15^{\text{5}} \)) Antiviral therapy, consisting of a combination of zidovudine and interferon, which has been proposed as a standard first-line therapy in leukemic subtypes of ATL (\( n = 12^{\text{23}} \)) demonstrated a median OS of 3.0 months in acute or lymphoma subtypes of ATL patients who had been previously treated (\( n = 7 \)) or untreated (\( n = 12 \)). A phase II study of alemtuzumab in patients with ATL, who had been either previously treated (\( n = 20 \)) or untreated (\( n = 9 \)), has been reported. Patients consisted of 15 acute, 11 lymphoma, and three chronic subtypes, with a median PFS and OS of 2.0 and 5.9 months, respectively. \( n=24 \) Collectively, although a patient selection bias may have occurred at study enrolment, \( n=14,15 \) and a direct comparison between the two different studies may not be appropriate, some patients with relapsed aggressive ATL who were enrolled in phase I and II studies and who received mogamulizumab monotherapy actually survived for a long time. Most recently, in a phase II study of lenalidomide in relapsed or recurrent ATL in Japan, median PFS and OS of 3.8 and 20.3 months, respectively, were observed. \( n=25 \) The lenalidomide study showed a relatively longer OS despite a relatively shorter PFS and, in this context, the fact that this study was conducted in the era after mogamulizumab approval, should be kept in mind.

Although the sample size of the present study was small, a poor PS, older age, and lower serum Alb levels were not significantly associated with PFS and OS in patients with relapsed aggressive ATL. A poor PS, older age, and lower serum Alb levels were previously identified as unfavorable prognostic factors in acute or lymphoma subtype ATL patients in a large-scale retrospective analysis (ATL-P1). \( n=19 \) A poor PS was also one of the components of the JCOG-PI, \( n=26 \) which was established by three independent JCOG prospective clinical trials, \( n=27–29 \) and applied to aggressive ATL. Although these two PI were established based on ATL patients who were previously untreated, the unfavorable prognostic factors of these widely acceptable PIs \( n=26 \) were not applicable to the present, relapsed patients. We think that the most probable reason for this is that the treatment strategies applied to the patients were different. This indicates that in the era of mogamulizumab the establishment of a novel PI in ATL patients is warranted.

The present study demonstrated that the development of rashes had a positive impact not only on PFS, but also on OS. In this context, with respect to a phase I study among 13 ATL patients, one (number 412) patient developed a rash, with this patient surviving more than 5 years. These findings seem to be important, and almost consistent with other reports of retrospective analyses. \( n=30,31 \) Because CCR4 is highly expressed on effector Treg, \( n=32–34 \) mogamulizumab also has Treg depletion activities. \( n=35 \) Such Treg depletion by mogamulizumab is likely to lead to stimulation of various types of immunity such as antitumor immune responses targeting ATL-related antigens \( n=36–38 \), possibly including the neoantigens caused by the abundant mutations of ATL cells \( n=39,40 \) in addition to autoimmune responses targeting autoantigens. It appears that the former results in therapeutic efficacies such as prolonged PFS and OS, and the latter results in immune-related AE, including rashes. We should pay particular attention to the fact that severe skin-related AE, such as Stevens-Johnson syndrome/toxic epidermal necrolysis, are themselves sometimes fatal. \( n=17 \)
Fig 2. Progression-free survival (PFS) and overall survival (OS) in relapsed adult T-cell leukemia-lymphoma (ATL) patients according to the presence of skin rash. (a) PFS curves for relapsed ATL patients who did (±) did not (−) develop a skin rash are shown. For patients who did not develop a rash after 1 year, median PFS was 0.8 months (95% confidence interval [CI], 0.4–1.2 months), and PFS rate was 0%. For patients who developed rashes after 1 year, median PFS was 10.3 months (95% CI, 5.2–18.2 months), and PFS rate was 41% (95% CI, 17%–63%). (b) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash after 1 year, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (c) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash after 3 years, median OS was 5.4 months (95% CI, 3.3–10.8 months), and OS rate was 11% (95% CI, 1%–39%). For patients who developed rashes after 3 years, median OS was 18.2 months (95% CI, 6.3–39.0 months), and OS rate was 23% (95% CI, 9%–46%). (d) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (e) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a rash after 1 year, median PFS was 0.8 months (95% CI, 0.4–1.2 months), and PFS rate was 0%. For patients who developed a grade 0 skin rash after 1 year, median PFS was 10.3 months (95% CI, 5.2–18.2 months), and PFS rate was 41% (95% CI, 17%–63%). (f) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (g) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (h) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (i) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (j) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (k) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (l) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (m) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (n) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (o) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (p) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (q) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (r) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (s) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (t) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (u) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (v) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (w) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (x) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (y) PFS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%). (z) OS curves for ATL patients who did/did not develop a skin rash are shown. For patients who did not develop a rash or who developed a grade 0 skin rash after 3 years, median OS was 23.7 months (95% CI, 10.6 months–not estimated [NE]), and the OS rate was 28% (95% CI, 11%–51%).

Additionally, when severe immune-related AE occur, we are forced to implement intensive immunosuppressive therapies such as systemic steroids, which not only attenuate antitumor immune responses but can also lead to various types of severe infectious complications. Therefore, a not too mild and not too severe, but moderate, provocation of immune response seems...
Table 3. Characteristics of relapsed ATL patients according to a rash induced by mogamulizumab

| Patients’ characteristics before mogamulizumab treatment | Rash grade | P-value |
|----------------------------------------------------------|------------|---------|
| Total patients, number (%)                               |            |         |
| <70                                                      | 9 (47)     | 10 (53) | 1.00   |
| ≥71                                                      | 3 (43)     | 4 (57)  |         |
| Sex                                                      |            |         |
| Female                                                   | 6 (40)     | 9 (60)  | 0.69   |
| Male                                                     | 6 (55)     | 5 (45)  |         |
| ECOG PS                                                  |            |         |
| 0, 1                                                     | 10 (48)    | 11 (52) | 1.00   |
| 2, 3, 4                                                  | 2 (40)     | 3 (60)  |         |
| ATL skin lesion                                          |            |         |
| Absent                                                   | 8 (44)     | 10 (56) | 1.00   |
| Present                                                  | 4 (50)     | 4 (50)  |         |
| Serum Alb, g/dL                                          |            |         |
| <3.5                                                     | 10 (43)    | 13 (57) | 0.58   |
| >3.5                                                     | 2 (67)     | 1 (33)  |         |
| Serum LDH†                                               |            |         |
| ≤2N                                                      | 6 (35)     | 11 (65) | 0.22   |
| >2N                                                      | 6 (67)     | 3 (33)  |         |
| Eosinophil count/μL                                      |            |         |
| ≤500                                                     | 11 (46)    | 13 (54) | 1.00   |
| >500                                                     | 1 (50)     | 1 (50)  |         |
| WBC/μL                                                   |            |         |
| Mean                                                     | 6373       | 12 995  | 0.05   |
| Median                                                   | 4510       | 7850    |         |
| Range                                                    | 2900–16 030| 3700–40 250|        |
| Abnormal lymphocyte count/μL                             |            |         |
| Mean                                                     | 1,045      | 6108    | 0.04   |
| Median                                                   | 672        | 3587    |         |
| Range                                                    | 0–4324     | 0–30 188|         |
| Hb, g/dL                                                 |            |         |
| Mean                                                     | 11.6       | 12.1    | 0.49   |
| Median                                                   | 11.9       | 12.1    |         |
| Range                                                    | 9.0–15.3   | 8.9–15.9|        |
| Plt, × 10^3/μL                                           |            |         |
| Mean                                                     | 192        | 174     | 0.43   |
| Median                                                   | 185        | 152     |         |
| Range                                                    | 70–338     | 90–328  |         |

†LDH is expressed as a ratio in which the patient’s LDH level was divided by the upper limit of normal for LDH as set by the respective hospital laboratory. Alb, albumin; ATL, adult T-cell leukemia-lymphoma; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; LDH, lactate dehydrogenase; Plt, platelet count; PS, performance status; WBC, white blood cell count.

to be important, and is consistent with the current observations that PFS in patients who developed a grade 2 rash showed a longer trend compared to the PFS of patients who developed a grade 3 rash. The finding that the induction of a moderate immune reaction is best for patient survival is similar to GVHD after allogeneic HCT for ATL. That is, the hazard ratios for the OS of ATL patients with grade I, II, III, and IV acute GVHD compared with the absence of acute GVHD were 0.568, 0.688, 1.199, and 2.245, respectively. (41) This type of positive effect of cutaneous immune-related AE on OS has also been reported for nivolumab (an immune checkpoint inhibitor, antiprogrammed cell death protein-1 mAb) treatment of metastatic melanoma. (42)

Among the clinical characteristics of patients, prior mogamulizumab treatment, a higher WBC and higher abnormal lymphocyte count were associated with the development of a grade 2 or higher rash. Although the causal mechanisms are not fully clarified, we must pay special attention to an immune-related AE, the development of rashes, when we treat ATL patients that have high WBC and high abnormal lymphocyte counts with mogamulizumab. Simultaneously, these characteristics indicate such patients are more likely to benefit from mogamulizumab monotherapy.

A recent phase II study of lenalidomide in relapsed or recurrent aggressive ATL demonstrated promising antitumor activity. (42) Lenalidomide also has immunomodulatory effects, including stimulation of NK cell function; (43) thus when combined with antibody agents in vitro, lenalidomide enhanced ADCC by augmenting NK cells. (44) Combination therapy consisting of lenalidomide plus an antibody agent, rituximab, was active as an initial therapy for mantle cell lymphoma not only in in vitro preclinical experiments, but also in the clinic. (45) In this context, because the antitumor activity of mogamulizumab is completely dependent on ADCC, mainly by NK cells as effector cells, (42,43) combination therapy consisting of mogamulizumab plus lenalidomide should be considered as having potential in the treatment of ATL.

Although this up-to-date analysis offers novel and important findings on mogamulizumab use for ATL, several limitations should also be borne in mind. First, the previous phase I and II studies (14,15) mentioned were relatively small and, thus, definitive conclusions about the long-term efficacies on survival by mogamulizumab cannot be drawn. Second, although an allogeneic HCT is considered the only curative treatment strategy for aggressive ATL, (6,41,46) the present study did not collect data about allogeneic HCT in corresponding patients. This information seems to be important as mogamulizumab treatment prior to allogeneic HCT has been reported to be associated with an unfavorable prognosis caused by increased transplantation-related AE, mainly acute GVHD. (47)

In conclusion, this updated analysis suggests that mogamulizumab monotherapy may improve PFS and OS in some patients with relapsed aggressive ATL, especially in those with a moderate immune-related AE in the form of a skin rash. Further investigation of mogamulizumab treatment for ATL is warranted to clarify the mechanisms involved in the present observations.

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**Abbreviations**

ADCC antibody-dependent cellular cytotoxicity
AE adverse event
Alb albumin
ATL adult T-cell leukemia–lymphoma
CCCR4 CC chemokine receptor 4
CI confidence interval
CTCL cutaneous T-cell lymphoma
ECOG Eastern Cooperative Oncology Group
GVHD graft-versus-host disease
HCT hematopoietic cell transplantation
JCOG Japan Clinical Oncology Group
LDH lactate dehydrogenase
NK natural killer
OS overall survival
PFS progression-free survival
PI prognostic index
PS performance status
PTCL-NOS peripheral T-cell lymphoma, not otherwise specified
Treg regulatory T cells
WBC white blood cell count

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Fig. S1. PFS and OS of relapsed ATL patients enrolled in the phase II study according to unfavorable prognostic factors.

Fig. S2. PFS and OS in relapsed ATL patients who developed no rash or a grade 1–2 skin rash, and a grade 3 or higher skin rash.