Effects of mogamulizumab in adult T-cell leukemia/lymphoma in clinical practice

Masaaki Sekine[1], Yoko Kubuki[1], Takuro Kameda[1], Masaki Takeuchi[2], Takanori Toyama[3], Noriaki Kawano[4], Kouichi Maeda[5], Seiichi Sato[6], Junzo Ishizaki[7], Hiroshi Kawano[2], Ayako Kamiunten[1], Keiichi Akizuki[1], Yuki Tahira[1], Haruko Shimoda[1], Kotaro Shide[1], Tomonori Hidaka[1], Akira Kitanaka[8], Kiyoshi Yamashita[4], Hitoshi Matsuoka[2], Kazuya Shimoda[1]

Abstract word count: 199 words

Manuscript word count: 3339 words

Number of references: 19 references

Number of figures and tables: 2 figures and 3 tables

Number of supplemental illustration/tables: 1 supplemental figure

Running head: Mogamulizumab for ATLL

Condensed abstract:
Mogamulizumab therapy showed clinically meaningful activity in relapsed/refractory ATLL patients, with acceptable toxicity in clinical practice. Mogamulizumab improved the survival of patients with ATLL relative to a historical cohort without mogamulizumab therapy.

Proposed type of manuscript: Original article

Funding: No funding

Name of the department and institution in which the work was done:
Department of Gastroenterology and Hematology, Faculty of Medicine, University of

Miyazaki

[1]Department of Gastroenterology and Hematology, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan
[2]Koga General Hospital, 1749-1 Sudaki, Ikeuchi machi, Miyazaki 880-0041, Japan
[3]Miyazaki Prefectural Nobeoka Hospital, 2-1-10 Shinkouji, Nobeoka 882-0835, Japan
[4]Miyazaki Prefectural Miyazaki Hospital, 5-30 Kitatakamatsu, Miyazaki 880-8510, Japan
[5]Miyakonojo Medical Center, 5033-1 Iwayoshi-cho, Miyakonojo 880-8510, Japan
[6]Fujimoto Genral Hospital, 17-1 Hayasuzumachi, Miyakonojo 885-0055, Japan
[7]Miyazaki Aisenkai Nichinan hospital, 3649-2 Kazeta, Nichinan 887-0034, Japan
[8] Department of Laboratory Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192

§ Correspondence should be addressed to Kazuya Shimoda.
Department of Gastroenterology and Hematology, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan
Tel: 81-985-85-9121; Fax: 81-985-85-5194; E-mail:kshimoda@med.miyazaki-u.ac.jp

Abstract

Objective: The efficacy of mogamulizumab in ATLL was reported in a previous phase 2 study. Compared with patients in clinical trials, however, most patients in real-life settings have demonstrated worse outcomes.

Method: We retrospectively analyzed 96 patients with relapsed/refractory ATLL who received mogamulizumab treatment.

Results: Relapsed/refractory ATLL patients with a median age of 70 years received a median of five courses of mogamulizumab. Hematologic toxicity and skin rash were the most common adverse events, and both were manageable. Of 96 patients, 87 were evaluable for efficacy. The overall response rate was 36%, and the median progression-free survival (PFS) and overall survival (OS) from the start of mogamulizumab therapy were 1.8 and 4.0 months, respectively. Of the original 96 patients, only 25 fulfilled the inclusion criteria of the phase 2 study. Those who met the criteria demonstrated longer median PFS and OS durations of 2.7 and 8.5 months, respectively. The median OS from diagnosis in relapsed/refractory ATLL patients receiving mogamulizumab was 12 months, longer than the 5.8 months in a historical cohort without mogamulizumab.

Conclusion: In clinical practice, mogamulizumab exhibited antitumor activity in patients with relapsed/refractory ATLL, with an acceptable toxicity profile. Mogamulizumab therapy improved the OS of ATLL patients.

Keywords: adult T-cell leukemia/lymphoma, CCR4, mogamulizumab, retrospective, antibody therapy

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is an aggressive peripheral T-cell neoplasm characterized by the clonal proliferation of human T-cell lymphotropic virus type 1 (HTLV-1)-infected T cells (1-3). ATLL is classified into four subtypes, namely acute type, lymphoma type, chronic type, and smoldering type (4). The current standard chemotherapy for aggressive ATLLs (acute, lymphoma, or unfavorable chronic type) is the dose-intensified multidrug regimen VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone, respectively), which resulted in median progression-free survival (PFS) and overall survival (OS) of 7.0 and 12.7 months, respectively, in a phase 3 clinical trial (5). As many ATLL patients are resistant to chemotherapy and demonstrate unfavorable OS, allogenic hematopoietic stem cell transplantation (allo-HSCT) is an alternative ATLL treatment option, which was shown to result in longer survival in 30-40% of patients (6).

Mogamulizumab is a humanized anti-CC chemokine receptor 4 (CCR4) immunoglobulin G1 monoclonal antibody with a defucosylated Fc region (7), and was developed for ATLL treatment because most ATLL cells were found to express CCR4 (8, 9). A phase 2 study evaluating mogamulizumab monotherapy in relapsed ATLL patients showed an overall response rate (ORR) of 50%, and median PFS and OS of 5.2 and 13.7 months, respectively (10). The usefulness of mogamulizumab in combination with chemotherapy (VCAP-AMP-VECP) in newly diagnosed patients with aggressive ATLL patients has also been reported, with a complete response (CR) rate and ORR of 52%

and 86%, respectively, compared to 33% and 75% in patients receiving chemotherapy alone (11).

In contrast with patients in clinical trials, patients in real-life settings often have worse treatment outcomes due primarily to organ dysfunction, poor performance status (PS), and infection (12). Two studies retrospectively evaluated the effect of mogamulizumab in real-life settings, and reported ORRs of 64% and 48.7% in 14 and 33 ATLL patients, respectively (13, 14). We describe here the impact of mogamulizumab therapy in patients with relapsed/refractory ATLL in clinical practice.

Patients and methods

Patients

In this study, 101 CCR4-positive patients with aggressive ATLL (acute, lymphoma, or unfavorable chronic type) who received at least one course of mogamulizumab treatment (mogamulizumab therapy group) were enrolled from any of seven institutions within Miyazaki Prefecture, an HTLV-1 endemic area in Southwestern Japan, between May 2012 and April 2016. A historical cohort who received conventional chemotherapy without mogamulizumab therapy (historical chemotherapy group) comprised 89 patients with aggressive ATLL who received initial therapy for ATLL from 2010 to 2012 at the same seven institutions. The unfavorable chronic type of ATLL was defined by the presence of at least one of the following: low serum albumin, high lactate dehydrogenase (LDH), or high blood urea nitrogen (15).

Before the administration of mogamulizumab, the expression of CCR4 on

ATLL cells was confirmed by flow cytometry or immunohistochemical analysis in all patients. Patients received intravenous infusions of mogamulizumab once a week at a dose of 1.0 mg/kg until the loss of clinical benefit as assessed by attending physicians. Data were collected from medical records.

Adverse events (AEs) were evaluated using the National Cancer Institute Common Terminology Criteria for AEs, version 4.0 (16). For each patient, the highest toxicity grade during the entire course of treatment was recorded. Objective responses were assessed according to the modified response criteria for ATLL (15).

This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Miyazaki.

Statistical analysis

Differences between categorical variables were compared with chi-square tests. Age, LDH and soluble interleukin-2 receptor (sIL2R) levels, and corrected calcium concentrations were compared with the Wilcoxon rank-sum test because data were heavily skewed. Two-sided *P* values were assessed and those less than 0.05 were considered significant. The Kaplan-Meier method was used to estimate the probabilities of PFS and OS, and the log-rank test was used to compare PFS and OS between two or four groups. All data were analyzed using SPSS version 20 software (SPSS Inc., Chicago, IL, USA).

Results

Patients

Of 101 patients in the mogamulizumab therapy group, five received mogamulizumab as initial treatment, while the remaining 96 were relapsed or refractory to conventional chemotherapies and received mogamulizumab as salvage therapy. Of 89 patients in the historical chemotherapy group, nine demonstrated extended survival without relapse after receiving initial chemotherapy regimens, and 12 died during or just after the initial chemotherapy; the remaining 68 patients were defined in this study as relapsed/refractory ATLL patients. The clinical characteristics at diagnosis of patients in the mogamulizumab therapy group and in the historical chemotherapy group, and their initial chemotherapy regimens, are shown in Table 1. Initial chemotherapy regimens consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), THP-COP (pirarubicin, vincristine, cyclophosphamide, and prednisone), VCAP-AMP-VECP, CHOP-VMMV (cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide, vindesine, ramunistine, and mitoxantrone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin), or CHASE (cyclophosphamide, cytosine arabinoside, etoposide, and dexamethasone) therapies. More than half of patients received CHOP or a CHOP-like regimen (THP-COP) as the initial therapy, followed by VCAP-AMP-VECP or VCAP-AMP-VECP-like regimens (CHOP-VMMV).

In the overall ATLL population, the presence or absence of mogamulizumab therapy was associated with no significant differences in clinical characteristics at

diagnosis. In the relapsed/refractory cases, however, these characteristics were not identical between two groups; the median age, LDH levels, and corrected calcium concentrations at diagnosis of relapsed/refractory ATL patients in the historical chemotherapy group were higher than those in patients treated with mogamulizumab (P<0.05). There was no difference between the two groups in ATLL subtypes, sIL2R levels, or initial chemotherapy regimens.

The effect of mogamulizumab was retrospectively analyzed in 96 relapsed/refractory ATLL patients who received at least one course of mogamulizumab treatment. Their demographics and clinical characteristics at the start of mogamulizumab therapy are summarized in Table 2. The median age was 70 years (range, 45 to 90), and 50 (52%) were ≥70 years old. According to Shimoyama's criteria (4), 62 patients (65%) were classified as acute type, 32 (33%) as lymphoma type, and two (2%) as chronic type. Both patients with chronic type ATLL had at least one unfavorable risk factor (15). As the initial therapy, CHOP or a CHOP-like regimen (THP-COP) were used in 50 patients (52%) while VCAP-AMP-VECP or a VCAP-AMP-VECP-like regimen (CHOP-VMMV) were used in 41 patients (43%). Patients received an average of two regimens prior to the start of mogamulizumab.

Patients were treated with a median of five courses of mogamulizumab; 49 patients (51%) were treated with one to four courses, and the remaining 47 patients (49%) were treated with five or more courses. Mogamulizumab monotherapy was administered to 84 patients (88%), while 12 patients (12%) received combination therapy with mogamulizumab and conventional chemotherapy.

Adverse events

AEs associated with mogamulizumab therapy were analyzed (Table 3). The most common nonhematologic AE was skin rash (24%). In addition, infusion reaction and its associated AE of fever were observed in 17% and 9% of patients, respectively. All three of these AEs were transient, while skin rashes occurred after four or more infusions. Grade 3 or higher skin rashes were observed in 16% of patients, of whom 43% required systemic steroid administration. As for hematologic AEs, thrombocytopenia, neutropenia, and anemia of any grade were observed in 44%, 38%, and 53% of patients, respectively. These AEs frequently occurred in patients treated with the combination of mogamulizumab and another chemotherapy regimen. Thrombocytopenia, neutropenia, and anemia of grade 3 or higher occurred in 42%, 50%, and 33% of patients with combination therapy, respectively, and in 21%, 15%, and 17% of patients with mogamulizumab monotherapy, respectively (P=0.126, 0.04, and 0.194, respectively).

Efficacy of mogamulizumab

Of the 96 relapsed/refractory patients in the mogamulizumab therapy group, nine were excluded from the response analysis due to lack of data on response. Of the 87 patients in whom response could be evaluated, objective response was noted in 31 patients (36%), including 15 with CR (17%). According to ATLL subtypes, responses were achieved in 24 of 59 (41%) patients with acute type, and 6 of 26 (23%) with

lymphoma type. There was no statistically significant difference in ORR between these two ATLL subtypes (P=0.065). In patients who had one, two, three, or four or more prior chemotherapy regimens, the response rates were 42% (22 of 52 patients), 21% (four of 19 patients), 50% (four of eight patients), and 13% (one of eight patients), respectively (P=0.114). The ORR was 45% (five of 11 patients) in patients who received five to seven courses of mogamulizumab, and 71% (25 of 35 patients) in those who received eight or more courses. Patients with five or more courses of mogamulizumab showed superior values for both ORR and CR rate, of 65% (30 of 46 patients) and 33% (15 of 46 patients), respectively, in comparison with 2% (1 of 42 patients) and 0% (0 of 42 patients), respectively, in those who received one to four courses of mogamulizumab (P<0.001 for ORR, P<0.001 for CR rate). The ORR was higher in patients with grade 3 or higher skin rashes than in patients without skin rashes (57 % vs. 32%; P=0.02).

The median PFS and OS of the 96 relapsed/refractory cases from the start of mogamulizumab therapy were 1.8 and 4.0 months, respectively (Figure 1A). In patients who received one to four courses of mogamulizumab versus five or more courses, PFS was 0.6 versus 3.0 months (P<0.001) and OS was 1.6 versus 7.2 months (P<0.001), respectively (Figure 1B). There was no difference in PFS between patients receiving mogamulizumab monotherapy and combination therapy with mogamulizumab and chemotherapy (P=0.265), but OS from the start of mogamulizumab therapy was superior in the combination therapy group (P=0.004) (Supplemental Figure 1). Patients achieving CR had median PFS of 13.2 months, which was longer than that of patients

with PR or SD (P<0.001). Since the median PFS and OS from the start of mogamulizumab therapy in our cohort were much shorter than those in the reported phase 2 study (12), we evaluated them in view of our sample's baseline characteristics. Only 25 patients (26%) in our cohort fulfilled the phase 2 study's inclusion criteria (10), which included the following laboratory and systemic values: PS 0–2, absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥50 x 10^9/L, Hb ≥8 g/dL, aspartate aminotransferase ≤2.5 x the upper limit of the normal range (UNL), alanine aminotransferase ≤2.5 x UNL, total bilirubin ≤1.4 x UNL, creatinine ≤1.5 x UNL, corrected calcium concentration ≤1.1 mg/dL, arterial partial oxygen pressure ≥65 mmHg, no central nervous system involvement, no active infection, no bulky mass, no seropositivity for hepatitis B or C viruses or for human immunodeficiency virus, and no concurrent cancers. Among the patients who met these criteria, the median PFS and OS from the start of mogamulizumab therapy were 2.7 and 8.5 months, respectively, which were longer than the corresponding values, 1.3 and 3.0 months, among patients who did not meet the criteria (P=0.039 and P=0.053, respectively) (Figure 1C).

We next compared OS from diagnosis between the mogamulizumab therapy group and the historical chemotherapy group. In relapsed/refractory ATLL patients, the use of mogamulizumab improved OS from diagnosis; the median OS in cases receiving mogamulizumab therapy was 12 months, which was significantly longer than the 5.8 months in the historical chemotherapy group who did not receive mogamulizumab therapy (P<0.001) (Figure 2A). A positive effect of mogamulizumab on prognosis was also observed in the entire population, that is, the mogamulizumab therapy group

(n=101). This group included five patients who received mogamulizumab as the initial treatment. The historical chemotherapy group without mogamulizumab (n=89) included eight survivors who received only initial chemotherapy and 13 who died early during initial chemotherapy. As shown in Figure 2B, the use of mogamulizumab significantly improved OS from diagnosis in all cases, from a median of 7.9 months in the patients who did not receive mogamulizumab therapy to 13 months in those who did (P=0.002).

Discussion

This retrospective analysis demonstrated the therapeutic efficacy of mogamulizumab for the treatment of ATLL in clinical practice. Mogamulizumab exhibited promising antitumor activity, and its use improved OS this patient population.

There are several limitations to this study, including its retrospective design and missing data. In the entire ATLL population, the presence or absence of mogamulizumab therapy was associated with no significant differences in clinical characteristics at diagnosis. However, such differences were observed between relapsed/refractory cases in the mogamulizumab group versus the historical chemotherapy group, which made it difficult to draw definitive conclusions on survival.

Compared to patients in the phase 2 study (10) and reports in real-life settings (13, 14), our mogamulizumab therapy group consisted of more elderly patients and those with poor PS, and they received fewer courses of mogamulizumab. The median age and the proportion of PS 3–4 patients at the start of mogamulizumab therapy in this group were 70 years and 29%, respectively, which were higher than the 64 years and

0%, respectively, in the clinical phase 2 study (10). The median age in our cohort (66.7) was even higher than the two previous studies in real-life settings (13, 14). Simmilary, the proportion of PS 3–4 patients was higher in our cohort compared to one of those studies (29% vs 15.2%) (14). The median number of mogamulizumab courses in our cohort was five, which was fewer than the eight, eight, and seven, respectively, in the clinical phase 2 study (10) and the two studies in real-life settings (13, 14).

AEs associated with mogamulizumab therapy seemed to be neither frequent nor severe, considering that the majority of patients in this study had poor overall status. Infusion reactions and related symptoms such as fever, chills, and tachycardia are the most common AEs associated with mogamulizumab therapy, experienced by as many as 89% of patients in the phase 2 study (10). The frequencies of these AEs were lower in our cohort, however. Due to the retrospective nature of our study, prophylaxis for infusion reactions was administered at the discretion of each attending physician rather than according to a unified protocol. We are not sure at this time why infusion reactions and their related symptoms were lower in clinical practice.

In our cohort, skin rashes were the most frequently observed AEs associated with mogamulizumab therapy. Mogamulizumab treatment was previously found to result in a reduction of $CD4^+CD25^+FOXP3^+$ regulatory T cells (10). CCR4 is required for lymphocyte skin-specific homing (17), and skin lesions are considered to be immune-related AEs and have been reported to correlate with better response. In the reported phase 2 study (10), all 14 patients who received five or more courses of mogamulizumab treatment experienced grade 2 or higher skin rashes, whereas in our

cohort such rashes developed in only 26% of patients with five or more courses of mogamulizumab. As for hematologic AEs, when analysis was confined to patients with mogamulizumab monotherapy, grade 2 or higher thrombocytopenia or neutropenia were not as frequent in our cohort as in the phase 2 study. Currently we are unable to explain these differences, but we consider that mogamulizumab therapy should be safe in clinical practice.

ATLL patients receiving mogamulizumab therapy showed significant responses in clinical practice; the vast majority of these patients were previously chemotherapy resistant or intolerant. The ORR was 36%, and 17% of patients achieved CR. These values were lower than those in the reported phase 2 study, in which the ORR and CR rate were reported to be 50% and 31%, respectively (10). The ORR in our cohort was also lower than in two previous studies in real-life settings in which the ORRs were 64% and 48.7% in 14 and 33 ATLL patients, respectively (13, 14). One reason for the lesser effect in our cohort might be that our population received fewer mogamulizumab courses (a median of five courses in our cohort vs. eight, eight, and seven courses in the clinical phase 2 study (10) and the two studies in real-life settings (13, 14), respectively). In our cohort, only 36% of patients received eight or more courses, whereas in the phase 2 study 52% of patients received at least eight courses (10). In our study, the patients who received eight or more courses of mogamulizumab had a better ORR, 71%, than those who received fewer.

Another reason for the reduced effect of mogamulizumab in our cohort might be that patients in clinical practice often have primary organ dysfunction, poor PS, and

infections, in contrast with patients in clinical studies (12). In fact, only 26% of the patients in our cohort fulfilled the inclusion criteria of the mogamulizumab phase 2 study (10). In this subgroup, the ORR and CR rate were higher at 48% and 26%, respectively. Further, the median number of mogamulizumab courses in the patients who met the phase 2 study inclusion criteria was eight, compared to four in the patients who did not (P=0.006). The greater number of mogamulizumab courses in the patients with better status might have contributed to their relatively better response.

In the phase 2 study (10), higher rates of objective response to mogamulizumab were reported in patients with grade 2 or higher skin rashes (93% (13 of 14 patients)) compared to those without (10). This tendency was also observed in our cohort, however the ORR in patients with grade 2 or higher skin rashes was only 61%. When the analysis was restricted to patients with five or more mogamulizumab courses who experienced grade 2 or higher skin rashes, the ORR was 91%. We should also mention that objective responses were observed in 29% of patients without skin rashes, indicating that mogamulizumab has some effect even if skin rashes are absent. In terms of disease site, the previous study reported a higher ORR and CR rate in cases with involvement of blood and bone marrow (10), but we could not identify this pattern.

As for the survival effect of mogamulizumab in ATLL patients, we found a lesser benefit compared to that reported in the phase 2 study (10). The survival in our cohort (PFS of 1.8 months and OS of 4.0 months from the start of mogamulizumab therapy) was much shorter than that in the reported phase 2 study (PFS of 5.2 months and OS of 13.7 months) (10). Patients who fulfilled the phase 2 study inclusion criteria

had better PFS and OS from the start of mogamulizumab therapy, at 2.7 months and 8.5 months, respectively. The prognosis was worse in patients who did not fulfill the phase 2 study inclusion criteria, with PFS of 1.3 months and OS from the start of mogamulizumab therapy of 3.0 months, but we should note that these patients were refractory or resistant to previous chemotherapy and were usually not candidates for allo-HSCT because of their poor general status.

To clarify whether mogamulizumab therapy has some survival benefit for ATLL patients in clinical practice, where more than two-thirds of patients do not meet the phase 2 study inclusion criteria (10), we compared OS from diagnosis in patients with at least one course of mogamulizumab treatment with that in a historical cohort of patients without mogamulizumab treatment. In clinical practice, the use of mogamulizumab prolonged ATLL patients' survival by 6.2 months in refractory/relapsed cases and by 5.1 months in the entire cohort. Mogamulizumab had a more positive effect on the prognosis in relapsed/refractory cases. As mentioned above, the clinical characteristics at diagnosis in relapsed/refractory ATLL patients were not the same between the mogamulizumab treatment group and the historical chemotherapy cohort who did not receive mogamulizumab. The median age, LDH levels, and corrected calcium concentrations were higher in the relapsed/refractory ATLL patients in the historical chemotherapy cohort. In previous studies, advanced age (18) and higher corrected calcium concentrations (19) were reported to be adverse prognostic factors for survival in ATLL. Although the use of mogamulizumab prolonged survival in both the entire cohort and just the relapsed/refractory cases, differences in these baseline

characteristics may have resulted in the more positive effect of mogamulizumab on prognosis in the relapsed/refractory cases. Recently, Iyama et al. also reported that mogamulizumab therapy improved OS, from a median of 240 days to 382 days (14).

In conclusion, mogamulizumab therapy showed acceptable toxicity and clinically meaningful anti-ATLL activity in ATLL patients in clinical practice.

COI：We have no financial relationships to disclose.

References

1. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood. 1977; **50**(3): 481-92.

2. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008; **26**(25): 4124-30.

3. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Adult T-cell leukaemia/lymphoma (ed. by Swerdlow, S.H. et al.). IARC press. 2008; **Lyon**: 281-84.

4. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984-87). Br J Haematol. 1991; **79**(3): 428-37.

5. Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, Takatsuka Y, Ikeda S, Masuda M, Nagoshi H, Ueda R, Tamura K, Sano M, Momita S, Yamaguchi K, Kawano F, Hanada S, Tobinai K, Shimoyama M, Hotta T, Tomonaga M. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol. 2007; **25**(34): 5458-64.

6. Utsunomiya A, Miyazaki Y, Takatsuka Y, Hanada S, Uozumi K, Yashiki S, Tara M, Kawano F, Saburi Y, Kikuchi H, Hara M, Sao H, Morishima Y, Kodera Y, Sonoda S, Tomonaga M. Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001; **27**(1): 15-20.

7. Ito A, Ishida T, Yano H, Inagaki A, Suzuki S, Sato F, Takino H, Mori F, Ri M, Kusumoto S, Komatsu H, Iida S, Inagaki H, Ueda R. Defucosylated anti-CCR4 monoclonal antibody exercises potent ADCC-mediated antitumor effect in the novel tumor-bearing humanized NOD/Shi-scid, IL-2Rgamma(null) mouse model. Cancer Immunol Immunother. 2009; **58**(8): 1195-206.

8. Yoshie O, Fujisawa R, Nakayama T, Harasawa H, Tago H, Izawa D, Hieshima K, Tatsumi Y, Matsushima K, Hasegawa H, Kanamaru A, Kamihira S, Yamada Y. Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood. 2002; **99**(5): 1505-11.

9. Yamamoto K, Utsunomiya A, Tobinai K, Tsukasaki K, Uike N, Uozumi K, Yamaguchi K, Yamada Y, Hanada S, Tamura K, Nakamura S, Inagaki H, Ohshima K, Kiyoi H, Ishida T, Matsushima K, Akinaga S, Ogura M, Tomonaga M, Ueda R. 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**(9): 1591-8.

10. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, Saburi Y, Miyamoto T, Takemoto S, Suzushima H, Tsukasaki K, Nosaka K, Fujiwara H, Ishitsuka K, Inagaki H, Ogura M, Akinaga S, Tomonaga M, Tobinai K, Ueda R. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol. 2012; **30**(8): 837-42.

11. Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, Uike N, Saburi Y, Nosaka K, Utsunomiya A, Tobinai K, Fujiwara H, Ishitsuka K, Yoshida S, Taira N, Moriuchi Y, Imada K, Miyamoto T, Akinaga S, Tomonaga M, Ueda R. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol. 2015; **169**(5): 672-82.

12. Matsunaga T, Yamashita K, Kubuki Y, Toyama T, Imataki O, Maeda K, Kawano N, Satou S, Kawano H, Ishizaki J, Yoshida S, Kameda T, Sasaki T, Sekine M, Kamiunten A, Taniguchi Y, Hidaka T, Katayose K, H KS, Shide K, Yamamoto S, Moritake H, Nunoi H, Makino S, Kitanaka A, Matsuoka H, Shimoda K. Acute myeloid leukemia in clinical practice: a retrospective population-based cohort study in Miyazaki Prefecture, Japan. Int J Hematol. 2012; **96**(3): 342-9.

13. Kawano N, Kuriyama T, Sonoda KH, Yoshida S, Yamashita K, Ochiai H, Shimoda K, Ishikawa F, Ueda A, Kikuchi I. Clinical Impact of a Humanized CCR4 Antibody (Mogamulizumab) in 14 Patients with Aggressive Adult T-cell Leukemia-lymphoma Treated at a Single Institution During a Three-year Period (2012-2014). Intern Med. 2016; **55**(11): 1439-45.

14. Iyama S, Sato T, Ohnishi H, Kanisawa Y, Ohta S, Kondo T, Mori A, Tsutsumi Y, Kuroda H, Kakinoki Y, Yamamoto S, Takahashi T, Shindo M, Torimoto Y, Sato K, Iwasaki H, Haseyama Y, Kohda K, Nagamachi Y, Hirayama Y, Sakai H, Hirata Y, Fukuhara T, Ikeda H, Kobune M, Kato J, Kurosawa M. A Multicenter Retrospective Study of Mogamulizumab Efficacy in Adult T-Cell Leukemia/Lymphoma. Clin Lymphoma Myeloma Leuk. 2016.

15. Tsukasaki K, Hermine O, Bazarbachi A, Ratner L, Ramos JC, Harrington W, Jr., O'Mahony D, Janik JE, Bittencourt AL, Taylor GP, Yamaguchi K, Utsunomiya A, Tobinai K, Watanabe T. Definition, prognostic factors, treatment, and response criteria of adult T-cell

leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol. 2009; **27**(3): 453-9.

16. Institute NC. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC). NIH. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

17. Campbell JJ, Haraldsen G, Pan J, Rottman J, Qin S, Ponath P, Andrew DP, Warnke R, Ruffing N, Kassam N, Wu L, Butcher EC. The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. Nature. 1999; **400**(6746): 776-80.

18. Katsuya H, Yamanaka T, Ishitsuka K, Utsunomiya A, Sasaki H, Hanada S, Eto T, Moriuchi Y, Saburi Y, Miyahara M, Sueoka E, Uike N, Yoshida S, Yamashita K, Tsukasaki K, Suzushima H, Ohno Y, Matsuoka H, Jo T, Suzumiya J, Tamura K. Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. J Clin Oncol. 2012; **30**(14): 1635-40.

19. Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K. Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A). Br J Haematol. 2014; **166**(5): 739-48.

Table 1. Clinical characteristics at diagnosis of patients with or without mogamulizumab therapy

Characteristic	All patients			Relapsed/refractory patients		
	Mogamulizumab		P Value	Mogamulizumab		P Value
	Yes (n=101)	No (n=89)		Yes (n=96)	No (n=68)	
Age (years)						
Median (Range)	68 (45-90)	72 (44-92)	0.128	68 (45-90)	75 (51-92)	0.04
Sex						
Male	49(49%)	53 (60%)	0.233	47(49%)	29 (43%)	0.289
Female	52(51%)	36 (40%)		49(51%)	39 (57%)	
Subtype of ATL						
Unfavorable chronic	3 (3%)	0 (0%)	0.123	2 (2%)	0 (0%)	0.482
Acute	66 (65%)	57 (64%)		62 (65%)	44 (65%)	
Lymphoma	32 (32%)	32 (36%)		32 (33%)	24 (35%)	
LDH						
Median (Range)	429 (159-10,680)	520 (155-21,129)	0.163	429 (159-10,680)	539 (177-21,129)	0.044
sIL2R						
Median (Range)	16,000 (606-262,449)	17,300 (1,210-246,000)	0.454	15,100 (606-262,449)	18,450 (1,830-24,600)	0.510
Corrected calcium						
Median (Range)	9.6 (8.3-17.3)	9.83 (8.7-21.2)	0.053	9.6 (8.3-17.3)	10.56 (9.0-21.2)	0.038
Initial chemotherapy						
CHOP or CHOP-like regimen	50 (52%)	47 (53%)	0.186	50 (52%)	36 (53%)	0.080
VCAP-AMP-VECP or VCAP-AMP-VECP-like regimen	41 (43%)	31 (35%)		41 (43%)	22 (32%)	
Others	5* (5%)	11 (12%)		5 (5%)	10 (15%)	

* Five patients who received mogamulizumab as initial therapy were not included in the “others” category.

Table 2. Patient demographics and clinical characteristics at the start of mogamulizumab therapy (n=96)

Characteristic	No.	%
Age, years		
Median	70	
Range	45-90	
≥70	50	52
ECOG PS		
0	19	20
1	26	27
2	23	24
3-4	28	29
Prior chemotherapy regimens. No.		
1	56	58
2	22	23
3	8	8
≥4	10	11
Mogamulizumab cycle. No.		
1-4	49	51
5-7	12	13
≥8	35	36
Type of treatment		
Mogamulizumab monotherapy	84	88
Mogamulizumab with chemotherapy	12	12

Abbreviation:ECOG, Eastern Cooperative Oncology Group.

Table 3. Treatment-emergent adverse events

Adverse Event	Grade, No. of patients				All Grades		≧Grade3	
	1	2	3	4	No. of patients	%	No. of patients	%
Nonhematologic								
Infusion reaction	9	6	0	0	15	17	0	0
Fever	5	3	0	0	8	9	0	0
Rash	3	4	14	0	21	24	14	16
AST	0	0	1	0	1	1	1	1
Hypoxemia	1	0	0	0	1	1	0	0
Hematologic								
Thrombocytopenia	10	7	11	10	38	44	21	24
Neutropenia	14	2	6	11	33	38	17	20
Anemia	12	17	17	0	46	53	17	20

Figure legends

Figure 1. PFS (upper panel) and OS (lower panel) from the start of mogamulizumab therapy in patients with ATLL.

(A) All patients. (B) Patients categorized by number of mogamulizumab courses. (C) Patients categorized by eligibility for phase 2 study inclusion.

Figure 2. OS from diagnosis in patients with or without mogamulizumab.

(A) Relapsed/refractory patients. (B) All patients.

Supplemental Figure 1.

PFS (upper panel) and OS (lower panel) from the start of mogamulizumab therapy in patients with ATLL.

(A) Patients categorized by type of therapy (monotherapy vs. combination therapy). (B) Patients categorized by response to mogamulizumab therapy.

Figure 1

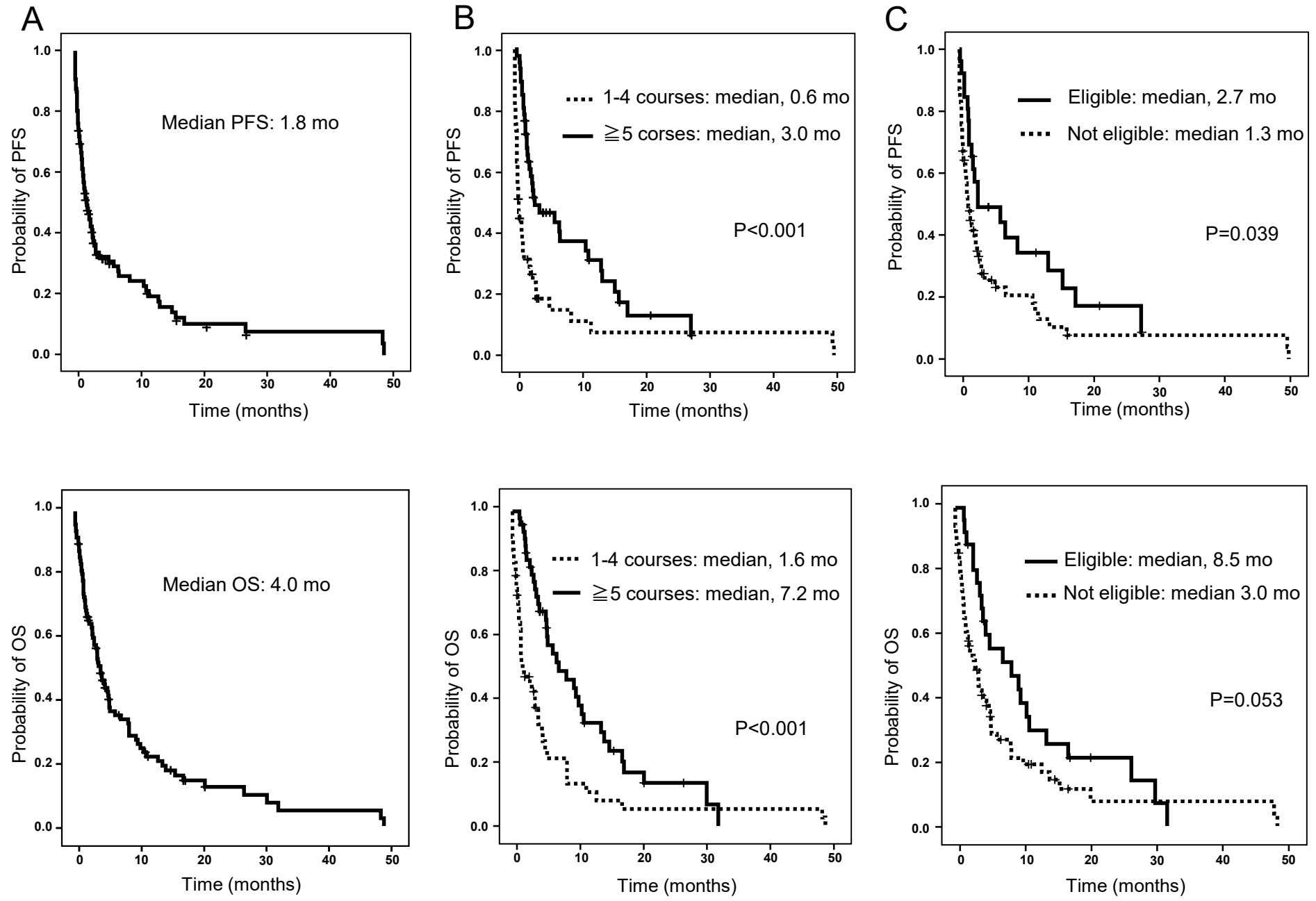
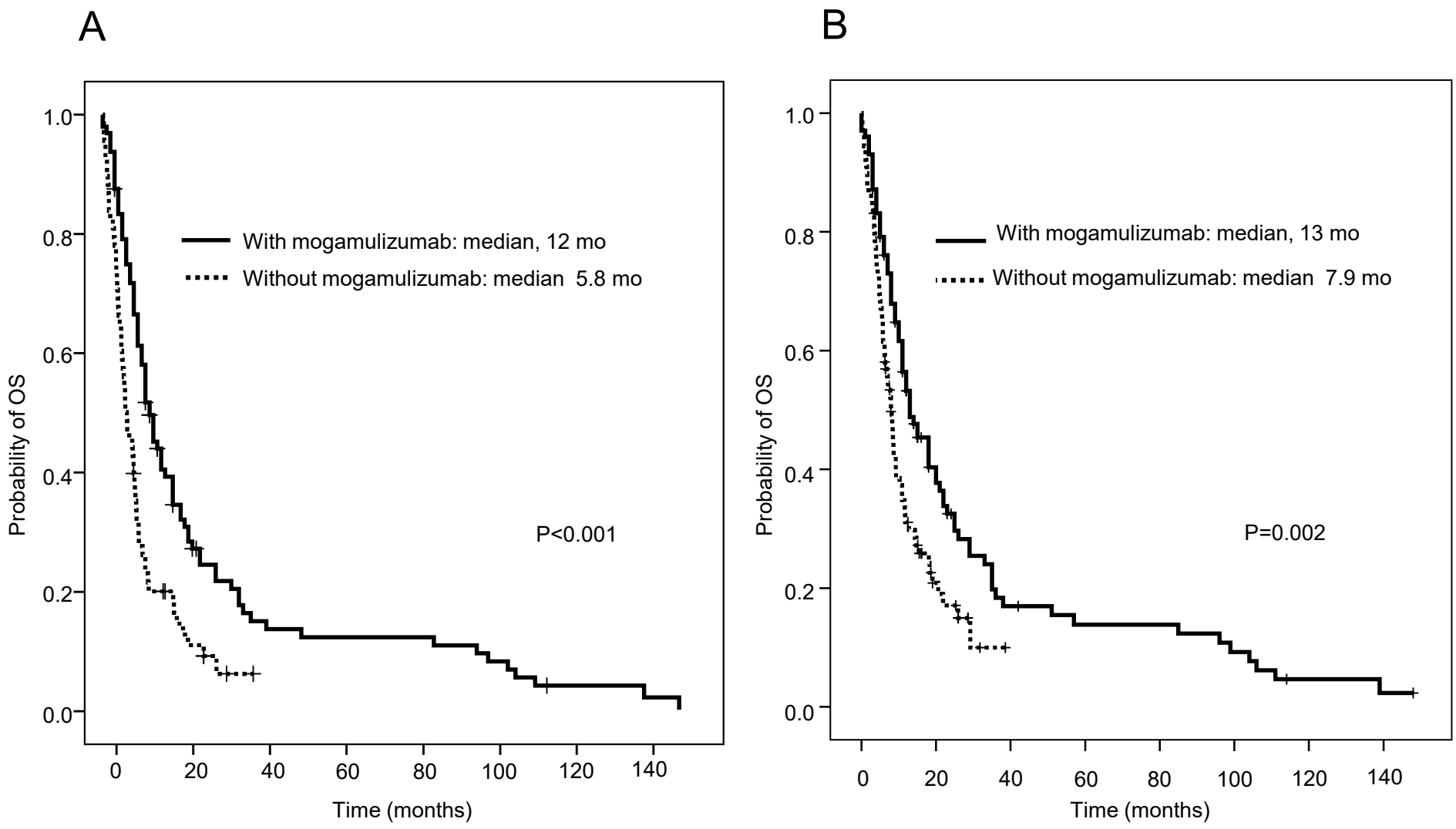

A
Median PFS: 1.8 mo
Probability of PFS
Time (months)
B
1-4 courses: median, 0.6 mo
≧5 corses: median, 3.0 mo
P<0.001
Probability of PFS
Time (months)
C
Eligible: median, 2.7 mo
Not eligible: median 1.3 mo
P=0.039
Probability of PFS
Time (months)
Median OS: 4.0 mo
Probability of OS
Time (months)
1-4 courses: median, 1.6 mo
≧5 courses: median, 7.2 mo
P<0.001
Probability of OS
Time (months)
Eligible: median, 8.5 mo
Not eligible: median 3.0 mo
P=0.053
Probability of OS
Time (months)

Figure 2


A
B
1.0
0.8
0.6
0.4
0.2
0.0
Probability of OS
With mogamulizumab: median, 12 mo
Without mogamulizumab: median 5.8 mo
P<0.001
With mogamulizumab: median, 13 mo
Without mogamulizumab: median 7.9 mo
P=0.002
0
20
40
60
80
100
120
140
Time (months)

Supplemental Figure 1