

Mogamulizumab versus investigator's choice of chemotherapy regimen in relapsed/refractory adult T-cell leukemia/lymphoma



Adrienne A. Phillips,¹ Paul A. Fields,² Olivier Hermine,³ Juan C. Ramos,⁴ Brady E. Beltran,⁵ Juliana Pereira,⁶ Farooq Wandroo,⁷ Tatyana Feldman,⁸ Graham P. Taylor,⁹ Ahmed Sawas,¹⁰ Jeffrey Humphrey,¹¹ Michael Kurman,¹¹ Junji Moriya,¹¹ Karen Dwyer,¹¹ Mollie Leoni,¹¹ Kevin Conlon,¹² Lucy Cook,¹³ Jason Gonsky¹⁴ and Steven M. Horwitz;¹⁵ on behalf of the 0761-009 Study Group

¹Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA; ²Department of Haematology Guy's and St Thomas' Hospitals NHS Trust Hospital, London, UK; ³Department of Hematology, Necker University Hospital, Paris, France; ⁴Division of Hematology/Oncology, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, FL, USA; ⁵Hospital Nacional Edgardo Rebagliati Martins and Centro de Investigación de Medicina de Precisión, Universidad de San Martín de Porres, Lima, Peru; ⁶Department of Hematology, University of São Paulo, Brazil; ⁷Sandwell and West Birmingham Hospitals NHS Trust, West Bromwich, and University of Birmingham, UK; ⁸John Theurer Cancer Center, Hackensack UMC, NJ, USA; ⁹National Centre for Human Retrovirology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK; ¹⁰Center for Lymphoid Malignancies, Columbia University Irving Medical Center, New York, NY, USA; ¹¹Kyowa Kirin, Princeton, NJ, USA; ¹²Warren Grant Magnuson Clinical Center, National Cancer Institute, Bethesda, MD, USA; ¹³Department of Haematology and National Centre for Human Retrovirology, Imperial College Healthcare NHS Trust, London, UK; ¹⁴Division of Hematology/Oncology, Department of Medicine, New York City Health + Hospitals/Kings County and SUNY Downstate Medical Center, Brooklyn, NY, USA and ¹⁵Hematology/Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Haematologica 2019
Volume 104(5):993-1003

ABSTRACT

Mogamulizumab, a humanized defucosylated anti-C-C chemokine receptor 4 monoclonal antibody, has been approved in Japan for the treatment of C-C chemokine receptor 4-positive adult T-cell leukemia/lymphoma (ATL). This phase II study evaluated efficacy and safety of mogamulizumab in ATL patients with acute, lymphoma, and chronic subtypes with relapsed/refractory, aggressive disease in the US, Europe, and Latin America. With stratification by subtype, patients were randomized 2:1 to intravenous mogamulizumab 1.0 mg/kg once weekly for 4 weeks and biweekly thereafter (n=47) or investigator's choice of chemotherapy (n=24). The primary end point was confirmed overall response rate (cORR) confirmed on a subsequent assessment at 8 weeks by blinded independent review. ORR was 11% (95%CI: 4-23%) and 0% (95%CI: 0-14%) in the mogamulizumab and chemotherapy arms, respectively. Best response was 28% and 8% in the respective arms. The observed hazard ratio for progression-free survival was 0.71 (95%CI: 0.41-1.21) and, after *post hoc* adjustment for performance status imbalance, 0.57 (95%CI: 0.337-0.983). The most frequent treatment-related adverse (grade ≥ 3) events with mogamulizumab were infusion-related reaction and thrombocytopenia (each 9%). Relapsed/refractory ATL is an aggressive, poor prognosis disease with a high unmet need. Investigator's choice chemotherapy did not result in tumor response in this trial; however, mogamulizumab treatment resulted in 11% cORR, with a tolerable safety profile. Trial registered at *clinicaltrials.gov* identifier: 01626664.

Correspondence:

ADRIENNE A. PHILLIPS
adp9002@med.cornell.edu

Received: August 22, 2018.

Accepted: December 18, 2018.

Pre-published: December 20 2018.

doi:10.3324/haematol.2018.205096

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/104/5/993

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Introduction

Adult T-cell leukemia/lymphoma (ATL) is an aggressive, rare, peripheral T-cell lymphoma (PTCL) caused by human T-cell lymphotropic virus type I (HTLV-1).¹⁻⁵ Approximately 2-7% of people infected with HTLV-1 develop ATL, often after decades of infection.⁶ HTLV-1 is endemic in Southern Japan, the Caribbean, Central and South America, Central and South Africa, parts of the Middle East and Melanesia, and aboriginal regions of Australia.⁷ In non-endemic areas such as North America and Europe, HTLV-1 infection and ATL have been linked to immigration from endemic areas.⁸⁻¹⁰ It is estimated that ATL accounts for 0.2% of lymphomas in the US but as many as 37% in Kyushu, Japan.¹¹ Compared to other subtypes of PTCL, ATL has the worst prognosis with 5-year overall survival (OS) of 14%.⁵

Adult T-cell leukemia/lymphoma is classified as smoldering, chronic, lymphoma, and acute subtypes.¹² In Japan, aggressive subtypes of ATL (acute and lymphoma) have a poor prognosis with median OS of around 12 months, even with intensive chemotherapy regimens.¹³ A long-term retrospective study has shown that even the indolent subtypes of ATL (smoldering, chronic) have a poorer than expected prognosis with median survival of only 4.1 years.¹⁴

Outside Japan, there is no approved treatment for ATL. In a retrospective series of 89 ATL patients at three New York City medical centers, median OS across subtypes was approximately 6 months.¹⁵ Allogeneic stem cell transplantation (allo-SCT) can significantly prolong survival, but there are few appropriate candidates because of age, availability of a stem cell source, lack of adequate response to primary therapy, and/or absence of effective agents in the relapsed/refractory setting.¹⁶⁻¹⁸

Almost all patients ($\geq 90\%$) with ATL over-express C-C chemokine receptor 4 (CCR4) on tumor cells.^{19,20} Mogamulizumab is a first-in-class defucosylated humanized IgG1 kappa monoclonal antibody that selectively binds to CCR4 and has enhanced antibody-dependent cellular cytotoxicity (ADCC) activity.²¹ Mogamulizumab is approved in Japan for the treatment of relapsed/refractory CCR4⁺ ATL on the basis of a phase II trial showing a 50% overall response rate (ORR) in a relapsed population.²² It was subsequently approved for chemotherapy-naïve CCR4⁺ ATL on the basis of a randomized phase II trial in combination with the mLSG15 regimen.²³

In order to study mogamulizumab outside Japan, we conducted a phase II randomized trial of mogamulizumab monotherapy compared to investigator's choice of chemotherapy in patients with relapsed/refractory ATL and, herein, report the results.

Methods

Patients

Patients ≥ 18 years of age with a confirmed diagnosis of ATL (HTLV-1 antibody positive) who met criteria for the acute, lymphoma, or chronic ATL subtypes¹² and who were refractory or relapsed after at least one prior systemic therapy were eligible to enroll [chronic patients were retrospectively designated favorable or unfavorable based on serum BUN, lactate dehydrogenase (LDH) and albumin levels]. Disease had to be evident in at least one compartment: lymph nodes, extranodal masses, spleen, liver,

skin, peripheral blood, or bone marrow. Patients were required to be Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , with adequate hematologic, hepatic, and renal function. Patients were excluded if they had a history of allo-SCT, active concurrent cancers, or central nervous system (CNS) involvement. Patients randomized to the investigator's choice arm could not receive a regimen that they had previously received or to which they had a contraindication.

Because the disease is aggressive, refractory patients enrolled early in the study had difficulty completing the first treatment cycle. To enroll a population able to receive adequate drug exposure and more likely to be able to benefit from treatment, the protocol was amended to exclude patients with acute or lymphoma subtypes who had received >2 prior systemic therapy regimens and had not achieved a response or maintained stable disease ≥ 12 weeks on immediate prior therapy.

The trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization consolidated good clinical practice guideline, and any applicable national and local laws and regulations. The protocol was reviewed and approved by institutional review boards or independent ethics committees at each site. All patients provided written informed consent.

Study design

This was an international, multicenter, open-label, randomized study conducted at 22 centers (see *Online Supplementary Appendix*) in Belgium, Brazil, France, Martinique, Peru, the UK, and the US; 18 centers screened and 17 randomized patients. A Steering Committee selected investigator's choice regimens: pralatrexate, GemOx (gemcitabine and oxaliplatin), or DHAP (dexamethasone, cisplatin, and cytarabine) which were appropriate for a relapsed/refractory population. Eligible patients were randomized 2:1 to mogamulizumab or investigator's choice arms with stratification by ATL subtype (acute, chronic, or lymphoma). Patients who progressed in the investigator's choice arm were permitted to cross over to mogamulizumab.

The primary objective of the study was to determine the ORR of mogamulizumab that persisted and was confirmed at a subsequent response evaluation, 8 weeks after initial response (confirmed ORR, cORR). Secondary objectives were to compare cORR, progression-free survival (PFS), OS, time to response, and duration of response (DoR) between the treatment arms and to assess safety.

Drug administration

Mogamulizumab 1.0 mg/kg was administered by intravenous (IV) infusion over ≥ 1 hour (h) once weekly during the first cycle (days 1, 8, 15 and 22 of the first 28-day cycle) and on days 1 and 15 of subsequent cycles without dose modification. Pralatrexate 30 mg/m² was administered IV over 3-5 minutes (min) once weekly for 3 weeks followed by 1 week without.²⁴ GemOx comprised IV gemcitabine 1000 mg/m² over 30 min followed by IV oxaliplatin 100 mg/m² over 2 h every 2 weeks. DHAP comprised IV dexamethasone 40 mg over 5-15 min on days 1 to 4 and IV cisplatin 100 mg/m² over 24 h on day 1 followed by IV cytarabine 2000 mg/m² over 3 h immediately after cisplatin and again 12 h later on day 2 every 4 weeks. For investigator's choice regimens, dose modifications were permitted and applicable treatment recommendations followed according to local prescribing information. Treatment continued until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.

Assessments

Efficacy was determined by an independent, blinded review

(Independent Review) and by the investigators (Investigator Assessment). Response, stringently and globally evaluated in six potential disease compartments (blood, skin, lymph nodes, extranodal masses, liver/spleen, and bone marrow), was determined according to published response criteria for ATL²⁵ that assessed skin *via* modified Severity Weighted Assessment Tool; lymph nodes, extranodal masses, liver, and spleen by PET and/or CT; and bone marrow by biopsy at baseline and to confirm PD or CR; central flow cytometry rather than morphology was used for blood evaluation. Response was determined at the end of the first treatment cycle and every 8 weeks thereafter. cORR required confirmation and maintenance of response at the next successive evaluation. Best response included all responses at any time point. PFS, OS, time to response, and DoR were defined according to standard methods.

Adverse events (AEs) were coded by Medical Dictionary for Regulatory Activities, v.15.0 and graded using the National Cancer Institute Common Terminology Criteria v.4.0. For patients receiving mogamulizumab who developed a grade 2 or greater skin rash, treatment was to be interrupted and the rash treated with topical steroids.

Validated electrochemiluminescence immunoassays were used to determine anti-mogamulizumab and neutralizing anti-mogamulizumab antibodies. Correlative studies were done to study mogamulizumab pharmacokinetics and neutralizing antibody. CCR4 expression status was determined by flow cytometry in patients with blood disease (CD45⁺CD4⁺CD25⁺CCR4⁺CD7⁻ $\geq 5\%$ considered positive) or by immunohistochemistry (positive value defined as $\geq 10\%$) in those without blood involvement.

Statistical analysis

The sample size was estimated based on a feasible accrual of approximately 70 patients, which was predicted to require 3 years. The primary end point, cORR by Independent Review, was estimated using an exact 95% confidence interval (CI). The mogamulizumab arm sample size (n=47) was chosen to yield a maximum width of a 95%CI on ORR to be <30%. This does not assume a target value for ORR due to the rarity of ATL and the lack of published efficacy data for the investigator's choice options in the relapsed and refractory setting. With 2:1 randomization approximately 23 patients would be enrolled in the investigator's choice arm.

All analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC, USA). Comparison of cORR between treatment arms was performed using an exact 95% unconditional confidence for the risk difference. Survival estimates were calculated using the Kaplan-Meier method. PFS and OS were analyzed using Cox proportional hazards models, and, if data warranted, for PFS using a multivariate Cox proportional model adjusting for selected potential prognostic factors. Other results are shown descriptively.

Results

Patients

A total of 71 patients were enrolled to the mogamulizumab (n=47) and investigator's choice (n=24) arms between August 2012 and May 2015 (Figure 1). Two patients, both in the mogamulizumab arm, remained on treatment at time of efficacy data cut-off on March 31, 2016. A final data cut-off for survival data was made on December 31, 2017. Investigator's choice regimens were GemOx (n=21), pralatrexate (n=2), and DHAP (n=1). All 71 randomized patients were included in the intent-to-treat (ITT) and safety populations. Eighteen of the 24

patients (75%) from the investigator's choice arm crossed over to receive mogamulizumab as administered in the randomized study.

Characteristics of the randomized patients are shown in Table 1. Despite randomization, there were imbalances between the treatment arms in known prognostic factors.¹⁵ The mogamulizumab arm had a higher median age (55.0 vs. 50.5 years), with a consequently higher proportion of patients aged >65 years (23% vs. 4%) and fewer aged <40 years (13% vs. 29%) compared to the investigator's choice arm. More patients had an ECOG performance status of 2 in the mogamulizumab arm (40% vs. 29%). In addition, patients randomized to investigator's choice of chemotherapy were more likely to have been responsive to their most immediate prior therapy *versus* those randomized to mogamulizumab (46% vs. 26%, respectively) and were less likely to have bone marrow involvement (33% vs. 57%). The treatment arms were well balanced with respect to other characteristics including gender, geographical region, ATL subtype, and prior ATL regimens. Tumor CCR4-positivity was 96% in each arm.

Despite amending the protocol to enroll patients less heavily pre-treated and more likely to benefit, the number of patients with ECOG performance status of 2 and those responding to immediate prior therapy was virtually the same pre- and post-amendment (*Online Supplementary Table S1*). Furthermore, the percentage of patients who completed ≤ 1 cycle was the same pre- and post-amendment (65% for both), indicative of the aggressive nature of their disease. These patients were considered non-responders in the ITT analysis.

Efficacy

Confirmed ORR by Independent Review for mogamulizumab was 11% [1 complete response (CR), 4 partial response (PR); 95%CI: 4-23%] compared to 0% (95%CI: 0-14%) for the investigator's choice arm. Best response was 28% (95%CI: 16-43%) *versus* 8% (95%CI: 1-27%) for mogamulizumab and investigator's choice, respectively. A secondary analysis comparing cORR by treatment as assessed by Independent Review did not detect a significant difference (risk difference 10.6%; 95%CI: -14%-34%).

By Investigator Assessment, cORR was 15% (95%CI: 6-28%) for mogamulizumab compared to 0% (95%CI: 0-14%) for the investigator's choice arm. Best response was 34% (95%CI: 21-49%) *versus* 0% (95%CI: 0-14%) (Table 2), respectively.

Independent and investigator review identified a largely concordant group of responding patients, suggesting response assessment was not influenced by investigator bias. Because Investigator Assessments were considered to provide a more comprehensive evaluation of the patients' disease status and potential clinical improvement (investigators had access to all local labs, physical exam findings, and skin rash/infusion reaction, which was withheld from independent review to preserve blind conditions), the following, secondary efficacy results are described based upon Investigator Assessment only.

By compartment responses to mogamulizumab (Table 2 and *Online Supplementary Table S3*) were highest in blood (21/39; 54%, all CR) and skin (8/18; 44%). Responses by compartment to investigator's choice of chemotherapy were only seen in skin (5/9, 56%) and blood (1/18, 6%). In

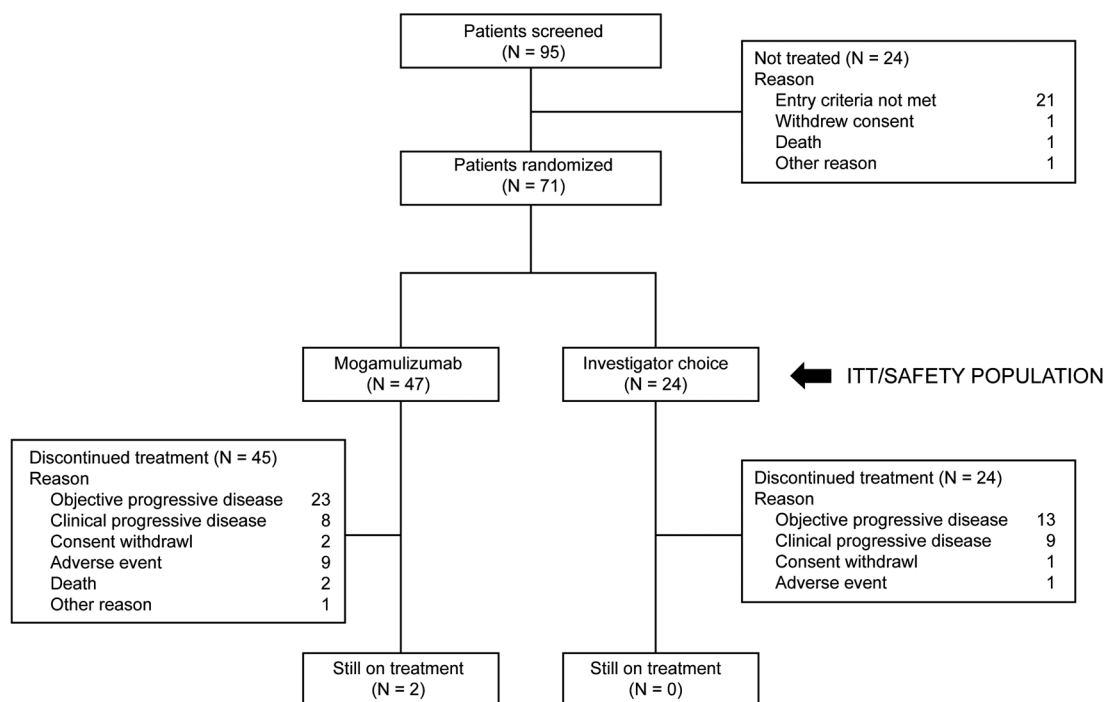


Figure 1. CONSORT diagram. ITT: intent-to-treat.

the 18 patients crossed over to mogamulizumab, three (17%) demonstrated a response.

Responses to mogamulizumab were seen in all enrolled subtypes. Best and confirmed responses by ATL subtype to mogamulizumab were chronic 71% (5/7) and 43% (3/7); lymphoma 32% (6/19) and 5% (1/19); and acute 24% (5/21) and 5% (1/21), respectively. In the mogamulizumab arm, four out of the seven chronic patients had unfavorable characteristics; of those three had a response. Of the three patients with favorable characteristics, two had a response. Three chronic patients initially received Investigator's Choice regimen. All three crossed over to treatment with mogamulizumab; there were no responses to either treatment in these patients.

In the mogamulizumab arm, best response was 46% (13/28) for patients with ECOG 0/1 and 16% (3/19) for ECOG 2. In the Investigator's Choice group, no responses were observed.

Median time to response in the mogamulizumab arm was 1.13 (95%CI: 0.87-3.40) months, with most (75%) responses occurring by the first assessment at 4 weeks. Median DoR in the mogamulizumab arm was 5.65 (95%CI: 3.63-not reached) months.

Median PFS was 0.93 (95%CI: 0.87-1.13) and 0.88 (95%CI: 0.50-0.93) months in the mogamulizumab and investigator's choice arms, respectively. The observed hazard ratio (HR) for PFS was 0.71 (95%CI: 0.41-1.21) (Figure 2). As PFS may have been affected by imbalances in baseline prognostic characteristics, *post hoc* sensitivity analyses adjusting for these imbalances were performed (Figure 3). Adjusting for the imbalances in ECOG performance status and for response to last prior ATL therapy yielded an HR for PFS of 0.57 (95%CI: 0.327-0.983) and

0.58 (95%CI: 0.330-1.006), respectively. Survival analysis was confounded by the one-way crossover design; however, there was no apparent overall survival advantage or disadvantage associated with mogamulizumab use (*Online Supplementary Figure S1*).

Five patients (1 acute, 2 lymphoma, and 2 chronic) progressed per protocol in a single compartment but derived clinical benefit according to Investigator Assessment. These patients were allowed to continue treatment after discussion with the study sponsor (Figure 4 and *Online Supplementary Figure S2*). These patients remained on mogamulizumab with clinical improvement and/or disease control for a median of 230 (range, 182-463) days. Four of the five patients had blood disease, and response continued through to the end of data collection for this group. Of these four patients, one is alive 56 months post initial treatment with subsequent spot radiation to 3 skin lesions. Another subject is alive 41 months post initial treatment and progressed in lymph nodes per size criteria; however, the investigator felt these were more likely to be reactive nodes. Two patients progressed in skin and an additional patient in skin and nodes. No subjects directly bridged to transplant without subsequent therapy in either arm of the study (Figure 4).

Safety

Mean (\pm Standard Deviation) duration of randomized treatment (78.0 \pm 141.51 vs. 26.5 \pm 33.61 days) and the number of treatment cycles initiated (3.1 \pm 4.60 vs. 1.5 \pm 0.98) were higher in the mogamulizumab arm than the investigator's choice arm.

The overall incidence of treatment-related any-grade (83% vs. 88%), grade \geq 3 (32% vs. 29%), or serious (23%

Table 1. Patients' demographic and clinical characteristics.

Characteristic	Mogamulizumab (n = 47)	Investigator's choice (n = 24)
Age (y)		
Median (range)	55.0 (22-82)	50.5 (24-80)
>65 years	11 (23)	1 (4)
<40 years	6 (13)	7 (29)
Gender		
Male	24 (51)	10 (42)
Female	23 (49)	14 (58)
Race		
Black	32 (68)	15 (63)
White	6 (13)	5 (21)
Asian	2 (4)	1 (4)
Other	1 (2)	0
Unknown*	6 (13)	3 (13)
Geographical region		
North America	25 (53)	14 (58)
Europe	14 (30)	7 (29)
South America and Caribbean	8 (17)	3 (13)
ECOG performance status		
0	12 (26)	11 (46)
1	16 (34)	6 (25)
2	19 (40)	7 (29)
ATL subtype at study entry		
Acute	21 (45)	12 (50)
Lymphoma	19 (40)	9 (38)
Chronic	7 (15)	3 (13)
Disease site		
Lymph nodes	41 (87)	20 (83)
Peripheral blood	37 (79)	17 (71)
Bone marrow	27 (57)	8 (33)
Skin	13 (28)	9 (38)
Extranodal masses	12 (26)	8 (33)
Spleen	10 (21)	4 (17)
Liver	2 (4)	3 (13)
Other	1 (2)	0
None reported	0	1 (4)†
Median time from initial ATL diagnosis, months (range)	9.1 (1.3-116.7)	6.6 (1.3-150.6)
CCR4 expression status		
Positive	43 (96)	22 (96)
Negative	2 (4)	1 (4)
Not done	2	1
Number of prior ATL regimens, median (range)	2.0 (1-6)	1.5 (1-5)
Prior ATL regimens		
AZT	19 (40)	9 (38)
CHOP	21 (45)	5 (21)
Interferon	15 (32)	9 (38)
EPOCH	9 (19)	6 (25)
Hyper-CVAD	5 (11)	1 (4)
ICE	3 (6)	3 (13)
Pralatrexate	4 (9)	0
Autologous SCT	1 (2)	1 (4)
Other	34 (72)	16 (67)
Best response to immediate prior ATL therapy		
CR	3 (6)	5 (21)
PR	9 (19)	6 (25)
SD	12 (26)	3 (13)
PD	19 (40)	9 (38)
Unknown	4 (9)	1 (4)

Data are given as n (%) unless otherwise stated. ATL: adult T-cell leukemia/lymphoma; AZT: zidovudine; CCR4: C-C chemokine receptor 4; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CR: complete response; CVAD: cyclophosphamide, vincristine, dexamethasone, and doxorubicin; ECOG: Eastern Cooperative Oncology Group; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ICE: ifosfamide, carboplatin, and etoposide; PD: progressive disease; PR: partial response; SCT: stem cell transplantation; SD: stable disease. *Not reported for those countries that do not allow race/ethnicity data to be collected. †This patient met eligibility criteria with disease in blood and not in lymph nodes according to the investigator but showed lymph node and no blood involvement on independent review.

vs. 17%) AEs were similar between mogamulizumab and investigator's choice arms, respectively, while the overall incidence of treatment-related AEs leading to discontinuation (19% vs. 0%) was higher in the mogamulizumab arm and were most frequently due to infusion reactions and drug eruptions [2 patients (4.3%) each]. There were no treatment-related deaths during randomization or after crossover to mogamulizumab.

The most common treatment-related AEs during randomization and after crossover to mogamulizumab are summarized in Table 3. The most common treatment-related AEs (any grade) in the mogamulizumab arm were infusion-related reaction (47%), drug eruption (19%), thrombocytopenia (13%), and anemia (11%). The most common treatment-related AEs in the investigator's choice arm were

neutropenia (25%), thrombocytopenia (21%), nausea (17%), diarrhea (17%), pyrexia (13%), headache (13%), constipation (13%), and vomiting (13%). The most common treatment-related AEs grade ≥ 3 in the randomized mogamulizumab arm were infusion-related reaction (9%) and thrombocytopenia (9%). The most common treatment-related AE grade ≥ 3 in the investigator's choice arm was thrombocytopenia (17%). Treatment-related AEs (any grade or grade ≥ 3) after crossover were generally similar to those seen in randomized patients. The only treatment-related serious AE occurring in more than one patient in the mogamulizumab arm was pneumonia (n=3).

None of the patients developed detectable anti-mogamulizumab or neutralizing anti-mogamulizumab antibody following treatment.

Table 2. Best overall response and by disease compartment response according to investigator assessment during randomization and after crossover to mogamulizumab (ITT population).

Best response overall and by disease compartment	Randomized		After crossover Mogamulizumab
	Mogamulizumab	Investigator's choice	
Overall	n = 47	n = 24	n = 18
CR	1 (2)	0	0
CRu	2 (4)	0	1 (6)
PR	13 (28)	0	2 (11)
SD	2 (4)	6 (25)	1 (6)
PD	12 (26)	11 (46)	6 (33)
Not evaluable [†]	17 (36)	7 (29)	8 (44)
Blood	n = 39	n = 18	n = 14
CR	21 (54)	1 (6)	7 (50)
CRu	0	0	0
PR	0	0	0
SD	3 (8)	10 (56)	1 (7)
PD	0	4 (22)	0
Not assessable*	15 (39)	3 (17)	6 (43)
Lymph nodes	n = 44	n = 22	n = 17
CR	0	0	0
CRu	1 (2)	0	0
PR	3 (7)	0	0
SD	13 (30)	10 (46)	5 (29)
PD	11 (25)	8 (36)	4 (24)
Not assessable*	16 (36)	4 (18)	7 (41)
Skin	n = 18	n = 9	n = 9
CR	3 (17)	0	2 (22)
CRu	0	0	0
PR	5 (28)	5 (56)	1 (11)
SD	2 (11)	3 (33)	4 (44)
PD	5 (28)	1 (11)	0
Not assessable*	3 (17)	0	2 (22)

Data are given as n (%) unless otherwise stated. CR: complete response; CRu: uncensored CR; ITT: intent-to-treat; PD: progressive disease; PR: partial response; SD: stable disease. [†]All but one patient considered not evaluable for overall response received ≤ 1 cycle of treatment and did not have assessments for response. Of these, on the mogamulizumab arm, reasons for treatment discontinuation from mogamulizumab were; adverse event (7), PD (6), death (2), withdrawal of consent (1), other (1); On the IC arm, PD (4), adverse event (2) withdrawal of consent (1). All were counted as non-responders for ORR in the ITT analysis. The patient on the IC arm who completed >1 treatment cycle, met eligibility criteria with disease in blood on local flow and not in lymph nodes according to the investigator but showed lymph node and no blood involvement on Independent Review and so was considered not evaluable for response by investigator assessment. One subject in crossover received 7 infusions of mogamulizumab and was discontinued from treatment due to an adverse event. Although this patient had a CR in blood and CR in skin, CT scan was not performed and so was not evaluable for overall response (See patient 19 in Figure 4). *If there was no post-baseline tumor assessment for response assessment, or there was no disease in that compartment, the response was designated not assessable.

Discussion

In this randomized phase II trial, the first of ATL outside Japan, mogamulizumab monotherapy demonstrated responses and predictable safety in patients with relapsed/refractory ATL, whereas the comparator arm (investigator's choice of chemotherapy) showed almost no activity. cORR was higher in those randomized to mogamulizumab *versus* the investigator's choice arm by blinded Independent Review for the ITT population: 11% vs. 0%.

This rate of response was less than that seen in the previous phase II study of mogamulizumab monotherapy in 26 evaluable (not in the ITT population) Japanese patients with relapsed CCR4+ ATL, which showed a 50% ORR.²²

Several key differences may account for the discrepancy in activity. The Japanese study only included relapsed, not refractory patients, and confirmation of response (although not required) was evaluated after 4 weeks (compared to 8 weeks in our study). In addition, randomized patients in this study had a higher incidence of poor prog-

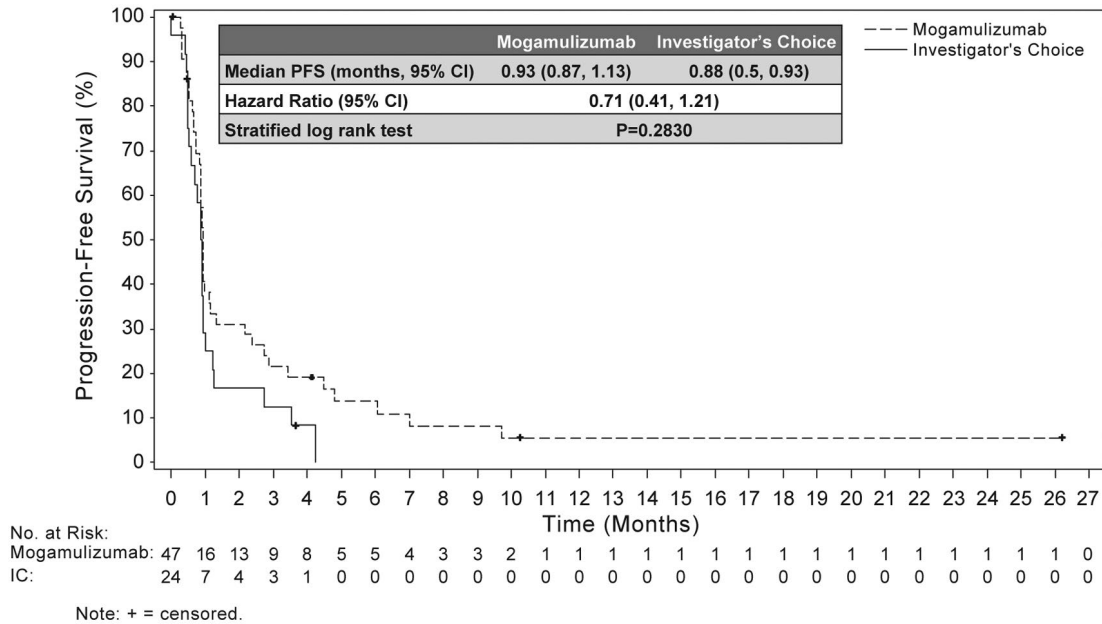


Figure 2. Kaplan-Meier analysis of progression-free survival during the randomized period.

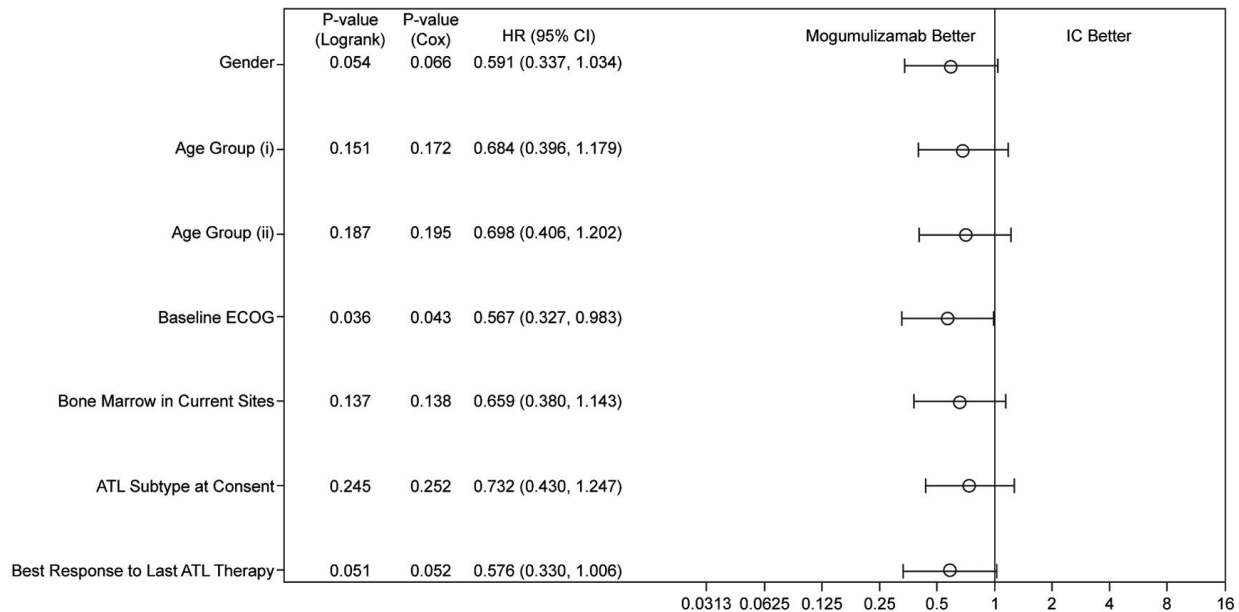


Figure 3. Forest plot of progression-free survival during randomization adjusted for baseline characteristics. Age group = (i) < versus ≥40 years; age group (ii) = ≤65 versus ≥65 years; baseline Eastern Cooperative Oncology Group (ECOG): 0/1 versus 2; bone marrow in current sites: yes versus no; ATL subtype at consent: acute versus chronic versus lymphoma; best response to last ATL therapy: CR+PR versus SD+PD+unknown. ATL: adult T-cell leukemia/lymphoma; CI: confidence interval; CR: complete response; HR: hazard ratio; IC: investigator choice; PFS: progression-free survival; PD: progressive disease; PR: partial response; SD: stable disease.

Table 3. Most common* treatment-related adverse events.

Adverse event	During randomization				After crossover	
	Mogamulizumab (n = 47)		Investigator's choice (n = 24)		Mogamulizumab (n = 18)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Non-hematologic						
Infusion-related reaction	22 (47)	4 (9)	0	0	8 (44)	1 (6)
Drug eruption	9 (19)	0	0	0	4 (22)	1 (6)
Pyrexia	3 (6)	0	3 (13)	1 (4)	1 (6)	0
Nausea	2 (4)	0	4 (17)	1 (4)	0	0
Headache	2 (4)	0	3 (13)	1 (4)	0	0
ALT increased	2 (4)	1 (2)	2 (8)	1 (4)	0	0
Diarrhea	0	0	4 (17)	0	2 (11)	0
Fatigue	2 (4)	0	2 (8)	0	2 (11)	1 (6)
Constipation	0	0	3 (13)	0	1 (6)	0
AST increased	2 (4)	1 (2)	2 (8)	1 (4)	0	0
Vomiting	0	0	3 (13)	0	0	0
Weight decreased	1 (2)	0	2 (8)	0	0	0
Decreased appetite	2 (4)	0	1 (4)	0	2 (11)	0
Mucosal inflammation	0	0	2 (8)	0	0	0
Tachycardia	0	0	0	0	2 (11)	0
Asthenia	0	0	0	0	2 (11)	0
Dyspnea	0	0	0	0	2 (11)	1 (6)
Infections [†]	7 (15)	5 (11)	3 (13)	0	2 (11)	0
Hematologic						
Neutropenia	2 (4)	1 (2)	6 (25)	0	3 (17)	2 (11)
Thrombocytopenia	6 (13)	4 (9)	5 (21)	4 (17)	1 (6)	1 (6)
Anemia	5 (11)	1 (2)	1 (4)	0	1 (6)	1 (6)
Leukopenia	3 (6)	0	0	0	0	0

Data are given as n (%) unless otherwise stated. ALT: alanine aminotransferase; AST: aspartate aminotransferase. *Most common all grade adverse events that occurred in $\geq 5\%$ of patients in either randomized group or ≥ 2 patients during crossover. [†]Incidence reported is for infections overall. Specific infections reported by ≥ 2 patients were: lower respiratory infection, oral candidiasis, cellulitis and neutropenic sepsis for investigator's choice regimens; lower respiratory infection, oral candidiasis, pneumonia, breast abscess, candidiasis, viral conjunctivitis, *Escherichia* urinary tract infection, oropharyngeal candidiasis, *pneumocystis jiroveci* pneumonia and urosepsis for mogamulizumab in randomized period; lower respiratory infection and upper respiratory infection for mogamulizumab in crossover period.

nostic factors at baseline, including older age, higher ECOG performance status, and greater bone marrow involvement than in the Japanese study. The aggressiveness of the disease in the patients on this study was reflected in the high number of subjects (65%) that completed ≤ 1 treatment cycle. Lastly, our study enrolled a more ethnically diverse patient population, and differences in disease biology, clinical presentation, and response to treatment have been suggested in Japanese patients compared to those in other regions,^{15,26} although this has not been studied prospectively.

The Shimoyama classification of ATL¹² and recommended response criteria for ATL²⁵ have been useful for the standardization and comparison of outcomes of Japanese patients with those in the other countries. However, a number of pitfalls in these schema have been reported²⁷ and these were observed in this trial. Complex presentations with leukemic, lymphomatous, and skin compartments may complicate assessment, as disease control in one or more compartments, even alongside an increase in another compartment, may result in significant clinical improvement in a patient, although the patient technically meets progression criteria as the overall response.

Protocol-defined progression was based on Tsukasaki criteria for composite scoring using data from all disease compartments (blood, skin, lymph nodes, extranodal masses, liver/spleen, and bone marrow), which are often involved to various degrees in a single patient and may have led to the clinical benefit being underestimated. In an aggressive, rapidly progressive disease such as ATL, clinical benefit may be apparent to the treating physician, and remains important even if a later blinded composite response is PD. Notable responses were observed in this study in peripheral blood (54%, all with CR) and skin (44%), and several subjects described were considered to be benefiting from mogamulizumab besides those represented in the cORR data.

There is no approved ATL treatment outside Japan. Investigator's choice of chemotherapy regimen in the trial was between GemOx, pralatrexate, and DHAP, with almost all (87%) allocated to GemOx. These regimens were most commonly used for the treatment of relapsed/refractory ATL in the countries where this study was conducted, although there is virtually no published evidence of clinical efficacy. Other studies or series have indicated little evidence of clinical efficacy in relapsed/refractory ATL with regimens such as cladrib-

ine,²⁸ irinotecan,²⁹ or bortezomib.³⁰ A study of 26 patients in Japan published subsequent to enrollment of our trial reported an ORR of 42% with lenalidomide,³¹ and a report on the use of alemtuzumab in relapsed/ refractory patients demonstrated an ORR of 50% in a lower-risk population.³² A recent phase I study examining the combination of romidepsin with pralatrexate included six relapsed/refractory ATL patients and reported a preliminary response rate of 50%.³³ Landmark therapeutic trials leading to US Food and Drug Administration approval in the US of belinostat, pralatrexate, romidepsin, and brentuximab vedotin

in relapsed/refractory PTCL included solitary or no patients with ATL,³⁴⁻³⁷ precluding extrapolation of results to ATL.

The safety profile for mogamulizumab was manageable and consistent with previous reports, with infusion-related reactions and drug eruptions as the most common AEs.^{22,38,39} The rate of discontinuation for drug eruption was similar to the recently reported phase III study of mogamulizumab in CTCL.³⁹ As in that study, use of systemic steroids was not permitted by protocol and most rashes were successfully managed with topical steroids.

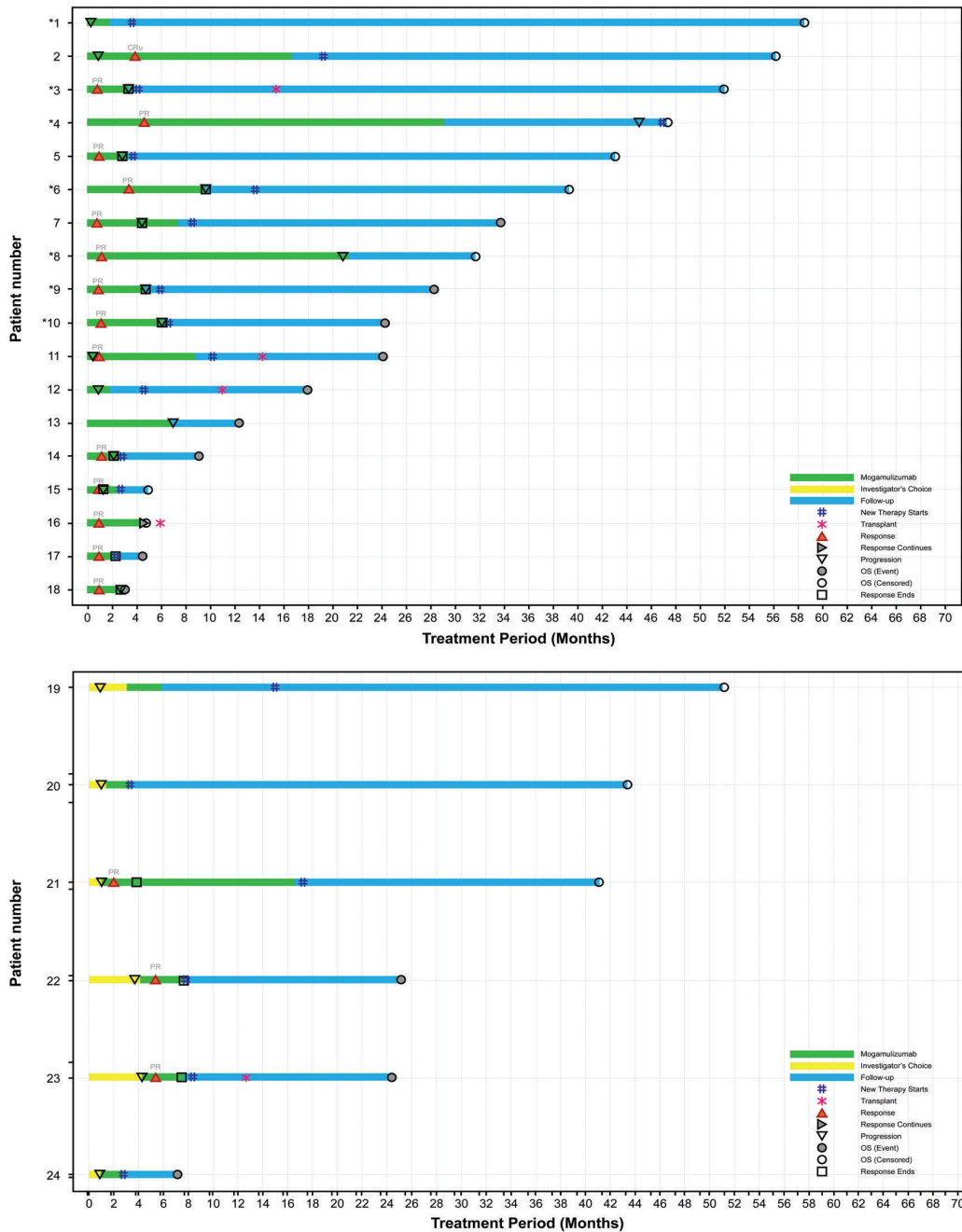


Figure 4. Duration on study for patients receiving ≥ 2 cycles of mogamulizumab. (Top) Initially randomized to mogamulizumab. (Bottom) Initially randomized to investigator's choice of chemotherapy and then crossed over to mogamulizumab. Response as assessed by investigator. *Indicates confirmed response. Patient 16 had salvage chemotherapy prior to transplant but no date was provided.

Treatment-related AEs grade ≥ 3 were infrequent. Comparison of mogamulizumab and investigator's choice arms revealed little difference in the overall incidence of treatment-related AEs of any grade or grade ≥ 3 despite the fact that the duration of treatment exposure was approximately 3-fold longer in the mogamulizumab arm.

In summary, we have conducted the first, prospective, randomized therapeutic trial of ATL outside Japan. Because of the rarity of the disease, the study required a major collaborative effort across multiple international centers to achieve the target accrual within 3 years. Despite small numbers and unbalanced randomization, the trial demonstrated the efficacy of mogamulizumab (e.g. PFS, ORR, responses observed after crossover, durability of responses) in comparison to other frequently used agents. The safety profile in this ethnically diverse patient population with a high unmet medical need was manageable, while minimal benefit was demonstrated with commonly used chemotherapy agents. Given the rates of best response but overall short duration and PFS for many patients with this aggressive disease, future studies should explore combinations with other agents. For example, lenalidomide has demonstrated single agent activity and

may potentiate ADCC in other non-Hodgkin lymphoma subtypes.^{31,40} Earlier lines of therapy, prior to the relapsed/refractory setting, where there is greater possibility of impacting the disease course should also be investigated.

Funding

This study was supported by Kyowa Kirin (Princeton, NJ, USA). We thank the investigators and co-ordinators at each of the participating study centers, the patients who volunteered to participate in this study and their families, and the sponsor staff involved in data collection and analyses. Peter Todd (Tajut Ltd., Kaiapoi, New Zealand) provided editorial assistance in the development of the manuscript, for which he received financial compensation from Kyowa Kirin (Princeton, NJ, USA). The authors had complete access to all data and maintained control over the manuscript, including final wording and conclusions. AP was, in part, supported by The Harold Amos Medical Faculty Development Program (Robert Wood Johnson Foundation) for this research and career development. Researchers at the Memorial-Sloan Kettering Cancer Center were funded, in part, through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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